Day 2

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CARDIAC PACING IN HEART FAILURE

147 Chronic multisite pacing leads to reduced left ventricular volumes in selected patients with congestive heart failure

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Multisite pacing offers a new treatment option for patients (pts) with end-stage congestive heart failure (CHF). In the Path-CHF study pts with CHF, QRS > 120 ms and PR-Intervall > 150 ms are treated with VDD pacing at optimized AV delays and pacing sites. 2 DDD pacemakers (PM) allowed VDD pacing either from the right ventricular apex (RV), left ventricle (LV) or both ventricles (BV). After a 3 months cross-over period pts are chronically paced at an individually optimized AV delay and pacing site, determined by measuring acute dp/dt and pulse pressure (PP) changes at pre-implant (PRE). LV volumes and ejection fraction (EF), assessed by echocardiographic biplane volumetry, were compared between PRE and 6 months follow-up (6 M). A change of more than 10% from PRE was considered to be significant.

Results: 18 pts were available for analysis. 2 pts were chronically paced RV, 7 LV and 6 BV. At 6 M 9 pts responded to pacing (R) with a reduction in end-diastolic volumes (EDV), in 4 pts (NR) EDV increased and in 5 pts (S) it remained stable. EF did not change (22% ± 8 vs. 23% ± 7). 2/9 R did not improve in dP/dt and PP at PRE, whereas all NR improved. EDV-PRE was higher in NR compared to R. The 3 largest EDV were measured in 2 NR and in 1 S.

	All pts	R	S	NR
EDV-PRE (ml)	269 ± 102	248 ± 37	256 ± 157	332 ± 74*
EDV-6 M (ml)	258 ± 135	192 ± 76#	257 ± 166	408 ± 90*

*p < 0.05 vs. R, #p < 0.05 vs. PRE

Conclusions: Chronic VDD pacing at individually optimized AV delays and pacing sites reduces left ventricular volumes in selected patients with CHF and bundle-branch block. However, in pts with very large EDV pacing therapy may fail to reduce left ventricular cavity size, even if these pts improve significantly in dp/dt and PP during acute hemodynamic testing.

148 Mortality evaluation in the InSync trial of cardiac resynchronization for heart failure

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The InSync™ study is a prospective, multicenter, non-randomized trial evaluating cardiac resynchronization (CR) therapy in patients with advanced heart failure (NYHA Class III and IV), dilated cardiomyopathy (EF < 35%, LVEDD > 60 mm) and ventricular conduction delays (QRS > 150 ms). Mortality was followed in the trial with respect to measured clinical endpoints.

Methods: 96 patients were implanted with the InSync system, which included a transvenous left ventricular lead placed via the coronary sinus, were included in this analysis.

Results: Patient survival was 95% (4 deaths), 84% (13 deaths), and 82% (14 deaths) at 1, 3, and 6 months. There were two additional late deaths: one at 261 days and one at 491 days post-implant, for a total of 16 deaths. 9 of the 16 deaths were classified as sudden. Comparison between survivors (mean follow-up: 157 ± 100 days) and non-survivors (mean follow-up: 97 ± 124 days) did not show any statistical significance for differences in measured parameters. Paired parameters between baseline and the last follow-up visit for each group (*p < 0.05, significant improvement) is shown below:

	Survivors		Non-survivors	
	Baseline	Last FU	Baseline	Last FU
NYHA class	3.3 ± 0.5	2.2 ± 0.8*	3.4 ± 0.5	3.1 ± 0.9
Quality of Life	55 ± 18	35 ± 24*	50 ± 18	35 ± 24
6 min walk test, m	295 ± 112	347 ± 107*	325 ± 99	343 ± 94
QRS duration, ms	180 ± 27	156 ± 24*	177 ± 35	164 ± 32

Conclusion: The InSync trial suggests that permanent cardiac resynchronization may provide improved patient mortality in symptomatic heart failure patients with ventricular conduction abnormalities. While additional follow-up and randomized control studies are needed for validation, poor shortening of QRS duration and limited improvement in 6 min walk test may provide predictors of mortality in this patient group.

149 Can pre- and post-operative ECG data predict the clinical response to multisite biventricular pacing in advanced heart failure?

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Biventricular pacing (BiV-P) was recently shown as capable to improve symptoms and exercise tolerance in pts with refractory heart failure related to dilated cardiomyopathy, and broad QRS complex. The aim of this study was to try to identify ECG predictive factors of positive response after BiV-P implantation.

From 08/1994 to 05/1998, 31 pts in NYHA class III or IV (mean age = 67 ± 7 years; mean LVEF = 22 ± 5%) were implanted transvenously with a DDD-BiV PM (pts with normal sinus rhythm; n = 24) or with a VVIR-biV PM (pts with chronic AF; n = 7). 6 months after the implantation pts were classified into two groups depending on the individual response to pacing therapy. Responder pts (Gr I; n = 22) were defined by the association of survival, gain by ≥1 NYHA class and gain by ≥10% in peak VO^2. Non responder pts were classified in group II (n = 9). ECG data were compared before implant during intrinsic conduction and after implant during BiV-P.

	Gr. I (n = 22)	p	Gr II (n = 9)
Age (years)	66 ± 6	NS	67 ± 9
Etiology (ischemic)	9/22	NS	4/9
NYHA class	3.3 ± 0.5	NS	3.1 ± 0.7
LVEF (%)	22 ± 5	NS	21 ± 8
QRS-d (ms) Baseline	178 ± 22	NS	176 ± 30
QRS-d BiV-P	154 ± 15	0.016	177 ± 26
QRS axis Baseline	−27 + 46°	NS	22 ± 90
QRS axis BiV-P	6 ± 93°	NS	0 ± 104

Conclusion: The only ECG predictive factor of positive response was QRS duration after BiV-P with a significantly shorter value in responder pts. So the site of implantation of LV and RV leads has to be carefully selected to provide the shortest paced QRS duration.

150 Cardiac pacing and pulsed Doppler tissue imaging: comparison of myocardial systolic activation and left ventricular end-diastolic diameter in patients during sinus rhythm, DDD and biventricular pacing

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The optimal pacing configuration is the one that best corrects for electromechanical asynchrony within the left ventricle. We evaluated systolic amplitudes, durations, and timings of the basal interventricular septum (IVS), basal lateral left ventricular wall (LW), and posterior wall (PW) by pulsed Doppler Tissue technique (DTI) in eighteen patients during sinus rhythm (SR) and DDD-pacemaker stimulation. These data were compared with the left ventricle enddiastolic diameter [LVEDD] (44–77 mm mean 56 mm). Echocardiographic Images: IVS, LW from an apically four chamber view, PW from the parasternal short axis view.

Results: In patients with enlarged LVEDD and during SR the interval between Q wave in the electrocardiogram and beginning of the systolic myocardial velocities were inhomogenous between the PW and IVS (r = 0.62; p = 0.006). During DDD stimulation the differences of the onset of the systolic velocities from the ventricular impulse (VI – Sb) between LW and IVS showed a significant correlation with the LVEDD (r = 0.60; p = 0.009). In one patient (LVEDD 77 mm) an extreme mechanical asynchrony between the intervals of the onset of the Q wave and beginning of the systolic myocardial velocities in IVS (136 ms), LW (184 ms) and PW (220 ms) was documented during SR. A biventricular pacemaker system (InSync 8040 Medtronic) was implanted. During biventricular pacing (BVP) VI–Sb intervals were homogenous in IVS (220 ms), LW (224 ms), PW (222 ms). Stroke volume increased from 54 ml (SR) to 61 ml (BVP) and peak myocardial systolic velocities measured by pulsed DTI were higher in case of BVP (IVS: 2.8 vs. 4.8 cm/s; PW: 2.3 vs 3.1 cm/s).

Conclusion: 1) If heart failure symptoms occur in dilated cardiomyopathy, pulsed DTI can be used to identify patients with inhomogenous systolic function of the left ventricle. 2) If highly inhomogenous systolic activation is documented by pulsed DTI, biventricular pacing should be taken into consideration to improve hemodynamics by synchronizing left ventricular myocardial systolic contractility. 3) Pulsed DTI technique may be the method of choice for selection of candidates for BVP and monitoring of cardiodynamics and hemodynamics changes during follow up.

151 Abnormal renal haemodynamics and neurohormones in heart failure patients treated with biventricular pacemakers

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Aim: Biventricular pacing improves symptoms and functional capacity in heart failure. There is however little information on its effect on the neurohumoral axis, which has clear prognostic implications.

Methods: We prospectively assessed atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), endothelin-1 (E-1),plasma renin activity (PRA) and noradrenaline (N) levels in 14 patients who underwent biventriclar pacing for heart failure. All patients received a Medtronic Biventricular Pacing System programmed optimally. We also measured sodium excretion and creatinine clearance on 24 hour urine collections and performed cardiopulmonary exercise tests and echocardiograms.All tests were done at baseline, 1 and 3 months, with no changes in drug therapy during this period.

Results: There were notable correlations between neurhormones and echocardiographic parameters. ANP correlated with transmitral filling time ($r = -0.54$ $p = 0.06$),BNP with fractional shortening [FS] ($r = -0.49$ $p = 0.15$), E-1 with stroke distance ($r = -0.66$ $p = 0.02$) and filling time ($r = -0.67$, $p = 0.02$),noradrenaline with LV systolic dimension ($r = 0.58$, $p = 0.038$).

Results: These are summarised in the accompanying table.There were no significant changes in ANP, BNP, PRA, N or sodium excretion at 1 and 3 months.Endothelin-1 levels however rose significantly with a concurrent fall in creatinine clearance.

Neurohumeral changes

Parameter	Baseline	1 month	p value	3 months	p value
Exercise Duratn/min	6.4 ± 2.3	8.2+/3.2	0.05	8.7 ± 3.2	0.05
VO_2 max ml/kg/min	16.4 ± 5.2	19.9 ± 8.2	0.04	17.7 ± 6	0.03
FS /%	10 ± 2.6	13 ± 3.8	0.004	15 ± 1.8	0.04
ANP pg/ml	76 ± 30	88.6 ± 31	0.7	66 ± 38	0.5
BNP pg/ml	63 ± 40	73 ± 40	0.4	81 ± 30	0.7
E-1 pg/ml	5.7 ± 0.6	5.8 ± 0.8	0.65	6.2 ± 0.9	0.04
Noradrenaline nmol/ml	3.5 ± 1.6	3.4 ± 2	0.9	3.4 ± 11.9	0.2
Creat. Clearance ml/min	66 ± 28	57 ± 26	0.46	50 ± 29	0.08
Sodium Excretion/24 hr	84 ± 39	102 ± 58	0.15	101 ± 57	0.1

Conclusion: Despite significant haemodynamic improvement, these changes in glomerular filtration rate and endothelin levels, suggest an adverse effect of biventricular pacing. This may in part, explain the lack of prognostic benefit.

152 Is an altered heart rate increase responsible for the functional exercise capacity in dilated cardiomyopathy? Implications for rate adaptive pacing

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In pts. with dilated cardiomyopathy (DCM) the anaerobic threshold (AT) is frequently not detected due to reduced exercise capacity. We studied, whether those patients can be characterized by a different exercise heart rate (HR) response, offering the potential for therapy with rate adaptive pacemakers.

Methods: We studied 40 pts (31 m, 9 f, aged 50 ± 13 y) with DCM and an ejection fraction (EF) < 0.40 (0.27 ± 0.08). All were on stable medication consisting of digitalis, ACE-inhibitors and diuretics, but without beta-blocking agents. They performed a symptom-limited cardiopulmonary peak exercise test on the bicycle using a ramp protocol starting at 20 W with an increase of 10 W/min. The HR to work rate (WR) slope was determined using linear regression analysis.

Results: In group 1 (n = 16, EF 0.29 ± 0.09) exercise was terminated before the AT could be detected. The HR increased from a resting value of 90 ± 17 bpm to a maximum of 132 ± 22 bpm at a WR of 93 ± 31 W. In group 2 (n = 24, EF 0.27 ± 0.07) the HR at rest was 86 ± 15 (n.s.), and increased at AT to 114 ± 20 (WR: 73 ± 42 W) and at peak exercise to 138 ± 19 bpm (WR: 107 ± 50 W). In group 1 the HR/WR slope from rest to peak exercise was 0.54 ± 0.28 bpm/W. This slope was not different from those pts who achieved the AT: 0.62 ± 0.30 bpm/W, but was steeper than the slope known for normals with 0.37 ± 0.13 bpm/W. Above the AT to peak exercise, no further increase occurred in group 2: 0.68 ± 0.38 bpm/W (n.s.).

Conclusion: During exercise in patients with dilated cardiomyopathy, functional capacity is dependent upon an elevated heart rate increase relative to metabolic demand. Compared to values published for healthy subjects, both groups showed a steeper heart rate to work rate slope. Therefore a more agressive rate response factor programming is suggested in order to meet metabolic demands.

SINGLE AND MULTISITE PACING IN ATRIAL FIBRILLATION

153 Biatrial synchronous pacing for atrial arrhythmia prevention: the SYNBIAPACE Study

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Biatrial synchronous pacing (BASP) was introduced some years ago as a new pacing modality for atrial arrhythmia (AA) prevention and was shown to be technically feasible and safe. The SYNBIAPACE Study was a prospective randomized crossover trial comparing 3 pacing modes during 3 periods of 3 months each: BASP at a basic pacing rate of 70 bpm, single site high right atrial DDD pacing à 70 bpm, and the same at 40 bpm ("inhibited" mode) used as reference mode. Criteria for inclusion were long lasting history (≥1 year) of recurrent and drug refractory AA associated with atrial conduction block as defined by a P wave duration ≥ 120 ms and by interatrial conduction time ≥ 100 ms. BASP was provided by using a specific coronary sinus lead (Medtronic SP 2188) and a specific algorithm loaded into the RAM memory of the device (Chorus 7034, Ela Medical). The primary end-point was to compare the time to first AA reccurence as monitored by the Holter functions of the pacemaker (specific algorithm of intracardiac electrogram storage) among the 3 pacing modes.

Results: 43 pts (M = 24; F = 19), mean age 64 ± 12 years, were included from March 1995 to December 1997. The mean P wave duration was 148 ± 31 ms.

	BASP	DDD 70	Inhibited
Time to 1st AA (days)	62 ± 24	37 ± 22	39 ± 22
Time in AA (days)	4 ± 10	7 ± 16	5 ± 13

Concerning the primary end-point no statistically significant difference was found between the 3 pacing modes.

Conclusion: despite a trend to a reduction in the incidence of AA during BASP, no real benefit of this pacing mode was demonstrated in this selected population.

154 Biatrial pacing as an effective therapy of lone atrial fibrillation

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For effective management of drug-refractory atrial fibrillation (AF) as the most common arrhythmia new methods are needed. In case of existing interatrial conduction disturbance the use of biatrial pacemaker with standart right atrial lead and additive coronary sinus lead for left atrial pacing shows an antiarrhythmic effect due to atrial resynchronisation. In order to demonstrate the antiarrhythmic effect of biatrial pacing from November 1997 to February 1999 51 pts. (19 f/32 m, mean age 63.6 ± 8.8 y) received a biatrial pacemaker (AAD-mode, AV-delay 0 msec., LOGOS, Fa. BIOTRONIK). All patients had a prolongation of P-wave duration more than 100 msec (mean 125 ± 21 msec).

Preoperatively 5/51 (9.8%) pts. had monthly, 31/51 pts. (61%) had weekly, and 9/51 pts. (17.6%) had daily episodes of atrial fibrillation. Permanent atrial fibrillation >6 month was seen in 3/51 pts. (5.8%, preoperative cardioversion) and syncopal episodes due to paroxymal AF in 3/51 (5.8%) pts.

The intraoperative right atrial pacing threshold was 0.95 ± 0.7 V (0.5 msec pulse width), the atrial signal amplitude 2.4 ± 0.9 mV. Voltage recording in the coronary sinus showed a pacing threshold of 1.5 ± 0.8 V (0.5 msec pulse width) and a potential of 3.5 ± 1.4 mV. The obtained P-wave duration reduced for 35 ± 20 msec.

In 9/51 pts. (17.6%) we found a dislocation and in 3/51 pts. (5.8%) an excessive high pacing threshold of coronary sinus lead >4 V/0.5 msec. All pts. with dislocated lead were reoperated. There were no perforations and thromboses of coronary sinus.

The intervention leads to a significant inhibition of atrial fibrillation in 15/51 pts. (29.4%) without and in 4/51 pts. (7.8%) with antiarrhythmic drugs. 18/51 pts. (35.2%) had a reduction of episodes without and 7/51 pts. (13.7%) with concomitant medication. The treatment did not have any influence on the prevalence of atrial fibrillation in 7/51 pts. (13.7%).

In conclusion, the implantation of biatrial pacemaker leads to a significant reduction of atrial fibrillation episodes and has proven practicable and safe for clinical use.

155 Prevention of atrial arrhythmias by overdriving and the rest rate: preliminary results from the PROVE study

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In the literature short-term data suggest that atrial overdrive prevents or reduces atrial arrhythmia episodes (AA). The aim of the PROVE study is to evaluate this hypothesis in a population of patients (pts) implanted with Chorum® and Talent® pacemakers (Ela Medical Montrouge France) during 2 phases (I and II) of 3 months each.

Methods: All patients (pts) are monitored during 1 month (Phase 0) with the Memory Function (AIDA) of the pacemaker in order to identify the number of AA during this period.

Thereafter, the pts are classified in 2 classes and randomized with respect to the order in which two different pacemaker settings are applied. Class I (CI): pts with at least 2 fallback mode switch episodes and Class II (CII): all other pts.

Class I pts are programmed with a) their basic rates (BR) at 60 bpm or b) set with an atrial overdriving (O) at 10 bpm over the mean atrial rate stored by AIDA, with the automatic rest rate being activated, and the rate responsive mode enabled.

Class II pts are programmed c) with a higher basic rate of 70 bpm associated with the rest rate in comparison to d) a standard DDD(R) programming at 60 bpm. Within each group the two pacemaker settings are applied in a random order. The results of Phase I are compared to Phase II within both classes of pts. AIDA is activated during the entire study.

39 patients (pts) were included: 14 in CI (5 males, 73 ± 7.8 years), 1 had AV block (AVB), 4 sinus node dysfunction (SND), 4 brady-tachy syndrome (BTS), 4 AV block and SND, 1 other indication implantation. 11 pts had a previous history of AA and 10 pts received antiarrhythmic drugs (AAD). 25 pts were included in CII (17 males, 72.2 ± 7.1 years), 8 had AVB, 9 SND, 2 BTS, 6 AVB and SND. 7 pts had a previous history of AA and 11 pts received AAD.

Results: 12 out of 14 pts of CI developed AA during both phase I and II. During the phase with *O* the number of fallbacks (FMS) was reduced by 58% (62 to 44) and the total duration of the episodes by 72%. In CII only 1 pt developed AA during both phases and 3 pts developed AA in one phase.

Conclusion: These preliminary results seem to show that Overdriving combined with automatic Rest Rate are useful to prevent AA since they reduce the number of FMS by 58% and the total duration of the episodes by 72%. More data have to be collected before statistical significance and definite conclusions can be given.

156 Long-term results of a pilot study on biatrial synchronous pacing for prevention of drug-refractory atrial tachyarrhythmias

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Results of previous studies suggest that atrial resynchronization with multisite atrial pacing may contribute to prevent recurrences in pts with drug-refractory atrial tachyarrhythmias (AT) and significant atrial conduction block.

To assess this hypothesis, a pilot study was conducted in a single center between Jan. 1989 and Nov. 1997 in 86 pts, mean age 66 ± 10 yrs. Inclusion criteria were P-wave duration ≥ 120 ms with interatrial conduction time ≥ 100 ms, and history of multiple recurences of AT (mean = 7 ± 3 episodes) evolving in a persistent mode from at least 6 months despite optimized drug treatment (mean = 2.7 ± 1/pt). Pts were chronically implanted with a pacing system providing permanent biatrial pacing with two atrial leads, one placed in the high right atrium and the other into the mid or distal part of CS. P wave duration decreased from a mean value of 187 ± 29 ms before implant to 106 ± 14 ms ($p < 0.0001$) during biatrial pacing.

After a mean follow-up time of 33 months (range: 6–109), 55 pts (64%) remained in stable sinus rhythm, including 28 pts (32.6%) without any documented recurrence and 27 pts with one or more recurrences in a paroxysmal or in a persistent form. In those pts, drug treatment was significantly reduced in comparison with the pre-implantation period (1.4 ± 0.6 vs 1.7 ± 0.5 drug/pt; $p = 0.01$). Other 31 pts went to chronic AT after a mean time of 26 months. The only predictive factor of positive response was P wave duration > 160 ms at baseline.

These results are consistent with a preventive effect of permanent biatrial pacing in recurrent and drug-refractory AT associated with atrial conduction block.

157 Coronary sinus – a site for chronic left atrial pacing? An electrophysiological and anatomical study

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Multisite pacing strategies for prevention of atrial tachyarrhythmias may include left atrial pacing via the coronary sinus (CS). The aim of the study was to evaluate the electrophysiological and anatomical conditions of the CS with respect to chronic pacing therapy.

Methods: EP-study: 20 consecutive patients were studied during a routine EP-study. The left atrial and ventricular pacing thresholds (LAP/LVP), and signal amplitudes (LAA/LVA) were measured in four different parts of the CS using steerable EP catheters. Pathology: Formalin-fixed postmortem hearts of 40 adults (age: 17–78 years; weight: 250–910 g) were evaluated. CS, adjacent epi- and myocardium were dissected from the AV sulcus and completely cross sectioned in 3–4 mm thick tissue blocks (HE, Goldner's, Trichrome).

Results:

	Posterior CS	Post-lateral CS	Lateral CS	Antero-lat. CS
LAP (V/0.5)	1.0 ± 0.4	1.6 ± 1.3	3.8 ± 2.0	4.1 ± 1.3
LVP (V/0.5)	>7.5	>7.5	5.0	6.1 ± 0.4
LAA (mV)	2.9 ± 1.0	2.9 ± 1.2	1.5 ± 0.8	1.4 ± 0.8
LVA-(mV)	0.4 ± 0.4	0.6 ± 0.5	0.9 ± 0.6	1.2 ± 0.8

Histological examinations show that the CS was concentrically surrounded by cardiac muscle tissue from the os to the lateral aspect of the CS but not in lateral and anterolateral parts of the CS. Cardiac muscle surrounding the CS were connected to LA myocardium. The length of "muscularized" CS, ranging from 1.9 to 5.4 cm, was correlated with the heart weight ($r = 0.54$; $p < 0.001$).

Conclusions: The differences in proximal and distal sections of the CS wall regarding muscular connections to LA myocardium is the explanation for the observed increase in LA-pacing thresholds and reduction in LA signal amplitudes in the more distally parts of the CS. These findings may have importance for the design of chronic pacing leads for LA-pacing via the CS.

158 To prevent or to induce fibrillation? A new concept in the non-pharmacological therapy of refractory paroxysmal atrial fibrillation

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The benefit of atrial pacing (AP) in preventing atrial fibrillation (AF) has been suggested only for patients (pts) with sick sinus syndrome and vagally-induced AF. We tried AP in 25 highly symptomatic pts (18 m., 7 f., aged 65 ± 11 years) with paroxysmal AF and normal sinus node, occurring at least weekly despite drug treatment of amiodarone + flecainide. A 4-step protocol was used:

- implant of a DDD-R pacemaker with 75 bpm minimal rate
- specific pause-prevention algorithm (Medtronic Inc)
- induction of AF by repetitive systematic 64 Hz atrial pacing
- His bundle ablation (HBA) procedure.

Each step of the protocol was done in case of persistance of symptoms and documented AF with the previous one.

After a follow-up of 12.5 ± 5 months, simple AP was clinically efficient in 17 pts. Pause-prevention algorithm was efficient in 1 case, and 3 pts developped spontaneous permanent AF, with a clinical improvement due to relief of palpitations. One pt refused AF-induction step and preferred HBA. Only 3 pts reached AF-induction step. It was efficient in only 1 pt but sinus rhythm recurred 1 week after cessation of 64 Hz pacing; in 1 pt AF could be induced only at night, and in the 3rd pt only atrial tachycardia was obtained, without true AF.

Conclusion: A preventive effect of AP is frequent, even in non bradycardia-dependent AF and should be systematically tried before HBA. Induction of permanent AF, desirable in some pts to decrease symptoms, is not so easy than expected from animal experiments, suggesting a lack of remodelling process in highly diseased atria.

ATRIAL BEHAVIOUR AFTER ELECTRICAL CARDIOVERSION

159 Antiarrhythmic drug effect on the left atrial mechanical properties post electrical cardioversion of persistent atrial fibrillation

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The atrial contractility is known to improve after electrical cardioversion (EC of atrial fibrillation (AF). We investigated the effect of antiarrhythic drugs prescribed to maintain sinus rhythm (SR) on the mechanical properties of the left atrium (LA) in patients (pts) with persistent AF.

Methods: Fifty-seven pts, 34 males (mean age 61 ± 8 years), underwent EC for AF (mean duration 3.9 ± 3 months). Pts with LVEF < 40%, LA > 55 mm, thyrotoxicosis, unstable coronary artery disease or valvular heart disease were excluded. The pts were allocated to propafenone (n = 23), sotalol (n = 12) and amiodarone (n = 18). Left atrial active emptying (LAAE), atrial wave flow velocity integral (LAFV), pulmonary vein atrial reverse velocity (PVAR) and pulmonary vein systolic wave integral (PVSW) were prospectively evaluated at 0, 15, 30 and 90 days post cardioversion.

Results: Of the 57 pts, 53 were successfully cardioverted and after a follow up period of 13 ± 6 months, 25 (47.2%) of the cardioverted pts maintained SR. Mean age, LVEF, LA size, AF duration, electrical energy required and SR maintenance rate were not significantly different between the three groups.

		Day 0	Day 15	Day 30	Day 90	0 vs 15	15 vs 90
Group 1	LAAE (%)	14 ± 9	28 ± 12	32 ± 11	32 ± 15	0.006	0.647
(Propafe	LAFV (cm)	3.1 ± 1.7	5.9 ± 1.1	6.7 ± 2.1	6.7 ± 2.2	0.007	0.552
none)	PVAR (cm/s)	5 ± 9	26 ± 4	29 ± 7	27 ± 5	0.001	0.631
	PVSW (cm)	6 ± 4	14 ± 2	17 ± 6	19 ± 6	0.001	0.115
Group 2	LAAE (%)	11 ± 5	23 ± 10	35 ± 6	29 ± 6	0.044	0.298
(Sotalol)	LAFV (cm)	1.7 ± 1.2	4.7 ± 0.5	5.3 ± 0.5	5.5 ± 0.8	0.011	0.302
	PVAR (cm/s)	10 ± 16	7 ± 14	30 ± 4	29 ± 7	0.109	0.228
	PVSW (cm)	9 ± 5	16 ± 3	17 ± 4	15 ± 6	0.123	0.935
Group 3	LAAE (%)	8 ± 9	25 ± 11	28 ± 6	33 ± 10	0.022	0.028
(Amioda	LAFV (cm)	2.8 ± 3.0	5.4 ± 0.7	7.3 ± 2.7	7.4 ± 2.1	0.085	0.054
none)	PVAR (cm/s)	16 ± 5	28 ± 5	31 ± 6	28 ± 3	0.088	0.526
	PVSW (cm)	10 ± 6	16 ± 6	17 ± 6	16 ± 5	0.002	0.601

Conclusions: 1) Left atrial contractility seems to already improve by day 15 post cardioversion. 2) However, in propafenone and sotalol groups it flattens out after day 15, possibly due to the drugs' negative inotropic effect. 3) On the contrary amiodarone seems to continue to exert its beneficial effect until day 90.

160 Postcardioversion atrial stunning after electrical cardioversion is caused by atrial fibrillation itself

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Background: Electrical cardioversion of atrial fibrillation may cause postcardioversion atrial stunning. The hypothesis of this prospective study was that atrial chamber and appendage stunning after electrical cardioversion is not caused by the applied energy but is related to the duration of atrial fibrillation (AF).

Methods: Transesophageal echocardiography (TEE) was performed in 9 patients with acute AF (duration 14 ± 3 h) and 9 patients with chronic AF (127 ± 104 days) to assess the effect of electrical shocks on left atrial chamber and appendage function. Peak emptying velocities of the left atrial appendage (LAAv) and spontaneous echo contrast (SEC) were assessed before and after the procedure. Seven patients with paroxysmal AF and spontaneous restoration of sinus rhythm (SR) during a TEE examination served as controls.

Results: In patients with spontaneous cardioversion, SEC was detected neither before nor after restoration of SR. In addition, LAAv were not affected by spontaneous restoration of SR (0.7 ± 0.13 m/s versus 0.7 ± 0.14 m/s). Likewise, restoration of SR after electrical cardioversion of acute AF did not affect the degree of SEC and LAAv (0.61 ± 0.15 versus 0.57 ± 0.22). In contrast cardioversion of chronic AF resulted in the intensification and/or generation of SEC in 5 of 9 patients and LAAv decreased from 0.36 ± 0.11 m/s to 0.25 ± 0.09 m/s (p = 0.002) after the procedure. Furthermore, ineffective shocks during both acute and chronic AF affected neither LAAv nor SEC.

Conclusions: Atrial chamber and appendage stunning after electrical cardioversion is caused by AF itself and is related to its duration. These findings have important clinical implications for anticoagulation therapy in patients with paroxysmal AF.

161 Transthoracic echocardiography for the exclusion of left atrial chamber and appendage thrombi before cardioversion of atrial fibrillation/flutter

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Background and methods: Transesophageal echocardiography (TEE) prior to cardioversion of atrial fibrillation (AF) is a reliable but expensive procedure to exclude atrial thrombi. To evaluate the value of current transthoracic echocardiographic systems (TTE) and TEE for detecting atrial thrombi and assessing atrial function prior to cardioversion, 87 patients with atrial fibrillation (AF) and 32 patients with atrial flutter (AFl) were investigated prior to the procedure by two different investigators by both methods.

Results: Transthoracic imaging of the atrium was considered adequate in 75 of 87 patients with AF and in 28 of 32 cases with AFl. In patients with AF, TTE disclosed 5 thrombi in the left atrium. In patients with AFl thrombi were not detected. The transthoracic exclusion and detection of thrombi were confirmed by TEE in all cases with adequate transthoracic echogenicity. In patients with transthoracic exclusion of atrial thrombi, thromboembolic complications after cardioversion did not occur. Transthoracic recording of the flow velocity profile over the appendage was feasible in 69 patients with AF (0.36 ± 0.16 m/s) and in 27 patients with AFl (0.48 ± 0.12 m/s).

Conclusions: If transthoracic echogenicity of patients is optimal, new generation transthoracic echocardiographic systems allow the detection or exclusion of atrial thrombi with a high degree of confidence prior to cardioversion. TEE examinations may therefore be limited to cases of suboptimal transthoracic imaging or where there is clinical concern despite negative transthoracic results.

162 Coagulation indicators in patients with non-valvular atrial fibrillation: a comparison with transoesophageal echocardiography (a prospective 4 years study)

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Background: Both left atrial appendage (LAA) spontaneous echo contrast and thrombus are associated with major risk of thromboembolism in patients (P) with nonvalvular atrial fibrillation (NVAF). However, their coagulation determinantshave not been fully elucidated. Furthermore, the predictive value of coagulation indicators has not been yet explored in term of thromboembolic events.

Aim of the study. (a) To verify whether NVAF is associated with abnormalities of fibrinogen, D-dimer and fibrinopeptide A (FpA)plasma levels;

(b) to verify if there is a relationship between those coagulation indicators and echocardiographic finding of LAA thrombosis or prothrombotic condition;

(c) to verify whether echo data, D-dimer or Fibrinopeptide A can be usefull predictors of thromboembolic events.

Methods: We determined fibrinogen, D-dimer and FpA in 77 consecutive P with chronic NVAF who were undergoing to TEE the same day and in 117 matched controls. P were followed for a 4-years period.

Results: LAA thombus was found in 27 P (35%), a spontaneous echocontrast alone in 14 P (18%). Fibrinogen, D-dimer and FpA were significantly higher in study population than in control group (Fibrinogen 335 ± 106 vs 283 ± 71 mg/dl $p < 0.05$, D-dimer 436 ± 271 vs 306 ± 271 ng/ml $p < 0.01$, FpA 8.6 ± 6.2 vs 2.0 ± 0.4 ng/ml $p < 0.001$).

In study population P with LAA had higher FpA plasma levels (10.2 ± 3.5 vs 5.3 ± 2.5 ng/ml $p < 0.01$).

Thromboembolic events: P with a lower LAA flow profile during the follow up demonstrated a relative risk of 2.0; P within the upper tertile of FpA have a relative risk of 8.2 times.

Conclusions: Abnormal plasma levels of fibrinogen, D-dimer and FpA indicate that the coagulation system is activated in P with chronic NVAF.

FpA plasma levels are significantly higher in P with LAA thrombosis than in other groups. FpA is the most efficient predictors of embolic events after 4-years follow up.

163 The role of transthoracic echocardiography before cardioversion of atrial fibrillation in patients at low thromboembolic risk

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Transesophageal echocardiography (TEE) is currently used to identify patients (pts) with atrial fibrillation (AF) at low risk for embolism after cardioversion (CV). However, TEE is not always available and feasible; moreover, pts without significant heart disease are considered to be at low thromboembolic risk even in the setting of AF $\geq$ 3 days. In this subset of pts also transthoracic echocardiography (TTE) might accurately identify pts at low risk cadidates to short-term anticoagulation for CV. On January 1998 we started a prospective protocol aimed to evaluate the safety of CV for AF after short-term anticoagulation with warfarin (plus calcic heparin until INR > 2.0) if admission TTE ruled out mitral stenosis, significant mitral regurgitation, left atrial size (LAS) > 50 mm, left ventricular end-diastolic diameter (LVEDD) > 60 mm, ejection fraction (EF) < 45%, or other significant heart disease. Evidence of heart failure, previous thromboembolism, or stroke were also exclusion criteria. We identified 51 out of 172 consecutive pts (mean age 69.2 $\pm$ 11.0 years, 24 males, 27 females) with AF $\geq$ 3 days (mean 24.0 $\pm$ 45.4 days), who underwent successful CV (pharmacological 25, electrical 26); 33 (65%) pts were hypertensive. Mean LAS was 46 $\pm$ 3 mm, mean LVEDD 53 $\pm$ 3 mm, mean EF 51 $\pm$ 3%. TEE was also performed in 15 pts (30%) and in no case showed left atrial thrombus or features contraindicating CV. The mean duration of pre-CV anticoagulation was 3.8 $\pm$ 3.1 days; No patient had in-hospital complications. The length of hospital stay was 4.1 $\pm$ 1.0 days. Oral anticoagulation continued for 18 $\pm$ 9 days after CV. At follow-up (mean 80 $\pm$ 42 days) no thromboembolic or hemorrhagic complications occurred; 38 pts (75%) were free of recurrence of AF or new hospitalizations for cardiac causes. In conclusion, TTE can accurately identify pts at low thromboembolic risk who can receive short anticoagulation for CV. However, larger prospective randomized trials are warranted.

164 Antioxidant therapy can influence the recovery of left atrial contraction after external electrical cardioversion

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Recent studies have shown that in pts. with atrial fibrillation (AF), external electrical cardioversion (EEC) induces a state of atrial stunning that follows for several days. It is well known that direct current (DC) shock generates free radicals that may contribute to atrial mechanical dysfunction. The aim of the study was to evaluate the effects of an antioxidant therapy on atrial function recovery in pts. with non rheumatic AF.

Methods: we enrolled 51 consecutive pts. who underwent successful EC for AF. A standard medical treatment was given in 25 pts. (G1). Three days before EC the remaining 26 pts. (G2) received an antioxidant therapy (Glucose 20% 500 cc with regular insuline 20 UI, K+ 40 mEq, MgSO4 24 mMol, vitamine C 2 gr). A single 25 mg dose of Captopril before EEC and Vitamin E 300 mg/die during the following 21 days was also given. Pulsed doppler indices of left atrial mechanical function were measured within 1 hour (T0), at 1 day (T1), three days (T2), one week (T3), and three weeks (T4) after DC shock.

Results: At T1 and T2 G2 showed a significant increase ($^*p < 0.001$) of peak A wave velocity (PA), integrated late atrial velocities (A-VTI), atrial contribution to total transmitral flow (AVTI/VTI), and atrial ejection force (AEF). At T4 there was no more significant difference betwen G1 and G2.

	T0		T1		T2		T3		T4	
	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2
PA	39±3	38±4	46±6	53±5*	50±4	62±5*	61±4	63±6	62±5	64±4
AVTI	5±2	5±4	5.7±2	6±2*	5.2±2	6.5±2*	6.5±2	6.8±2	6.6±2	6.9±2
AVTI/VTI	28±5	28±5	29±5	33±5*	30±4	35±4*	35±3	36±2	36±3	36±4
AEF	5±2	4.8±2	5±3	8±3*	6±2	10±3*	10±3	13±4*	13±2	14±3

Conclusions: Our findings suggest that an antioxidant therapy can accelerate atrial mechanical recovery from stunning after EEC. This could have a favorable impact on the risk of embolic complications due to atrial disfunction following EEC.

ARRHYTHMIAS IN ISCHAEMIC AND NON-ISCHAEMIC CARDIOMYOPATHIES

165 QT interval dynamicity in idiopathic dilated cardiomyopathy: relationships with haemodynamic status and prognostic value

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QT dispersion has shown to be a poor predictor of cardiac death in patients with idiopathic dilated cardiomyopathy (IDC). QT interval dynamicity has been proposed as another tool for assessment of the risk of cardiac events or ventricular arrhythmias. This study evaluated the relationships of QT interval dynamicity with hemodynamic status and assessed its usefulness for risk stratification in patients with IDC.

Methods: We performed 24-h ECG recording in 100 patients with IDC who were in sinus rhythm (WHO criteria; mean age 50 years; range 18–70; 75 men; left ventricular ejection fraction 35 $\pm$ 12%) and in 60 healthy subjects. The QT intervals (QT end and QT apex) were measured automatically with a validated computerized Holter system (Elatec, Ela medical, France). The rate dependence of repolarization was evaluated over 24 hours, during a daytime period (9 AM–9 PM) and during a nighttime period (11 PM–6 AM) with measurement of QT/RR slopes.

Results: QTend/RR slopes (24 hours, day and night) were significantly increased in patients with IDC ($p < 0.001$) whereas QTapex/RR slopes were not different from control subjects. All the QT/RR slopes were related to left ventricular end systolic diameter (R range 0.22 to 0.36, p = 0.04 to 0.001) and inversely related to left ventricular ejection fraction (R range −0.25 to −0.47, p = 0.03 to 0.0001). With a follow-up of 54 $\pm$ 39 months, 15 patients died (10 progressive CHF, 5 sudden deaths) and 11 underwent heart transplantation. Among QTc durations and QT/RR slopes, using multivariate analysis (proportional hazards model), the only independent predictor of cardiac events (cardiac death or heart transplantation) was an increased QT end/RR slope during the daytime period (p = 0.02). For this parameter, a cutoff level of 0.22 distinguished 2 groups of patients with significantly different survival curves of cardiac events (p = 0.008).

Conclusions: QT dynamicity is related to the hemodynamic status and provides a risk stratification of cardiac events in patients with IDC. Among the several parameters of QT interval dynamicity, an increased QT end/RR slope during the daytime is the most powerful predictor of cardiac events in these patients.

166 Clinical relevance of heart rate variability versus repolarization dispersion for the non-invasive electrocardiographic risk stratification in patients with ischaemic cardiomyopathy

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Heart rate variability (HRV) as well as repolarization dispersion (QT/JT dispersion) have been proposed as non-invasive risk indicators in patients (pts) with ischemic cardiomyopathy (ICM) but their prognostic value as predictors of sudden cardiac death and pump failure death remains controversial. The aim of the present prospective study was to assess the clinical relevance of HRV versus QT/JT dispersion in predicting cardiac events in ICM pts with chronic heart failure.

Methods and Results: A total of 115 pts with ICM and a left ventricular ejection fraction (LVEF) < 40% were included between June 1995 and March 1998. During follow-up (21 $\pm$ 11 months, range 3–38 months), 9 pts died of sudden cardiac death, 9 pts had ventricular tachyarrhythmic events, 8 pts died of pump failure death and 10 pts had a heart transplantation. Kaplan-Meier analysis and Cox regression model identified SDNN and QTd/JTd as the most predictive parameters for all cardiac events. However, none of the tested parameters proved to be sensitive for predicting sudden cardiac death.

	Dichotomy points	Log rank	P value
JTd	≥70 ms	13.01	0.0003
QTd	≥80 ms	10.4	0.0008
SDNN	≤100 ms	8.65	0.0017
LnLF	≤2.5	6.89	0.0022
LVEF	≤25%	6.46	0.0028
PCWPm	≥15 mmHg	3.08	0.032

JTd = JT interval dispersion, QTd = QT interval dispersion, SDNN = standard deviation of normal-to-normal RR intervals, LnLF = natural log of low frequency power, PCWPm = mean pulmonary capillary wedge pressure.

Conclusion: HRV and QT/JT dispersion are sensitive and equipotent parameters for the assessment of over-all cardiac risk in pts with ischemic cardiomyopathy.

167 Improved predictive ability of signal-averaged electrocardiogram by combined time and frequency domain analysis in patients with ischaemic cardiomyopathy

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Background: Although the prognostic value of late potential (LP) in signal-averaged electrocardiogram (SAECG) following acute myocardial infarction (AMI) is well established the independent prognostic significance of SAECG is controversial. The aim of this study was to assess the prognostic value of an abnormal SAECG in time domain (Td) or frequency domain (Fd) analysis in pts with ischemic cardiomyopathy.

Methods: We prospectively studied 310 consecutive pts in sinus rhythm, aged 63.6 ± 0.58 (SE) yrs, with ischemic cardiomyopathy due to an old (>6 months from acute phase) myocardial infarction and echocardiographically estimated EF < 35%. Pts with atrial fibrillation were excluded. SAECG (ART, 40 Hz filtered, noise < 0.5 μV) was recorded in all pts. As LP in Td analysis in pts with QRS in surface ECG < 120 ms the following values were taken fQRS > 114 ms and either LAS > 38 ms or RMS < 20 μV whereas in pts with QRS ≥ 120 ms values were taken fQRS > 155 ms and either LAS > 55 ms or RMS < 17 μV. In Fd analysis spectral, temporal mapping (STM) was considered abnormal (abn) if a normality factor of <30% was derived from analysis (ART, FFT plus, TM software) of x, y or z lead. Eighty-two pts had prior CABG surgery. The infact size was estimated from surface ECG by QRS score based on Q and R wave duration and R/Q and R/S ratio.*

Results: During a follow-up period of 32.45 ± 1.27 (SE) months there were 119 (38.3%) cardiac deaths. In univariate analysis the following parameters were significant predictors of mortality: age, EF, absence of CABG, fQRS, RMS, FFT plus Y, LP, STM and the combination of LP + STM. In multivariate logistic regression analysis the independent predictors, in the following order of importance, were: age (x^2 = 25.6, p = 0.000), EF (x^2 = 16.36, p = 0.000), combined LP and abnSTM (x^2 = 11.4, p = 0.0008), CABG negatively (x^2 = 5.44, p = 0.020), LP (x^2 = 4.88, p = 0.027) and abnSTM (x^2 = 4.85, p = 0.028).

Conclusions: In pts with ischemic cardiomyopathy in addition to age and EF the combination of LP and abn STM is the next most powerful independent predictor of mortality. The combined Td and Fd analysis improve the prog-nostic value of SAEG.

168 Arrhythmia risk stratification in idiopathic dilated cardiomyopathy based on echocardiography, ECG, signal-averaged ECG and 24-hour Holter ECG

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This prospective observational study was designed to investigate prediction of arrhythmic events in idiopathic dilated cardiomyopathy (IDC) by the following 11 predefined variables: age, gender, NYHA class, LV end-diastolic dimension (LVEDD) and LV ejection fraction (EF) by echocardiography, atrial fibrillation and left bundle branch block on ECG, time domain and spectral turbulance analysis of the signal-averaged ECG, frequent VPDs and nonsustained VT (NSVT) on Holter.

Methods: Between 1992 and 1997, 202 patients with IDC (age: 50 ± 13 years, EF: 30 ± 10%) without previous sustained VT or VF and without antiarrhythmic drugs were prospectively enrolled in this study.

Results: During 32 ± 15 months follow-up, arrhythmic events including sustained VT, VF or sudden death occurred in 32 pts (16%). By multivariate Cox regression analysis, after adjustment for medical therapy including antiarrhythmic drug treatment during follow-up, only LVEDD ≥ 70 mm and NSVT on Holter were identified as significant arrhythmia risk predictors: relative risk (RR) for LVEDD ≥ 70 mm: 2.8 (95% CI: 1.2–6.5, p = 0.015); RR for NSVT: 5.1 (95% CI: 2.3–11, p = 0.0001); RR for the combination of LVEDD ≥ 70 mm and NSVT: 14 (95% CI: 2.3–90). When EF ≤ 30% was forced to remain in the Cox regression model, only EF ≤ 30% and NSVT on Holter were found to be significant arrhythmia risk predictors: RR for EF ≤ 30%: 2.7 (95% CI: 1.1–6.5, p = 0.028); RR for NSVT: 5.4 (2.2–11, p = 0.0001), and RR for the combination of EF ≤ 30% and NSVT: 14 (95% CI: 2.2–97).

Conclusions: The combination of LVEDD ≥ 70 mm and NSVT as well as EF ≤ 30% and NSVT identify a subgroup of patients with IDC with a 14-fold increased risk for subsequent arrhythmic events. These findings have important implications for the design of future studies evaluating the role of prophylactic defibrillator therapy in IDC.

169 Heart rate variability and risk stratification for major arrhythmic events in idiopathic dilated cardiomyopathy

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Previous studies have shown that heart rate variability could predict arrhythmic events and sudden death in post infarction patients, but the prognostic value of heart rate variability for arrhythmic events or sudden death in patients with idiopathic dilated cardiomyopathy has not been established. This study was designed to evaluate the prognostic value of heart rate variability for sudden death, resuscitated ventricular fibrillation or sustained ventricular tachycardia in patients with idiopathic dilated cardiomyopathy. Time and frequency domain analysis of heart rate variability on 24-h electrocardiographic (ECG) recording was assessed in 116 patients with idiopathic dilated cardiomyopathy (WHO criteria, 91 men, age 51 ± 12 years, range 18–70; left ventricular ejection fraction 34 ± 12%). Patients had conventional treatment with ACE inhibitors, diuretics and/or digoxin.

Results: Mean follow-up was 53 ± 39 months. Sixteen patients reached one of the defined study end points (sudden death, resuscitated ventricular fibrillation or sustained ventricular tachycardia) during follow-up. Using multivariate analysis, only reduced SDNN (p = 0.02) and ventricular tachycardia during 24-h ECG recording (p = 0.02) predicted sudden death and/or arrhythmic events. For SDNN, a cutoff level of 100 ms seemed the best for the risk stratification.

Conclusion: This study is the first one to suggest that a decrease in heart rate variability is an independent predictor of arrhythmic events and sudden death in idiopathic dilated cardiomyopathy, whether the mechanism of sudden death is ventricular tachyarrhythmia or not, and to suggest that this method is of interest for stratification of major arrhythmic events in CHF without coronary artery disease.

170 Non-invasive identification of patients prone to ventricular fibrillation with dilated cardiomyopathy even in the presence of bundle-branch block or atrial fibrillation by T-wave spectral variance

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Background: Conventional noninvasive risk stratification by Holter-ECG-recordings in patients with dilated cardiomyopathy prone to ventricular fibrillation (VF) having atrial fibrillation (AF) or bundle branch block (BBB) is difficult. We therefore investigated whether spectral assessment of beat-to-beat alternations of repolarisation in these patients is associated with ventricular fibrillation.

Methods: Twenty-four hour ECG-Holter recordings in 60 patients with dilative cardiomyopathy were used. 30 patients survived VF and 30 patients had no VF. In each group 10 patients had AF, 10 had BBB and 10 had sinus rhythm and no BBB. In each patient 1024 consecutive T-waves were aligned using cross-correlation methods. Two-dimensional Fourier transform (2D-FFT) uses the data matrix of 1024 consecutive 200 ms-segments centred to the T-wave peak. Power spectra of the 2D-FFT revealed the frequency content of the T-wave in the 1.dimension and the periodicity of this frequency content in the 2.dimension. The ratio between periodic frequency contents and the sum of non-periodic and periodic frequency contents between 0.5 and 50 Hz gives the T-wave-spectral variance (TWSV). Thereby TWSV = 0 means all 1024 T-waves identical and TWSV = 1 means 1024 T-waves are totally variable.

Results: The TWSV was significantly higher in patients with VF (0.93 ± 0.14) than in patients without VF (0.53 ± 0.13, p < 0.01). The best cut-off between patients with and without VF was TWSV = 0.75 (sensitivity = 89%, specificity = 86%). However, no significant differences were observed between patients with and without AF or with and without BBB.

Conclusions: Thus, spectral assessment of T-wave alternations by TWSV using two-dimensional fast Fourier transform in Holter-ECG recordings allows to identify patients with dilated cardiomyopathy at risk of VF even in the presence of BBB or AF.

INFECTION AND INFLAMMATION IN CORONARY ARTERY DISEASE

184 Fibrinogen correlates with angiographically proven extent of coronary artey disease: cause or consequence? Evaluation of a possible mediator role of inflammation markers and adhesions molecules

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Background: Fibrinogen (fib) is established as an independent risk factor for developement of coronary artery disease (CAD). An increase of fib serum level in acute coronary syndrome and an influence on the degree of restenosis after PTCA has already been demonstrated. We evaluated the influence of fib on the extent of angiographically proven atherosclerosis and the influence of elevated fibrinogen levels on inflammation markers and upregulation of adhesion molecules.

Methods: 1033 patients (pts) admitted to our hospital with suspected CAD underwent angiography. Vessel disease (VD) was defined as at least one stenosis > 50%. We divided pts in having 0 (without CAD), 1, 2, and 3 VD. Before angiography we determined serum levels of fibrinogen [mg/dl], soluble Intracellular Adhesion Molecule (sICAM) [ng/ml], high-sensitive C-reaktive Protein (CRP) [mg/l] and Tumor Necrosis Faktor α (TNF) [pg/ml].

Results: In 874 (84.6%) CAD could be evidenced. In pts without CAD geometric mean of fib was 310 (*25/75% percentile:* 265/352), in 1 VD 324 (274/387), 2 VD 342 (289/435), and 3 VD 342 (287/423) (p = 0.001; Jonckheere Terpstra Test). Elevated levels of fib correlate with the elevation of inflammation markers high-sensitive CRP (Spearman cor. coef. (SC): 0.564; p = 0.0001), TNF (SC: 0.188; p = 0.0001) and with upregulation of sICAM (SC: 0.143; p = 0.0001).

Conclusions: Serum level of fib correlates with the extent of CAD. Furthermore, serum level of fib is associated with the elevation of high-sensitive CRP and TNF as serum markers for an ongoing inflammatory process. In pts with high fib levels an increase of sICAM could be demonstrated. These results could be interpreted as an atherogenetic ability of Fib. Fib has not only to be considered as an acute phase reactant but also as an atherogenetic risk factor for CAD.

185 Intra-individual long-term variability of C-reactive protein in the MONICA-Augsburg project

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C-reactive protein (CRP), a sensitive marker of systemic inflammation has been shown to be an independent predictor of cardiovascular risk in several prospective studies. In all of these studies, risk prediction was based on a simple ("baseline") measurement and no data are available on the long-term variability of this risk marker.

To determine variability over time, we measured CRP (high-sensitivity IRMA) in 936 men aged 45–64 years from a random sample of the population in 1984/5 and remeasured it 3 years later in 704 men (response rate 75%) from the same cohort.

The CRP mean difference (bias) was practically zero. However, as expected for this classical acute phase reactant with a plasma t $\frac{1}{2}$ of 19 h and a 10,000 fold dynamic range, the 95% range of agreement was rather large with a ratio of 0.12–8.6. Nevertheless the reliability coefficient (R) was 0.53 (0.47–0.58) for the average of 3 measurements, which compares favourably with other well established risk factors. Stratified analyses of reliability in various groups revealed similar coefficients.

Our results suggest that, based on the concept of "regression dilution", the true association between CRP and cardiovascular risk is likely to be underestimated by single CRP measurements, and that for prognostic use in clinical practice, several serial CRP measurements would be desirable.

186 Infections and the risk of premature ischaemic heart disease

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Infectious agents may be associated with ischemic heart disease (IHD).

Methods: to investigate the role of infections by Chlamydia pneumoniae (Chlam), Cytomegalovirus (CMV) and Herpes virus 1 (HSV-1) in promoting the premature onset of IHD, IgG specific antibodies to these pathogens and C-reactive Protein (C-react P) as a marker of flogosis were measured in 120 patients (pts), less than 50 years old, and in 120 age-matched controls (C).

Results: seropositivity (sero+) to Chlam and HSV-1 and elevated titres of anti-CMV IgGs (≥100 EU/ml) were more frequent in pts than in C ($p < 0.01$), whereas sero+ to CMV was similar. After adjustment for age, sex, traditional risk factors, educational level and occupation, the risk of premature IHD was 2.4 (95%CI = 1.3–4.6, p = 0.007) for Chlam infection, 2.9 (95% CI = 1.5–5.8, p = 0.002) for CMV and 10.4 (95%CI = 2.4–46, p = 0.002) for HSV-1. Sero+ to Chlam increased the risk of premature IHD in smokers (OR = 3.7, CI = 1.8–7.6, p = 0.001) but not in ever smokers (OR = 0.5, CI = 0.1–2.6, p = 0.7) and the risk was higher in subjects with both elevated anti-CMV titres and increased levels of C-react P (SI = 3.4, 95%CI = 0.9–13.6). The combined sero+ to all three pathogens increased the risk of four times as compared with subjects with sero+ to two of them (OR = 4.1 95%CI = 1.8–9.4 $p < 0.001$). The most unfavourable combination of infections was sero+ to Chlam associated with elevated CMV titres (35% of pts vs 8% of C, p = 0.001), which increased the risk of about 12 times as compared with subjects without any of the two infections (OR = 12.5, 95%CI = 4–38.9), and about 5 times if only one was present (OR = 4.9, 95%CI = 2.2–10.9). Furthermore, C-react P was higher in carriers of this combination than in pts without any infection ($p < 0.01$).

In conclusion: after adjustment for traditional coronary risk factors and socioeconomic status, Chlam, CMV and HSV-1 infections all increase the risk of premature IHD. The combination of seropositivity to Chlam and elevated titres to CMV, is associated with an abnormal inflammatory response and represents the most unfavourable immunologic profile for increased risk of premature IHD.

187 Chlamydia pneumonia and Helicobacter pylori are present only in human atherosclerotic plaques but not the healthy segments

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Background: Recent epidemiological and serological studies suggested chronic infections with C. pneumonia (C) and H. pylori (H) to be associated with the development of the atherosclerotic plaque. However seropositivity does not correlate with the presence or extent of atherosclerosis.

Methods: To asses the direct involvement of these organisms, the prevalence of C and H in the arterial wall was determined in 58 patients (age 60 ± 9, 53 M, 5 F) undergoing vascular surgery of the coronaries, carotids and abdominal aorta. Forty specimens from atherosclerotic lesions and 18 specimens from healthy regions of the ascending aorta were excised. The patients were clinically evaluated for stable/unstable angina, other risk factors and presence of peptic ulcus due to H. The presence of microorganisms in arterial wall was assessed by polymerase chain reaction technique.

Results: C was present in 27.5% of lesions and none of the healthy vascular wall specimens (p = 0.01) while H was found in 32.5% of lesions and none of the controls (p = 0.003). Either C or H was positive in 47.5% of patients and none of the controls (p = 0.00036). The presence of C and H did not differ between those with stable or unstable clinical manifestations of the patient. While H was evenly distributed, C was found more frequently in plaques from the abdominal aorta location (p = 0.022).

	Coronary (%)	Carotid (%)	Abdominal (%)	*p* value
C (+)	18	27	55	0.022
H (+)	29	21	43	0.058

Conclusion: The absence of C and H in healthy vascular wall and the presence in the atherosclerotic vessel specimens supports the role of these microorganisms in the development of atherosclerosis. Since the distribution of C was preferentially in the abdominal location whereas H was evenly distributed these microorganisms may have different roles in the pathogenesis.

188 Chlamydia pneumoniae in association with cardiovascular risk factors: innocent bystander or pathologic agent?

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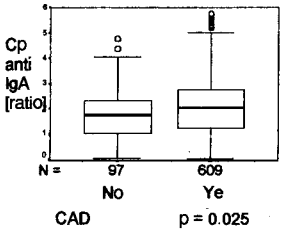
Introduction: The association between Cp-seropositivity and coronary artery disease (CAD) is documented, less is known between the correlation of Cp infection and inflammation markers and adhesion molecules. We evaluated, whether Cp infection is associated with elevated inflammation markers, activated coagulation system and up-regulation of adhesion molecules.

Methods: In 706 patients (pat) with suspected CAD coronary angiography was performed. CAD was defined as at least one stenosis > 50%. Antiplasmin-plasmin-complex (APP), thrombin-antithrombin III complex (TAT), soluble intracellular adhesion molecule (sICAM), CRP and fibrinogen (Fib) were determined. Anti *Cp* IgA (chronic active infection) and anti IgG (previous infection) were measured by ELISA.

Results. In 609 pat (86.3%) CAD was diagnosed.

Risk marker	Cp_IgA−	Cp_IgA+	p**	Cp_IgG−	Cp_IgG+	p
CRP [mg/l]	4	4	*0.238*	4	4	*0.797*
Fib [mg/dl]	328	332	**0.028***	331.5	331	*0.322*
APP [ng/ml]	432	450	*0.246*	425	455	*0.766*
TAT [ng/ml]	3.3	3	*0.475*	3.2	3	*0.370*
sICAM [ng[ml]	272.8	274.1	*0.623*	265	274	*0.038**



In conclusion seropositivity of Cp IgA can be considered as a rf for CAD. Furthermore there is a significant association of Cp infection and increase of fib level. No association could be demonstrated between Cp infection and an activated coagulation system, whereas seropositivity of Cp correlates with an up-regulation of sICAM.

189 Epidemiology of Chlamydia pneumoniae, Helicobacter pylori, herpes simplex virus and cytomegalovirus in patients with peripheral arterial occlusions considering markers of inflammation

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Background: Chronic inflammations due to Chlamydia pneumoniae, Helicobacter pylori, herpes simplex-virus and cytomegalovirus has been supposed to be associated to the origin and progress of atherosclerosis. Such chronic infections may correlate with changes in markers of inflammation. We investigated the role of earlier infection and markers of inflammation in patients with peripheral arterial occlusive disease.

Methods: In 227 patients with severe peripheral arterial occlusive disease (PAOD) due to advanced atherosclerosis we analysed the presence of antibodies for Chlamydia pneumoniae, Helicobacter pylori, herpes simplex-virus and cytomegalovirus. In addition to this we analysed fibrinogen, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and the presence of diabetes mellitus. The mean age was 61.7 ± 12.5 years. According to Fontaine classification 6 were in stage I, 23 in stage II a, 117 in stage II b, 14 in stage III and 67 in stage IV of PAOD. In 171 patients (75.3%) there were antibodies against chlamydia pneumoniae, all of them showed IgG-antibodies, but only 5 had also IgM-antibodies.

Results: The mean age of patients with antibodies for Chlamydia pneumoniae was 62.7 ± 11.9 years, of the patients without 58.8 ± 13.7 years. Fibrinogen was 445.1 ± 160.2 mg/dl, CRP was 2.1 ± 2.9 mg/dl and ESR was 28/47 mm (Westergreen) in the group of patients with negative serology. If there were antibodies for chlamydia pneumoniae fibrinogen was 444.6 ± 177.8 mg/dl, CRP was 2.7 ± 4.3 mg/dl and ESR was 29/48 mm (Westergreen). A higher rate of diabetes mellitus, that could favour an infection with chlamydia pneumoniae, could not be seen. There was a high rate of additional IgG-antibodies for helicobacter pylori (48.0%), herpes simplex-virus (94.7%) and cytomegalovirus (72.5%).

Conclusion: The patients with and without antibodies for chlamydia pneumoniae did not show specific differences. Fibrinogen was nearly equal in both groups, as well as CRP, ESR and the rate of diabetic patients.

NEW ASPECTS OF OLDER PEOPLE

190 Functional status and quality of life in older people with heart failure – a community-based study

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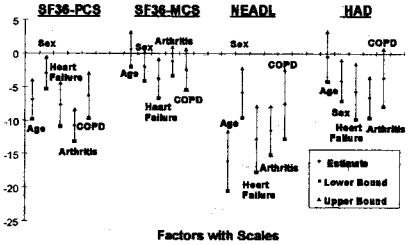
There is increasing emphasis today on not just extending life but also improving quality of life (QoL) of our ageing population. We have examined the effects of age, gender and chronic illnesses such as heart failure on function and QoL in older people in the community.

Methods: A stratified random sample of 500 subjects was drawn from a population of 5002 subjects aged 70years and over living at home. Nottingham Extended ADL (NEADL), Hospital Anxiety and Depression Scale (HAD) and a generic QoL measure (SF-36) were administered and clinical assessments were performed. Scores for SF-36 were aggregrated into physical (PCS) and mental (MCS) cumulative summative scores. Arthritis was self-reported, chronic obstructive pulmonary disease (COPD) was defined as FEV1/FVC < predicted normal and heart failure was defined as left ventricular systolic dysfunction on echocardiogram. Data were analysed by multivariate analysis of variance.

Results: 452 of the 500 (90%) participated in the study. The population prevalence amongst older people of significant dyspnoea (MRC Grade 3–5) was 33%, arthritis 36%, COPD 11% and heart failure 8%. The 95% confidence intervals for the effects of advancing age, sex and chronic illnesses on function and QoL are shown in the figure, scores expressed as percentage differences.



In conclusion, heart failure has the greatest effect after age, on daily functioning in older people. It also has a significant adverse effect on QoL Improving recognition and treatment of heart failure should be a major priority for health services to reduce disability and improve QoL in older people.

191 Effect of age on tilt-induced collapse patterns in those with syncope of unknown origin

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In those with syncope of unknown origin the tilt induced collapse patterns (i.e. heart rate (HR) and arterial pressure (AP)) were assessed.

Methods: Using the 45 min. 60° head up Westminster protocol 102 consecutive patients were studied. Sublingual GTN 300 μg was given to those with a negative passive tilt. VASIS collapse patterns were compared between those <35 years (YG) with those >65 years (OG).

Results: In a total of 330 patients there were 114 YG (age mean 25.1 years ± standard deviation 6.8, 58 female) and 115 OG (age 74.1 ± 5.8, 44 female). Tilt testing was tolerated in 97% of YG vs. 89% of OG and negative despite the use of GTN 17% vs. 21%. Comparing the distribution of the VASIS classes between YG and OG in those with a positive result. *Type 1* mixed Arterial Pressure (AP) and Heart Rate (FIR) fall without severe bradycardia- 47% (YG) vs. 53% (OG), p = non-sig. *Type 2A* cardioinhibition AP falls before HR- 8% vs. 18%, p < 0.05. *Type 2B* cardioinhibition HR falls before or coincident with AP- 37% vs. 5%, p < 0.01. *Type 3* AP falls without HR fall- 0% vs. 10%. p < 0.05. *Exception 1* chronotropic incompetence – 0% vs. 13%, p < 0.05. *Exception 2* excessive HR rise – 7% vs. 1.3%, p = non-sig.

Conclusion: There are differences in the collapse patterns in the two age groups. In those ≤ 35 there is greater cardioinhibition (IIA and IIB) and excessive HR rise suggesting that collapse may a consequence of an exaggerated neurocardiogenic reflexes. Conversely, in those ≥65 few had cardioinhibition and there was a chronotropic incompetent subgroup. This suggests that with increasing age collapse may be the consequence of diminished neurocardiogenic reflexes.

192 Total and HDL cholesterol predict coronary heart disease mortality in elderly men in Finland, Italy and the Netherlands

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Serum total and HDL cholesterol are important predictors of coronary heart disease mortality in middle-aged men. Whether this relationship holds in the elderly is not clear. It is also important to know whether the relation between serum cholesterol and coronary heart disease mortality in elderly men differs between countries. We studied the relationship between serum total and HDL cholesterol and 10-year coronary heart disease mortality in elderly men in different European countries.

The FINE Study is a prospective follow-up study in 2132 elderly men aged 65 to 84 years in Finland, The Netherlands and Italy. During 10 years of follow-up 140 men in Finland, 88 men in The Netherlands and 48 men in Italy died from coronary heart disease. Relative risks (RRs) were estimated using Cox's proportional-hazard analysis with time-dependent covariates.

Total cholesterol was positively related to coronary heart disease mortality in all three countries. This association was statistically significant in The Netherlands (RR = 1.29; 95% Confidence Interval 1.07–1.56). The combined relative risk for the total population of the FINE Study was 1.17 (95% CI 1.06–1.29) for each 1.00 mmol/L increase in total cholesterol. HDL cholesterol was inversely related to coronary heart disease mortality in Finland, but not in The Netherlands and Italy. In Italy, an interaction was noted between HDL cholesterol, body mass index and alcohol intake. There was an inverse association between HDL cholesterol and coronary heart disease mortality in lean men (body mass index < 25 kg/m^2) with no or moderate alcohol intake (<40 g/day) (RR = 0.76; 95% CI 0.59–0.97, per 0.10 mmol/L increase) and a significantly positive association in overweight men (body mass index ≥ 25 kg/m^2) with a high alcohol intake (≥ 40 g/day) (RR = 1.25; 95% CI 1.07–1.46, per 0.10 mmol/L increase). In a combined analyses of all three countries HDL cholesterol was inversely associated with coronary heart disease mortality in lean men with no or moderate alcohol intake (RR 0.92; 95% CI 0.86–0.99, per 0.10 mmol/L increase).

Serum total and HDL cholesterol are important predictors of coronary heart disease mortality in elderly men in different European countries, although the effect of HDL cholesterol seems to be confined to lean men with no or moderate alcohol intake.

193 Mitral annular calcification and significant internal carotid artery stenosis in elderly: is there a link?

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Background. It has been recently suggested that mitral annular calcification (MAC) could be a cardiac manifestation of atherosclerosis in elderly; an association between MAC and both coronary artery disease and aortic atheroma has been indeed observed. Furthermore a relationship between MAC and stroke has been found, but it is still unclear if MAC can be considered an independent risk factor of stroke. With regard of this hypothesis little information is available in the literature about a possible association between MAC and carotid artery disease.

Methods. Consecutive patients (pts) with a diagnosis of MAC and with a carotid Echo-Doppler examination done within 1 year of echocardiogram were identified from a prospective clinical database (Group MAC+: 128 pts, 69 females, 59 males, aged 74 ± 7 years). As control group, 128 age/sex-matched pts with absence of MAC and similar clinical indication to carotid Echo-Doppler examination were randomly selected from the database. In the two groups the prevalence of stenosis ≥ 50% of the internal carotid artery were blindly assessed.

Results. A carotid artery stenosis was found in 43.8% of MAC+ pts and in 22.6% of controls ($p < 0.001$). The difference was significant in both sexes: among males 50.8% vs 28.8% ($p < 0.05$), among females 37.7% vs 17.4% ($p < 0.05$). A higher prevalence of carotid artery stenosis in MAC+ group was observed both in pts ≥75 years (47.1% vs 25.0%; $p < 0.05$) and in pts <75 years (40.0% vs 20.0%; $p < 0.05$). The Table shows the prevalences of carotid artery stenosis in different age/sex groups.

	MAC+ group	Control group	
Males < 75 years	16/29 (55.2%)	7/29 (24.1%)	p < 0.05
Females < 75 years	8/31 (25.8%)	5/31 (16.1%)	p = ns
Males ≥ 75 years	14/30 (46.7%)	10/30 (33.3%)	p = ns
Females ≥ 75 years	18/38 (47.4%)	7/38 (18.4%)	p < 0.05

Conclusion. MAC is an important echocardiographic marker of significant carotid artery stenosis in elderly. The association seems to be particularly relevant in males <75 years and in females >75 years. Further studies are needed to evaluate if the increased risk of stroke observed in pts with MAC is related to MAC itself or to the associated carotid artery stenosis.

194 Direct infarct intervention in octogenarians: a step in the right direction?

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With increasing longevity of the population, octogenarians presenting with acute myocardial infarction (MI) are becoming increasingly frequent. The elderly patients have a reported higher mortality following acute MI. This clinical subset is routinely treated less aggressively than younger patients, since they are believed to be at higher risk for complications. We report the clinical course and mortality rate for up to 1 year in patients aged ≥80 years, following direct coronary intervention (d-PTCA) for acute MI. From 1/96 to 12/98, 54 patients in this age group (mean age 83.5) underwent d-PTCA within 24 hours of onset of acute MI. This included 49% females; 40.8% with a history of angina, 37% with history of CHF, and 31.6% with a history of smoking. Prior MI was reported in 16.7% and 7.4% had prior CABG surgery. The LAD was the culprit vessel in 39%; 63% lesions were ostial or proximal, subtending large territories of myocardium. Intracoronary stenting was performed in 15 patients (27.8%) electively or for suboptimal result. Adjunctive IABP support was employed in 51.9% cases. Indications for IABP use included poorly protected large volume of myocardium, pulmonary edema, shock, LVEF ≤ 25%, severe multivessel disease, large clot burden, and "slow-flow" post-PTCA. Oral GP IIb/IIIa inhibitors were used in 24% cases.

Results: Procedural success (residual stenosis ≤ 20%; TIMI 3 flow) was achieved in 52 patients (96.3%). Mean time to reperfusion was 10.2 hours from onset of chest pain. There was 1 acute reclosure requiring re-PTCA. There were no in-hospital deaths. There were no acute neurological events or subacute stent thrombosis. Mean hospital stay was 2.98 days. Mean global LVEF at discharge was 43.7%*.

12-month Follow-Up [95.4% complete; Mean Follow-Up 6.74 months]

Re-MI	Re-PTCA	CABG	Stroke	Death	Event-Free	Mean LVEF
1 (1.9%)	1 (1.9%)	1 (1.9%)	2 (3.7%)	4 (7.4%)	47 (87%)	52.0%; *p = 0.046

Conclusions: (1) The strategy of direct infarct angioplasty that is effective in younger patients is also effective in octogenarians. (2) It is a safe therapeutic option with high procedural success and low incidence of in-hospital cardiac events. (3) Favorable 1-year event-free survival is obtained. (4) Improvement in global LV systolic performance was *statistically significant*, suggesting that prompt and successful salvage of substantial at-risk myocardium may have contributed to improved long-term outcomes. (5) Our series supports the view that age in itself is not a contraindication to an invasive strategy in octogenarians presenting with AMI. In fact, given the high mortality and poor outcomes historically associated with AMI in this age group, aggressive therapeutic strategies may be particularly warranted.

195 Coronary stenting in patients over 75 years: clinical profile, initial outcome and long-term evolution

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To assess the clinical profile and the evolution after stenting of pts over 75 years, we compared two groups of consecutive pts. Group A included 80 pts (87 lesions) over 75 years (77 ± 2.4 years; range: 76–86) and group B consisted of 903 pts (1024 lesions) under 76 years (60 ± 10 years; range: 27–75). Group A had a lower rate of smokers (29 vs. 59%, $p < 0.001$) and a higher incidence of heart failure (12 vs. 5%, $p < 0.01$). Angioplasty indication for unstable angina was more frequent in group A (80 vs. 60%; $p < 0.001$). The rest of clinical, angiographic and procedural variables did not differ between the two groups.

Although clinical success (angiographic success without events at one month) was similar for both groups (A = 89%, B = 94%, p = 0.08), hospital death was higher among pts over 75 years (8 vs. 2% p = 0.006). There were no differences in the incidence of angiographic restenosis (Gr A: 22%, Gr B: 28%). Clinical follow-up was completed in 94% of pts at 3.0 ± 1.5 years. Death during follow-up occurred in 15% of pts from group A and in 6% of pts from group B (p = 0.005). Need of new revascularization was less frequent in pts older than 75 years (9% vs 18%, $P < 0.05$). The incidence of major adverse cardiac events was similar for both groups (A = 27, B = 27%). A multivariate analysis from the data of group A identified previous myocardial infarction, hypertension and acute myocardial infarction during the procedure as independent predictors of further events.

Thus, patients over 75 years have a less favourable baseline profile and higher hospital and long-term mortality. However, the incidence of major adverse cardiac events in the short and long-term is acceptable and similar to that of younger pts. These data suggest that coronary stenting is a reasonable therapeutic alternative for patients older than 75 years.

ANGIOGENESIS: EXPERIMENTAL AND CLINICAL

208 Intramuscular injection of plasmid DNA encoding fibroblast growth factor-1 induces angiogenesis in a rabbit hindlimb model of peripheral ischaemia

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The purpose of this study was to evaluate the usefulness of direct intramuscular (i.m.) injection of a plasmid encoding FGF-1 (= acidic FGF) to augment collateral formation and tissue perfusion in a rabbit ischemic hindlimb model. Truncated FGF-1 (residues 21–154) fused to the human fibroblast interferon signal peptide was expressed from an expression vector with a conditional origin of replication (pCOR-spFGF1). Rabbits injected with pCOR plasmid encoding b-galactosidase served as control group.

Results: Successful transgene expression could be demonstrated by FGF-1 immunostaining and X-Gal staining at different time points after gene application. 500 and 1000 μg pCOR-spFGF1, when injected into ischemic muscle areas of rabbits (n = 8 each) 10 days after ligation of the external iliac artery, exhibited a pronounced therapeutic effect on collateral formation to the ischemic hindlimb in a dose-depending manner, as assessed by physiological (Doppler-derived blood pressure ratio, maximal intraarterial Doppler Flow) and anatomical (angiographic score, histologic evaluation of capillary density) measurements 30 days after therapy, compared to b-galactosidase control plasmid, as shown in the table. Application of 100 μg pCOR-spFGF1 was not sufficient to induce any beneficial effect.

Angiogenic Potency of FGF-1

Day 30	b-galactos.	500 μg spFGF-1	1000 μg spFGF-1
Limb BP ratio (isch./normal)	0.57 ± 0.04	0.74 ± 0.04*	0.82 ± 0.02#
Max. intraart. Doppler flow	30.7 ± 3.1	42.4 ± 3.8*	50.6 ± 3.6#
Angiographic Score	0.54 ± 0.04	0.68 ± 0.02*	0.81 ± 0.04#
Capillary density [/mm^2]	169 ± 10.0	220 ± 18.7*	242 ± 17#

* = $p < 0.05$; # = $p < 0.005$

In conclusion, our results demonstrate the angiogenic potency of FGF-1 gene transfer. Intramuscular FGF-1 gene application could be useful to stimulate therapeutic angiogenesis in a situation of chronic periperal ischemia.

209 Vascular endothelial growth factor expression is down-regulated in human chronic heart failure

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Increased gene expression of growth factors, leading to enhanced angiogenesis, is a compensatory mechanism to myocardial hypoxia. In chronic heart failure (CHF), myocardial hypoxia may be caused by increased wall stress and endothelial dysfunction. Thus we investigated whether growth factors are expressed at higher levels in CHF, since such a phenomenon could potentially reverse myocardial hypoxia.

Methods. Right ventricular tissue biopsies from 27 patients with idiopathic dilated cardiomyopathy (NYHA class II–IV, mean LVEF: 31%) and 13 controls (con) were harvested and total RNA was isolated. Expression of vascular endothelial growth factor (VEGF), isoforms 121, 165, and 189, VEGF-receptor 2 (VEGF-R2), basic Fibroblast Growth Factor (bFGF), Atrial Natriuretic Peptide (ANP), and Sarcoplasmic Reticulum Ca^{2+}-ATPase (SERCA) was determined by semi-quantitative PCR, expressed as a ratio to the co-amplified glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

Results. In CHF patients, VEGF 121 mRNA is expressed at a lower level ($p < 0.001$). In addition, isoforms 165 and 189 also tended to be decreased ($p = 0.05$ and 0.10, resp). VEGFR-2 and bFGF were unchanged. Increased ANP and decreased SERCA expression, typical for CHF, were found. GAPDH expression did not differ between groups. See table for results.

	VEGF 121	VEGF 165	VEGF 189	VEGFR-2	bFGF	ANP	SERCA
Con	1.30	2.74	1.92	1.35	0.66	0.06	0.99
CHF	0.61*	2.21	1.56	1.29	0.64	0.59*	0.79*

*: $p < 0.05$, CBF vs. control.

Conclusion. These data suggest that VEGF expression, translating into angiogenesis, does not compensate for hypoxia reported in CHF. Moreover, the observed diminishing of VEGF mRNA in cardiomyocytes could further contribute to the imbalance of oxygen deprivation and vascularization.

210 Endogenous, local, vascular endothelial growth factor production in patients with chronic total coronary occlusions: further evidence for its role in angiogenesis

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Background: Intracoronary administration of Vascular Endothelial Growth Factor (VEGF) has been explored as a means of increasing collateralisation in patients with end-stage coronary artery disease. However, to date, no study has examined the role of endogenous VEGF production in the development of collaterals in patients with chronic total coronary occlusions. The aim of our study was to assess local, in vivo, VEGF production in patients with total occlusions and to compare this to patients with non-occlusive stenoses.

Method: VEGF levels in the coronary circulation and periphery were prospectively examined in 14 patients (7 patients with stenoses, 83 ± 6% (mean ± SEM) diameter stenosis, mean age 63 ± 2, 4 males and 7 patients with occlusion mean age 65 ± 4, 4 males) undergoing elective left coronary system intervention. Local (coronary sinus) and systemic (femoral) venous samples were obtained prior to coronary intervention. Blood samples were centrifuged and plasma separated for further analysis. The level of VEGF in plasma samples for the 14 patients was then determined using an enzyme-linked immunosorbent assay (ELISA) (R & D Systems, UK).

Results: There was a significant difference in the level of VEGF between local and systemic samples in the whole group (251.8 ± 94.8 vs 93.6 ± 14.1, P = 0.025). The difference was chiefly attributable to a four-fold increase in mean VEGF levels between the coronary sinus and periphery in the occlusion group (400.2 ± 176.7 vs 111.9 ± 22.9, P = 0.073) compared to the stenosis group (103.3 ± 19.8 vs 75.2 ± 15.1, P = 0.5). The basal VEGF level was significantly higher in the coronary sinus samples of patients with occlusions compared to those with stenoses (400.2 ± 176.7 vs 103.3 ± 19.8, P = 0.026).

Conclusion: Our study provides the first direct evidence for increased local VEGF production in the diseased coronary circulation. The high local endogenous level of VEGF in patients with total coronary occlusions suggests a potential role for this growth factor in pathophysiologic collateral formation and supports its use as a therapeutic tool for angiogenesis in patients with inoperable coronary heart disease.

211 Attraction of loaded monocytes via MCP-1: a novel strategy for therapeutic arteriogenesis

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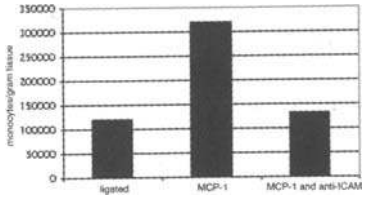
Introduction: Local infusion of MCP-1 after femoral artery occlusion in the rabbit hindlimb enhances arteriogenesis via attraction of circulating monocytes. This stimulatory effect of MCP–1 could be further enhanced by delivering arteriogenic proteins directly to the place of action via loaded monocytes resulting in high local concentrations of the arteriogenic protein. This study evaluates whether the selective attraction of microsphere loaded monocytes to the growing collateral artery can be promoted with MCP-1.

Methods: 12 rabbits were treated with local infusion of either MCP-1 alone or MCP-1 plus monoclonal ICAM-antibodies via osmotic minipumps after ligation of the a. femoralis. Non-ligated animals and ligated animals infused with PBS served as control. Isolated rabbit monocytes were loaded with fluorescent microspheres (*2 mm) and reinfused intravenously. 48 hours after reinfusion animals were killed and biopsies were taken of the adductor and quadriceps muscle in both hindlimbs. With FACS analysis the total number of monocytes/gram tissue was quantified.

Results: Number of monocytes: unligated; 35,000 ± 7,200, ligated; 120,000 ± 10,500, MCP-1 treatment: 320,000 ± 28,000, MCP-1 treatment and anti-ICAM antibodies; 132,000 ± 11,000. The number of monocytes was significantly different for all groups except for the ligated group and the group treated with the combination of MCP-1 and anti-ICAM antibodies (see figure).



Conclusion: This study shows that MCP-1 is a potent chemoattractant for loaded monocytes homing to collateral arteries. This process can be blocked by ICAM-antibodies. This new concept of selective local enhancement and blocking of accumulation of circulating loaded monocytes may be the base of a new therapeutical concept to enhance arteriogenesis.

212 Intramyocardial application of vascular endothelial growth factor induces angiogenesis but does not augment myocardial perfusion in the rat heart

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Background. Direct application of the plasmid of vascular endothelial growth factor (VEGF) has been shown to augment collateral flow and induce new vessel formation in models with peripheral ischemia. Controversy exists concerning the ability to induce angiogenesis and enhance coronary flow in the myocardium.

Objective. We investigated the effects of direct intramyocardial injection of the plasmid encoding VEGF in the border zone of myocardial infarct tissue in rat hearts.

Methods and Results. Sprague-Dawley rats received a ligation at the base of the left coronary artery to induce myocardial infarction. At 4 weeks, the rats were injected with VEGF plasmid (500 ug DNA, n = 24) or saline (n = 16). After one month, the hearts were excised and examined histologically. Twentythree/24 VEGF-treated hearts showed macroscopic angiogenesis with angioma-like structures at the injection site while controls did not. By histology, 21/24 VEGF-treated hearts showed increased focal epicardial blood vessel density and angioma-like formation, whereas only 1/14 control hearts showed increased vessel density ($p < 0.001$). Quantitative morphometric evaluation of vascular density in a subgroup of 20 VEGF-treated and 10 saline-treated control hearts revealed 44.4 ± 10.5 vascular structures per field in VEGF-treated hearts versus 21.1 ± 3.0 in controls ($p < 0.05$). Regional myocardial blood flow ratios between the injection site and non-infarcted area were measured by radioactive microspheres in 18 rats and did not demonstrate any difference between VEGF-treated hearts (0.9 ± 0.2) and saline-treated hearts (0.7 ± 0.1).

Conclusion. Injection of DNA for VEGF in the border zone of myocardial infarction in rat hearts induced angiogenesis. Moreover, angioma occurred at the injection site. However, that did not contribute to regional myocardial blood flow.

213 VEGF induces integrin expression and L-selectin shedding in human monocytes

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Monocyte invasion into the perivascular tissue of developing collateral vessels is the first morphological sign of arteriogenesis (rapid proliferation of collateral arteries). Therefore the arteriogenic potency of growth factors is dependent on its monocyte-attractant activity. However, monocytes are also known to be involved in angiogenesis, which is, in contrast to arteriogenesis, the sprouting of new capillaries. VEGF is known to be a very effective inducer of angiogenesis. In this study we investigated the monocyte stimulatory effect of physiological VEGF concentrations (100 ng/ml). Therefore, the expression of several monocytic activation markers were analyzed via FACS-analysis. Monocytes were isolated from healthy blood donors using a Beckman elutriation chamber and cultured for 24 hours, incubated either with medium alone, with VEGF or, as a positive activation control, with LPS. Monocyte activation was detected via FITC conjugated monoclonal antibodies against CD11b/CD18 (Mac-1), L-Selectin and Tissue Factor.

Results:

	L-Selectin	CD 11b	CD18	p-value
Unstimulated	42.7	116.9	562.2	
VEG	20.1	316.4	853.5	<0.005
LPS	10.2	429.6	1518.8	<0.005

Conclusion: This is the first report about upregulation of integrins on the monocyte surface after exposure to physiological VEGF concentrations in vitro. These data indicate that VEGF has monocyte activating and thereby potentially arteriogenic properties.

NON-INVASIVE RISK ASSESSMENT IN ACUTE CORONARY SYNDROMES

214 ST-segment monitoring with continuous 12-lead ECG identifies patients at high risk for subsequent cardiac events after an episode of unstable coronary artery disease

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Patients with unstable coronary artery disease (UCAD) still have a high risk of subsequent cardiac events. However, this is a heterogeneous population in which early risk stratification is essential. The aim of the present FRISC II substudy was to evaluate the prognostic value of continuous 12-lead ECG in this population.

Method: Continuous 12-lead ECG (ST-Guard, Marquette medical systems) was performed in 189 patients with UCAD included in the FRISC II trial and randomized to a non-invasive policy. Monitoring was performed from admission and for 12–24 h. Follow up concerning death and MI has so far been completed for 6 months.

Results: ST-episodes, defined as transient ST-segment deviations of ≥ 0.1 mV, lasting ≥ 1 minute, were present in 51 (27%) patients. Predictive values of detecting death and death or MI during follow up:

		No ST-episodes	ST-episodes	Log-rank p
Death	14 d	0	6%	0.04
	30 d	0	6%	0.04
	180 d	0	8%	<0.001
Death/MI	14 d	3%	12%	0.02
	30 d	4%	12%	0.06
	180 d	9%	16%	0.13

Conclusion: ST-segment monitoring with continuous 12-lead ECG provides important prognostic information early after admission, especially concerning short term outcome.

215 Prognosis of silent ischaemia after acute myocardial infarction: the Danish Trial in Acute Myocardial Infarction, DANAMI

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The purpose of the present analysis is to identify risk factors for cardiac morbidity in patients with post-MI silent ischemia.

The DANish trial in Acute Myocardial Infarction (DANAMI) study randomized 505 patients to conservative treatment after thrombolytic treated first MI.

A total of 287 patients had silent post infarct inducible ischemia during a symptom-limited bicycle exercise test. The one year incidence rate of combined cardiac endpoints defined as death, re-infarction or admission with unstable angina was 22% among patients with silent ischemia. According to level of maximum ST-change during stress-test, patients were categorized into three groups: A: ST-elevation (n = 51, 1-year event rate 15%); B: ≥ 1, <2 mm ST-depression (n = 85, 1-year event rate 21%) and C: ≥ 2 mm ST-depression (n = 145, 1-year event rate 26%). In both a univariate and multivariate Cox regression model, predictors of cardiac endpoints were angina prior to the index infarction (relative risk (RR) = 1.75, p = 0.04 versus no angina) and levels of ST-depression during stress-test (RR = 3.6, p = 0.04 (group C versus group A).

In conclusion, patients with silent post infarct inducible ischemia have a substantial one-year risk of cardiac morbidity. The level of maximum ST-depression during stress-test differentiate between high and low risk groups among patients with silent ischemia.

216 Exercise electrocardiography and pharmacological stress echo for long-term prognosis after uncomplicated myocardial infarction

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Background: the prognostic value of inducible ischemia after myocardial infarction (MI) is controversial. Stress echocardiography (SE) has been proposed as adjunctive test to exercise ECG (ExT); however, their relative role is not definitely established. Aim of the present study was to assess the long-term prognostic value of SE and ExT in pts. with uncomplicated MI using a probabilistic model including clinical data first, clinical data+ExT second and clinical data+ExT+SE last.

Methods: four-hundred ninty six patients undergoing maximal ExT and SE (406 dobutamine and 90 dipyridamole) within 15 days of MI were followed-up to 753 days (range 14–2255) for spontaneous events (reinfarction, unstable angina and cardiac death). Patients undergoing revascularization were censored at the time of the procedure.

Results: ExT was positive in 162 (33%) patients and low-threshold positive (<100 W) in 91 (18%). SE was positive in 239 (48%) patients (194 with dobutamine and 45 with dipyridamole). Concordant result was obtained in 311 cases (agreement = 63%, kappa value 0.24, 95%CI 0.15 to 0.33). Sixty-nine events (14 cardiac death, 26 reinfarction and 29 unstable angina requiring hospitalization) occurred, whilst 126 patients underwent revascularization (39 PTCA and 87 CABG). SE was significantly ($p < 0.05$) more sensitive (49% vs. 35%) and less specific (68% vs. 52%) than ExT. Incremental ROC curve analysis showed SE to add significantly, as compared to clinical data, in predicting the outcome; moreover, a 5-fold increase in risk was observed in patients with positive SE among those with high-threshold (>100 W) positive ExT. Finally, the event-free survival of patients having both positive tests was significantly ($p < 0.05$) lower than that of patients with just one positive test or with both negative tests.

Conclusions: 1) SE provides additional prognostic information to clinical data and ExT after uncomplicated MI. 2) The greatest gain is obtained in patients with high-threshold positive ExT.

217 Risk stratification following myocardial infarction: incremental value of an index of global myocardial function

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Aims: Systolic and diastolic dysfunction have been used individually as prognostic markers after myocardial infarction (MI) but a composite parameter of global myocardial function may provide optimal information. We evaluated the use of a simple index of global myocardial performance (IMP) to investigate if it provides incremental prognostic information compared to conventional echocardiographic methods.

Methods and results: We studied 135 patients within 4 days of MI and 56 matched controls. Systolic performance was assessed by ejection fraction (LVEF) and wall motion score (WMS). Diastolic function was assessed by the mitral deceleration time (MDT). The IMP was derived by dividing the sum of the left ventricular isovolumic contraction and relaxation times by the left ventricular ejection time. Feasibility of measurement in the MI group was 76% for LVEF, 80% for WMS, 83% for MDT and 100% for the IMP. LVEF and WMS differed between controls, patients with uncomplicated MI and patients with MI complicated by pulmonary oedema (60 ± 6, 47 ± 14, 40 ± 15 and 2.0 ± 0, 1.35 ± 0.39, 1.11 ± 0.37 respectively; $p < 0.05$ between all groups). IMP also differed between these groups (0.53 + 0.11, 0.59 + 0.17, 0.69 + 0.22 respectively; $p < 0.05$ between all groups). At a mean follow-up of 8 months there had been 10 cardiovascular deaths and 33 patients had developed heart failure (NYHA III/IV). Patients with an IMP value of >0.75 (mean + 2 SD in controls) had a lower survival than those with an IMP of ≤0.75 (relative risk 39, 95% CI 6 to 257; $p = 0.0001$). They were also more likely to have heart failure (relative risk 11, 95% CI 3 to 40; $p = 0.0002$). The IMP was the most powerful of the clinical and echocardiographic parameters in predicting death or heart failure.

Conclusion: The IMP is simple to perform and is the best single predictor of death and heart failure in the medium-term following MI. It is more predictive of adverse outcome than indicators of systolic or diastolic function alone.

218 Baseline left ventricular wall thickness is a predictor of subsequent left ventricular remodelling after anterior myocardial infarction: the Healing and Early Afterload Reducing Therapy (HEART) trial

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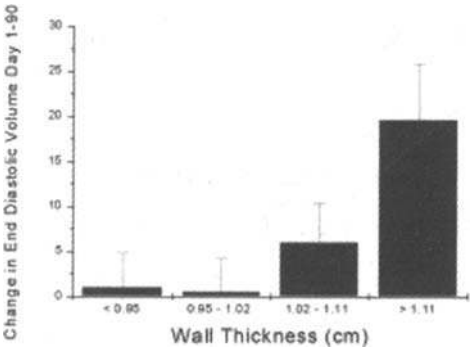
Objectives: To investigate the relationship between left ventricular hypertrophy (LVH) and post-MI remodeling.

Methods: We analyzed echocardiographic and clinical data from the Healing and Early Afterload Reducing Therapy (HEART) Trial, a study of early versus late ACE inhibition following anterior Q-wave myocardial infarction. Patients underwent echocardiography within 24 hours of MI, at 14 days and 90 days. LV wall thickness at day 1 was calculated from measured endocardial and epicardial borders from the short axis view of 129 patients at both the mitral and papillary muscle level by a single investigator in a blinded fashion. Data from three separate high quality cardiac cycles were averaged.

Results: Baseline average LV wall thickness was related to subsequent change in LV end diastolic volume from day 1 to 90 post-MI ($p = 0.001$), and this association remained significant after adjusting for age, sex, history of diabetes, history of hypertension, baseline end-diastolic volume, and HEART drug randomization group ($r = 0.31$; $p < 0.001$). Wall thickness was also related to maximal CK, an enzymatic estimate of infarct size ($p = 0.006$, $r = 0.24$).



Change in EDV with wall thickness.

Conclusion: Left ventricular hypertrophy predisposes to increased enzyme release and LV remodeling after myocardial infarction.

219 The prognostic value of myocardial viability recognized by low-dose dobutamine echocardiography in medically treated patients with chronic ischaemic left ventricular dysfunction

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Aim of this, large scale, prospective, multicenter, observational study was to assess the impact on survival of myocardial viability recognized by low dose dobutamine echo in medically treated patients with global left ventricular dysfunction. Thus, 204 patients (mean age 61 ± 10) with angiographically proven coronary artery disease, previous (>3 months) myocardial infarction and severe left ventricular dysfunction (ejection fraction < 35%, mean: 27 ± 7) underwent low dose (up to 10 μg/kg/min) dobutamine for the detection of myocardial viability. Myocardial viability was identified as rest-stress variation (D) in the wall motion score index (WMSI), each segment scored from 1 = normal to 4 = dyskinetic in a 16 segment model of left ventricle. Patients were followed up for a median of 36 months. The only end-point analyzed was cardiac death. Kaplan-Meier survival estimates showed a better outcome for patients with large viability (D WMSI > 0.4) compared to those with a small extent (DWMSI < 0.4) or with no myocardial viability (D WMSI = 0).Using Cox proportional hazards model, delta WMSI (HR 0.1, 95%CI 0.02–0.7, p = 0.022) exerted a protective effect on survival.

In medically treated patients with severe global chronic left ventricular dysfunction, myocardial viability identified by low dose dobutamine is associated with a better survival. The viability response should be titrated according to the entity and extent of contractile recovery.

MECHANISMS OF PLAQUE INSTABILITY

220 Cell proliferation and apoptosis during atherosclerotic lesion progression in human coronary arteries

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Background: Proliferation activity and apoptotic cell dead in atherosclerotic plaques has been documented as an essential determinant of lesion formation in animal experiments and human advanced lesions from aorta and carotid atherectomy specimens. In human coronary atherosclerotic plaques the role of either apoptotic or proliferative activities in distinct phases of the disease, especially in the earlier plaques, is undefined.

Methods: 60 human coronary plaques (obtained from excised hearts at transplant) were classified from intimal thickening (AIT) to type VIII lesion (AHA classification). 5 mm sections were incubated with antibodies anti CPP32, (ICE-like enzyme responsible for the initiation of apoptosis in mammalian cells), and Ki67 (proliferation marker expressed during all phases of the cell cycle except in quiescent Go cells). Specimens were evaluated by image analysis (Visilog 4.1.5. Noesis.) A ratio of the number of positive nucleus versus the number of total nucleus in 15 high magnification (600x) fields of each coronary was calculated. As cellular markers a-actin (smooth muscle cells), CD31 (endothelial cells), CD68 and Ham56 (monocites/macrophages), Cathepsin G(neutrophils), and CD45RO (Lymphocytes) were used. As secondary antibodies, anti mouse IgGs labeled with biotin, FITC and TRITC were used. DNA fragmentation of apoptotic cells was detected by TUNEL technique.

Results: Lesions type IV, V and VI show a significant amount of TUNEL positive cells, especially in the atheromatous core, while the others types of lesions show scattered positive nucleus in the neointimal area. CPP32 positive cells are present even in early lesions, reach a maximum in type V-VI ($p < 0.001$) to decrease in more advanced lesions. Ki67 shows low levels of expression in cells of plaques from AIT to type V. It shows a significant increase in expression in cells of type VI lesions ($p < 0.05$) and a significant reduction in type VII and VIII lesions ($p < 0.05$). Lesion cellularity (nucleus/unit surface) was not directly related to either one of the markers.

Conclusions: We found a low level of proliferative cells in atherosclerotic plaques. Type VI plaques that trigger thrombotic complications, showed a significantly higher proliferative state. Type V and VI show the highest index of cells initiating programmed cell dead. Atherosclerotic plaque progression is therefore highly regulated and vulnerable plaques, associated with presentation of acute coronary syndromes, show the highest index of cell activity not related with higher cellularity.

221 Inflammation and restenosis: immunohistological study of coronary atherectomy specimens

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The current knowledge of the coronary restenosis following percutaneous intervention suggests that inflammation play a central role in this process. To assess the inflammatory component in restenosis, we studied 97 specimens obtained by directional coronary atherectomy from 93 patients. Based on the presence of internal elastic lumina and cellular density of the sections (>30 cells per high power view), 40 specimens were selected (21 de novo, 19 restenotic). The presence of HLA class II antigens (DR), ICAM-1 (CD 54), macrophage (HAM 54), and SMC were assessed using monoclonal antibodies and an avidin-biotin complex method (LSAB"+/AP from DAKO). The intensity of staining was analyzed semi-quantitatively: 0 negative staining, 1+ mild staining, 2+ moderate and 3+ heavy staining. Only cells with staining indexes ≥ 2+ were considered to be positive and were used in calculations for this study. Quantitative analysis included images from sections digitized using a video 3CCD Sony camera (24 bit RGB resolution, TIFF format) and analyzed with Lucia 3.51 software. Positive cells were counted from three different images on the same slide (image area 200,000 pixels). The mean value was used for statistical analysis using the t-test for independent samples.

Quantitative analysis

	De novo	Restenotic	p value
HLA-DR	9.5 ± 2.9*	6.9 ± 3.4	0.04
ICAM-1	7.8 ± 1.1	6.6 ± 0.7	0.004
Mø	9.0 ± 2.5	6.0 ± 3.1	0.01

*Mean number of cells ± SD

Both HLA-DR and ICAM-1 immunoreactivity were prevalent on macrophages and endothelial cells from de novo lesions compared to restenotic lesions. No immunoreactivity for HLA-DR or ICAM-1 was present on smooth muscle cells in de novo or restenotic lesions.

Conclusions: De novo lesions express a significantly higher level of inflammatory component surface antigens than restenotic lesions. The inflammatory process appears to be mediated by macrophages and endothelial cells but not by smooth muscle cells. The inflammation appears to play less important role in restenosis that previously thought.

222 Clinical presentation of restenosis is associated with the extent of atherosclerotic inflammation of the initial coronary lesion

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Background: There is limited information regarding the association between the extent of atherosclerotic inflammation and the incidence of restenosis after coronary angioplasty.

Methods: A total of 110 patients with stable (n = 46) or unstable angina (n = 64), according to Braunwald's classification, underwent directional coronary atherectomy (DCA). Cryostat sections of atherectomy specimen were immunohistochemically stained with the monoclonal antibodies, a-actin (smooth muscle cells; SMC), CD-68 (macrophages; MAC), CD-3 (T-cells) and C3/43 (HLA-DR molecules; HLA). The extent of atherosclerotic inflammation of the initial lesion was determined by MAC and HLA-DR, planimetrically quantified as the percentage immunopositive tissue area of the total tissue area. T-cells were counted and expressed per mm^2. Patients were followed for one year after the procedure. Clinical restenosis developed in 35 patients (32%), presenting as stable angina in 19 patients and unstable angina in 16 patients.

Results: MAC and SMC areas were not different in patients with or without restenosis. (MAC: 16.1 ± 12.1 vs. 18.8 ± 13.9, SMC: 26.1 ± 14.7 vs. 25.9 ± 16.2). The table shows initial plaque inflammation in patients with clinical restenosis, presenting with either stable or unstable angina.

Table

	% MAC	T-cells/mm^2	% HLA-DR	% SMC
Stable (n = 19)	8.5 ± 4.6	13.2 ± 7.2	11.2 ± 7.8	30.1 ± 16.4
Unstable (n = 16)	25.1 ± 12.1*	24.5 ± 4.2#	19.5 ± 12.6#	21.4 ± 11.2

*$p < 0.0001$ compared to group stable, # $p < 0.05$ compared to group stable.

Conclusion: The extent of initial plaque inflammation is not related to the development of clinical restenosis, but shows a positive association with the severity of recurrent anginal symptoms.

223 Smooth muscle cell heterogeneity in coronary lesions: functional implications

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Mural thrombosis is associated to the presentation of acute ischemic events, progression of atherosclerosis and coronary revascularization procedures. In these processes platelets-released products (PR) seem to play a key role. Smooth muscle cells (SMC) phenotypic heterogeneity has been described but its relative importance in human lesions and its functional role in lesion progression is not known. We have studied SMC heterogeneity in human coronary lesions and their differential response to PR.

Methods and Results: Human coronary arteries from explanted hearts at transplant operations (HSCSP) were process for immunohistochemical analysis. All advanced lesions (type VI to VIII) analyzed (n = 15) displayed positive cells for a specific fibroblast surface protein (FSP) that did not co-localized with a-smooth muscle actin (a-SMA). FSP positive cells were absent in non-atherosclerotic areas (arterial intimal thickening). Cell cultures that express FSP (fibroblast-like cells, FB-like cells) or a-SMA (SMC), were isolated from atherosclerotic plaques. PR were obtained from platelets activated with either 10 μmol/L ADP, 5 μg/mL collagen or thrombin (4 or 10 U/mL) for 5 min. Cells were synchronized by incubation in serum-free media for 48 h and subsequently stimulated with PR in the presence of [^{3}H]-thymidine to measure cell DNA synthesis for 24 h. FB-like cells exhibited higher response (8 to 26-fold) to PR from all agonists than SMC either from non-atherosclerotic segments or atherosclerotic plaques. Only PR from thrombin (10 U/mL) differentially induce mitogenic response on SMC from atherosclerotic lesions (3.4-fold over unstimulated cells) and non-atherosclerotic segments (1.2-fold over unstimulated cells). PR induced by thrombin triggered significantly higher DNA doubling than those of the other platelet agonists and it was the only agonist that showed direct proliferative effects on human vascular cells.

In conclusion, we have identified a fibroblast-like cell subpopulation from human primary atherosclerotic lesions which strongly responds to human PR. FB-like cells could modify the responsiveness of atherosclerotic plaques to mitogenic stimuli.

224 Inflammatory and immune response markers in patients with stable angina pectoris, acute coronary syndromes and healthy controls

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Background: Inflammatory markers are known to be elevated in acute coronary syndromes. However their role in stable angina pectoris has been studied less extensively.

Methods: We investigated the inflammatory markers interleukin 4, 12, c-reactive protein (CRP), fibrinogen, ferritin, leukocytes, lymphocytes in 486 patients (29% female) with stable and unstable CAD and in controls who underwent coronary angiograpy (CA). Healthy controls were defined as patients without stenosis of coronary arteries in CA, stable angina was defined as effort chest pain and documented CAD in CA (≥50% stenosis) and negative troponin T. Acute coronary syndrome was defined as chest pain at rest, positive troponin T and documented CAD, including patients with acute myocardial infarction. Patients with infections within 4 weeks were excluded.

Results:

	Health controls n = 169	Stable Angina pectoris n = 454	Acute coronary syndromes n = 32	p all groups
Age	56 ± 12	63 ± 9**	60 ± 11	<0.001
Sex (% female)	48	23	2	<0.001
Interleukin 4 (ng/l)°	0.3 (0.02/0.8)	0.21 (0/0.69)*	0.35 (0.07/1.29)	0.029
Interleukin 12 (ng/l)°	69 (47/98)	78 (52/102)*	77 (55/102)	0.16
CRP (mg/l)	0.25	0.38	2.24	<0.001
Fibrinogen (mg/dl)	331 ± 67	378 ± 93**	537 ± 125	<0.001
Ferritin (ng/ml)	141	151	263	<0.001
Lymphocytes (%)	30 ± 8	27 ± 8**	23 ± 8	<0.001
Leukocytes (/nl)	6 ± 2	7 ± 3**	8 ± 2	0.002

°Median; *p < 0.05; ** < 0.001 vs healthy controls

Conclusions: As expected acute phase markers were most increased in acute coronary syndromes. Howeverr, even in stable angina there were noteable changes in these markers compared to controls. Especially of interest is a decrease in interleukin 4 and lymphocytes indicating an important role of the immune system.

225 Significant association of cagA positive Helicobacter pylori strains with risk of myocardial infarction

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A potentially clinically and pathophysiologically important association of Helicobacter pylori (H. pylori) infection with coronary heart disease (CHD) has been reported. However, different studies have produced conflicting results. We examined whether genetic diversity of H. pylori influenced the association and specifically whether the risk was confined to infection with the more virulent strains (Type 1) bearing the cytotoxin-associated gene-A (cagA) antigen.

Methods and Results: Serological status for cagA and H. pylori were determined in 342 cases of acute myocardial infarction (MI) and 214 population-based control subjects free of clinical CHD. 38.0% of cases and 30.8% of controls were cagA seropositive (p = 0.08). In subjects < 65 years old (153 cases, 153 controls), cagA seropositivity was associated with a 1.80-fold (95%CI: 1.07–3.03, p = 0.02) increase in MI risk, which increased further to 2.25-fold (95%CI: 1.12–4.53, p = 0.01) in subjects < 55 years. Logistic regression analysis showed a significant interaction (p = 0.03) between age and effect of cagA seropositivity on risk of MI with an average 30% decline in the odds ratio per decade. There was no significant association of cagA status with classical CHD risk factors. 60.2% of cases and 53.7% of controls were H. pylori seropositive (odds ratio 1.12(0.83–1.51, p = 0.43). H.pylori seropositivity was not increased in young cases and did not show any interaction with age.

Conclusion: The association of H. pylori infection with risk of MI appears to be restricted to Type I cagA bearing strains. The association is age-dependent and stronger in younger subjects. Genetic heterogeneity of H. pylori may explain some of the discordant findings with regard to the association of H. pylori with CHD.

NEW INSIGHTS IN HYPERTROPHIC CARDIOMYOPATHY

226 Prepartecipation military screening and echocardiographic (phenotypic) prevalence of hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is an important cause of sudden death (SD) in young people. It has been shown that an early identification of HCM during athletic screening can successfully prevent SD due to HCM. Because military duty is compulsory in Italy, every young male from the age of 17 undergoes medical screening, including history, physical examination, chest radiogram and 12-lead ECG. Thus we have assessed the prevalence of HCM in conscripts examined for cardiovascular abnormalities at the Military Hospital in Verona, January 1992 to July 1996. Of 8853 conscripts, 2596 (29.3%) were referred for echocardiography because of a positive initial screening, and 15 (age 18.6 ± 2.5 years; range 17–27) ultimately showed definitive evidence of HCM on echocardiography with otherwise unexplained left ventricular hypertrophy (prevalence 0.16%). In 9 patients (pts), HCM was diagnosed for the first time during the military screening; in these pts reasons for echocardiography included ECG abnormalities in 6 (one of whom had VPB at Holter monitoring), systolic murmur in 2, and a familial history of HCM in 1. None of these pts participated in competitive sports. In 6 pts HCM had been previously diagnosed, in 5 during preparticipation athletic screening and in 1 because of systolic murmur. All pts but one were asymptomatic. The maximal left ventricular thickness was 19.5 mm (range 15–35 mm).

In conclusion, preparticipation military screening shows a prevalence of HCM very similar to that previously reported in the general population (0.16–0.17%). Cardiovascular screening of a general military population identified HCM for the first time in young males who did not practice competitive sports. Screening programs based largely on electrocardiogram are an effective means to detect HCM in general population.

227 Atrial fibrillation is an important determinant of outcome in patients with hypertrophic cardiomyopathy

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The clinical impact of atrial fibrillation (AF) in patients with hypertrophic cardiomyopathy (HCM) is largely unresolved, with some studies suggesting that AF often leads to clinical deterioration, cardiac failure and systemic embolism, while others may have underestimated the consequences of this arrhythmia. In this study, we analyzed the prevalence and prognostic implications of AF in two large unselected populations of patients with HCM from Italy and the USA. Methods. Clinical documentation of AF and outcome in terms of cardiovascular mortality and stroke were analyzed in 480 patients with HCM (M/F 292/188) followed for 9.1 ± 6.4 years. Survival of those patients with AF was compared with that of a subgroup of HCM patients in sinus rhythm matched for the age, gender and NYHA class present at the time of first onset of AF, using the Cox regression analysis. Results. AF was documented in 107 of the 480 patients (prevalence 22%): 25 were in AF at the time of the first HCM diagnosis, whereas 82 developed AF subsequently, at a rate of 9 new cases or 1.9% per year. AF was exclusively paroxysmal in 45, paroxysmal leading to chronic in 32 and exclusively chronic in 30. Although its prevalence increased markedly with age, AF was present in a substantial proportion of younger patients (12% of patients < 50 years of age). AF was associated with an increased risk of HCM-related death (p < 0.0001), due to an excess stroke- and heart failure-related mortality, but sudden death occurrence was similar among patients with and without AF. At multivariate analysis, AF, age and NYHA were independent predictors of HCM-related mortality; odds ratio for AF was 3.7 (95% CI, 1.7–8.1, p < 0.002). Embolic events including stroke were nearly 9 times more frequent in patients with AF as compared to those in sinus rhythm (25% vs. 3%, p < 0.0001). Patients with AF also had a higher probability of developing severe functional limitation during follow-up (relative risk of a final NYHA class 3–4 was 2.8; 95% CI, 1.8–4.5, p < 0.0001). Conclusions. In an unselected population with HCM, atrial fibrillation 1) had a prevalence of 22% over a 9-year follow-up; and 2) was associated with disease progression, almost a 4-fold independent increase in cardiovascular mortality and a 9-fold increase in embolic events.

228 Prognostic value of non-sustained ventricular tachycardia in adult patiens with hypertrophic cardiomyopathy

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Background: Non-sustained ventricular tachycardia (NSVT) during Holter monitoring is associated with an increased risk of sudden death (SD) in adult patients with hypertrophic cardiomyopathy (HCM). It is suggested that NSVT is only of prognostic significance when repetitive, prolonged and/or associated with symptoms. This study assessed prognostic significance of NSVT and NSVT characteristics in adult patients with HCM.

Methods: We studied 532 patients with HCM (324 male, aged 39 ± 15 years, 96% in functional class NYHA I–II; 20% with exertional chest pain). Maximal left ventricular wall thickness (MLVWT) was 21 ± 7 mm, and 29% had a left ventricular outflow tract gradient ≥ 30 mmHg. All patients underwent ambulatory ECG monitoring (mean 41 ± 11 hours). NSVT was defined as ≥3 beats at ≥120 beats/min.

Results: 104 patients (19.5%) had NSVT. Mean follow up was 47 ± 32 months (range 1 to 157 months). There were 51 deaths in the 532 included patients (24 SD). We found no relation between NSVT characteristics and prognosis. There were no significant differences in the incidence of sudden death or all cause mortality between patients older than 30 with and without NSVT. In patients younger than 30, sudden death risk and all cause mortality were higher in patients with NSVT (Log Rank Test: sudden death $p = 0.04$; all cause mortality $p < 0.0001$). Five years cumulative survival was 54% in patients younger than 30 with NSVT versus 91% in patients older than 30 with NSVT ($p < 0.0001$). In a multivariate Cox regression mortality analisys, NSVT was a significant independent risk factor for all cause mortality after adjusting by MLVWT, left ventricular outflow tract gradient, abnormal blood pressure response, syncope or family history of SD.

In conclusion, NSVT is an important risk factor for sudden death and all cause, mortality in young adult patients (≤30 years old) with HCM. There is no direct relation between NSVT characteristics and sudden death risk.

229 A mutation of the cardiac troponin T gene causes familial hypertrophic cardiomyopathy with normal left ventricular mass

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The hallmark of familial hypertrophic cardiomyopathy is unexplained myocardial hypertrophy with disarray. However cases of widespread disarray in the absence of hypertrophy have been described. We screened the cardiac troponin T gene in the affected surviving relatives of such a family, in whom 4 members had died suddenly and unexpectedly before the age of 45. Heart weights and macroscopic appearance were normal in all 4 hearts. Histology however revealed widespread fibrosis with marked myocyte disarray.

Methods: A DNA based method for screening of the cardiac troponin T gene was devised. PCR products for each transcribed exon were screened by direct sequencing.

Results: A novel missense mutation of exon 9 (position 94 in the amino acid chain) resulted in a new restriction site for the enzyme Alu I. The mutation co-segregated with the disease and was confirmed in DNA extracted from fixed cardiac tissue of a family member who had died suddenly. This mutation at an evolutionary conserved site, results in a non conservative substitution of the amino acid arginine to leucine with an associated charge change. No mutation was found in the DNA of 100 normal control subjects.

Discussion: Patients with a mutation of a sarcomere protein may develop hypertrophic cardiomyopathy in the absence of an increase in LV mass detectable at the clinical or pathological level. These patients appear at high risk of sudden death and yet fail to exhibit the characteristic increase in wall thickness usually seen at clinical diagnosis.

230 Combined anterior mitral leaflet extension and myectomy in hypertrophic obstructive cardiomyopathy: long-term results

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Aim of the study: To examine the clinical and functional long-term results of combined septal myectomy and anterior mitral leaflet extension (MLE) in patients with hypertrophic obstructive cardiomyopathy (HOCM).

Background: MLE is a new surgical approach to the treatment of patients with HOCM. The procedure entails grafting a glutaraldehyde-preserved autologous pericardial patch onto the center portion of the anterior mitral leaflet. MLE in combination with septal myectomy provides more satisfactory haemodynamic results compared to those of myectomy alone. However, the long-term results of this new technique are not known.

Methods: Twenty-eight patients with HOCM underwent combined mitral leaflet extension and septal myectomy. Pre-operative data (NYHA functional class, width of the interventricular septum, left ventricular outflow tract gradient, severity of mitral insufficiency graded on a scale from 0 to 4+ and severity of the systolic anterior movement of the mitral valve graded on a scale from 0 to 3+) were compared to the postoperative findings at the latest outpatient follow-up.

Results: There were no deaths associated with surgery. One patient was re-operated within 3 months because of dehiscence of the pericardial patch. One patient died suddenly 2 years after surgical therapy. After a mean follow-up (± SD) of 3.4 ± 2.1 years (range 3 months–7.7 years), NYHA functional class had improved significantly (2.7 ± 0.5 preoperative vs. 1.3 ± 0.4 postoperative, $p < 0.05$). Furthermore, there was a reduction in width of the interventricular septum (23 ± 4 vs. 17 ± 2 mm, $p < 0.05$), a decrease of the left ventricular outflow tract gradient (100 ± 21 vs. 18 ± 14 mm Hg, $p < 0.01$) and a reduction in the severity of mitral insufficiency (2.6 ± 0.7 vs. 0.5 ± 0.6, $p < 0.01$) and systolic anterior motion of the mitral valve (2.9 ± 0.3 vs. 0.5 ± 0.7, $p < 0.01$) postoperatively.

Conclusions: MLE in combination with septal myectomy is an effective surgical approach to the treatment of patients with HOCM. The long-term results show sustained improvement in functional and haemodynamic parameters.

231 Remodelling after percutaneous transluminal septal myocardial ablation in hypertrophic obstructive cardiomyopathy results in ongoing outflow tract gradient reduction

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PTSMA by alcohol induced septal branch occlusion in pts. with HOCM results in acute reduction of left ventricular outflow tract gradients (LVOTG) in >90% of the pts.. We report on short- and midterm follow-up results.

In 159 symptomatic pts. (79 men; age 51.9 ± 15.8 years; 52 pts. with prior syncope; NYHA class 2.8 ± 0.5) reduction of LVOTG from 61.4 ± 35.4 to 21.3 ± 22.2 mmHg at rest and from 132.1 ± 50.2 to 65.2 ± 43.6 mmHg at stress (each $p < 0.00001$) was achieved by PTSMA. 14 (9%) pts. required a DDD-pacer due to permanent AV block. We report on 3 months follow-up in all 159 pts. and 1 year follow-up in 102 pts..

1 pt. had temporary atrial fibrillation 2 and 9 months after PTSMA, each. No other cardiac complications were observed during follow-up. After 3 months 150 (94.3%) pts. showed clinical impovement (NYHA 1.3 ± 1.0; $p < 0.00001$) with an increase of workload from 83.5 ± 55.3 to 114.2 ± 39.8 Watts ($p < 0.001$). 4 pts. underwent successful re-PTSMA. 98 (61.6%) pts. showed further LVOTG reduction to 9.3 ± 12.1 mmHg at rest ($p < 0.0001$) and to 31.6 ± 36.4 mmHg at stress ($p < 0.0001$). After 1 year 56 (50%) pts. showed further LVOTG reduction and ongoing symptomatic improvement (NYHA 1.2 ± 1.0). 36% of the pts. after 3 months compared to 62% of the pts. after 1 year had no LVOTG at rest and stress ($p < 0.001$). Furthermore, we observed significant reduction of left posterior wall (LVPW) thickness from 13.9 ± 2.3 to 12.7 ± 2.1 mm ($p < 0.0001$) after 3 months and to 11.9 ± 1.8 mm after 1 year ($p < 0.0001$).

Conclusion: After PTSMA pts. showed ongoing clinical improvement without increased risk of cardiac complications. Remodeling after circumscribed septal infarction results in further LVOTG reduction in >50% of the pts. and significant reduction of LVPW thickness.

MEDICAL AND INTERVENTIONAL TREATMENT OF VALVULAR HEART DISEASE

232 More pronounced unloading effect of long-term therapy with enalapril in patients with aortic than with mitral severe chronic regurgitation

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Previous studies demonstrated a favorable unloading effect of long-term therapy with enalapril (E) on asymptomatic pt with severe chronic aortic (AR) or mitral regurgitation (MR). To compare this effect on these two models of LV chronic volume overload we enrolled consecutively 60 pt with AR (n = 30) and MR (n = 30). After randomization 15 pt with AR (gr. ARE) and 15 pt with MR (gr. MRE) were allocated to enalapril therapy (26 + 6 mg/day) and 15 pt with AR (gr. ARC) and 15 pt with MR (gr. MRC) served as control (C). Changes (delta) of LV performance parameters were compared between ARE and MRE as well as between ARC and MRC groups after 6 months of therapy.

Results: There were no difference in baseline Echo parameters of LV diameters, volumes and mass between AR and MR groups and between E and C groups. After 6 months pt receiving E had a significant reduction in mean wall stress (MWS) (AR: 370 ± 93.6 to 284.2 ± 53.3 kdyne/cm2, $p < 0.001$; MR: 253.0 ± 36.1 to 223.6 ± 26.8 kdyne/cm2, $p < 0.01$), LV mass (AR: 214.0 ± 58.0 to 167.4 ± 37.7 g/m2, $p < 0.001$; MR: 176.5 ± 41.0 to 151.4 ± 22.6 g/m2, $p < 0.02$), EDVI (AR: 136.6 ± 28.9 to 113.9 ± 21.9, ml/m^2, $p < 0.001$; MR: 115.9 ± 21.4 to 102.9 ± 13.6 ml/m2, $p = 0.02$) and ESVI (only AR: 53.3 ± 19.6 to 42.6 ± 13.8 ml/m2, $p < 0.001$). In addition, there were a clear difference between E and C groups in MWS (AR: 284.2 ± 53.3 vs 365.9 ± 97.0 kdyne/cm2, $p < 0.01$; MR: 223.6 ± 26.8 vs 257.3 ± 31.0 kdyne/cm2, $p < 0.01$), LM mass (AR: 167.4 ± 37.7 vs 226.1 ± 51.5 g/m2, $p < 0.01$; MR: 151.4 ± 22.6 vs 168.3 ± 29.5 g/m2, $p < 0.05$), EDVI (AR: 113.9 ± 21.9 vs 143.4 ± 34.4 ml/m2, $p < 0.01$; MR: 102.9 ± 13.6 vs 117.9 ± 28.2 ml/m2, $p < 0.05$) and ESVI (only AR: 42.6 ± 13.8 vs 57.5 ± 19.6 ml/m2, $p = 0.02$) after 6 months. Changes (delta) of EDVI (22.7 ± 13.1 vs 13.0 ± 17.8 ml/m2, $p < 0.05$), ESVI (10.7 ± 8.9 vs 3.1 ± 11.4 ml/m2, $p < 0.05$), LV mass (46.6 ± 34.2 vs 25.1 ± 32.7 g/m2, $p < 0.05$) and MWS (85.8 ± 56.4 vs 29.4 ± 35.9 kdyne/cm2, $p < 0.05$) were more pronounced in ARE compared to MRE groups. Between ARC and MRC groups there were no any change on LV performance parameters after 6 months.

In conclusions: Unloading effect of long-term therapy with E in asymptomatic pt with severe chronic AR or MR reduce LV size and mass. This effect is more pronounced in AR than in MR groups of patients.

233 Vasodilatation with felodipine in chronic asymptomatic aortic regurgitation

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In aortic regurgitation, vasodilatation reduces the volume overload upon the left ventricle and may thereby delay the need for valve replacemant. In the present study, the acute and long-term hemodynamic effects of vasodilatation with felodipine in chronic asymptomatic aortic regurgitation were examined in a randomized double-blind, placebo-controlled trial.

Methods: Sixteen patients with chronic asymptomatic aortic regurgitation were randomized to either intravenous bolus of felodipine 0.3 mg or placebo followed by 3 months treatment with felodipine 10 mg or placebo orally once daily. The hemodynamic effects of the intervention were monitored by magnetic resonance (MR) imaging at baseline, 30 minutes after the intravenous bolus, and after 3 months of orally treatment. Forward and regurgitant volume flow through the aortic valves were quantified by MR velocity mapping, whereas left ventricular dimensions were measured using MR multislice technique. Wilcoxon's test for paired samples was used to evaluate the effects of intervention in each of the groups. The significance level was defined as $p < 0.05$.

Results: The intravenous felodipine bolus caused a statistically significant reduction in systemic vascular resistance from (mean ± SD) 1162 ± 399 to 976 ± 317 dyne s cm^{-5} ($p < 0.05$), regurgitant volume index from 1.5 ± 0.8 to 1.3 ± 0.8 L min^{-1} m^{-2} ($p < 0.05$), and regurgitant fraction from 0.31 ± 0.15 to 0.26 ± 0.14 ($p < 0.05$). Furthermore, the forward cardiac output index increased from 3.2 ± 0.9 to 3.5 ± 0.7 L min^{-1} m^{-2} ($p < 0.05$). No significant changes occurred the placebo group.

Three months orally treatment with felodipine caused a corresponding, but more pronounced change in systemic vascular resistance from 1162 ± 399 to 885 ± 335 dyne s cm^{-5} ($p < 0.05$), regurgitant volume index from 1.5 ± 0.8 to 1.2 ± 0.7 L min^{-1} m^{-2} ($p < 0.05$) and regurgitant fraction from 0.31 ± 0.15 to 0.25 ± 0.11 ($p < 0.05$). In addition, the forward net cardiac output index increased from 3.2 ± 0.9 to 3.6 ± 0.7 L min^{-1} m^{-2} ($p < 0.05$). Again no signifant changes were registered in the placebo group and, furthermore, left ventricular end-diastolic and end-systolic volumes, ejection fraction, and mass remained unaffected by the treatment in both groups.

Conclusions: In chronic asymptomatic aortic regurgitation, felodipine causes beneficial hemodynamic effects with an increased forward cardiac output and decreased regurgitant volume, although the total work load upon the left ventricle is unaffected. These results indicates, that felodipine may be able to delay the need for valve replacement in chronic asymptomatic aortic regurgitation.

234 Vasodilator treatment in aortic regurgitation: an echocardiographic follow-up

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Vasodilator agents are considered to be the treatment of choice in medical management of aortic regurgitation (AR). The aim of this study was to evaluate the benefit of treatment with nifedipine or enalapril in a blind follow-up by Doppler echocardiography. 76 patients (age 57 ± 17 y., 60 male, 16 female). with severe AR and a high-quality echo examination were included and randomly assigned to one of the following treatments: enalapril 20 mg/day (n = 28), nifedipine 40 mg/day (n = 22) or placebo (n = 26). The same observer performed an echo examination one day before the start of treatment and 2 years later. Left-ventricle end-diastolic (EDd) and end-systolic (ESd) diameter, mass index (MI), wide of the AR jet, and regurgitation fraction (RF) were measured. During follow-up, 4 patients underwent surgery (3 treated with enalapril, 1 with nifedipine). 8 patients abandoned nifedipine (36%) and one enalapril because of side effects.

Results ($^*p = 0.007$, $^\#p = 0.03$):

	EDd	ESd differences*	RF	RF difference$^\#$
Placebo	64 ± 5	2.6 ± 3	60 ± 13	2 ± 6
Enalapril	68 ± 6	−0.7 ± 5	62 ± 14	−3 ± 8
Nifedipine	64 ± 6	1.8 ± 3	59 ± 13	2 ± 7

There were no significant changes in ESd. When real treatment was considered, the results were the same, except for jet width, which decreased with enalapril 2 ± 3 mm and with nifedipine 1 ± 2 mm, versus placebo, 0 ± 3, $p = 0.03$. nifedipine did not improve EDd, but decreased MI (−10 ± 28) vs enalapril (16 ± 37) and placebo (21 ± 26).

Conclusions: After 2 years of treatment, enalapril has a favourable effect on decreasing left-ventricle end-diastolic diameter and aortic regurgitation. Nifedipine is tolerated worse, but also decreased aortic regurgitation and mass index.

235 Results of percutaneous mitral valvotomy with a metallic commissurotome in patients with a high echocardiographic score

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Severe mitral calcifications and retracted sub-valvular apparatus leading to a high echo-score (Sc) usually represent a poor indication to percutaneous balloon valvuloplasty for mitral stenosis. A new metallic commissurotome was developed and used in a series of 492 patients (Pts) divided into 3 groups: 242 Pts with low Sc (Sc < 8/16), 159 Pts with mid Sc (Sc: 8–9/16) and 73 Pts with high Sc (Sc ≥ 10/16).

The purpose of this study was to compare the 24-hour post-valvotomy results in the high Sc group with the low Sc and mid Sc groups.

In the high Sc group, Sc was 10/16 in 55%, 11/16 in 21%, 12/16 in 12% and ≥13/16 in 12%. Thickening of mitral valve was scored 3/4 in 71% and 4/4 in 9%. Calcifications were scored 3/4 in 33% and 4/4 in 11%. Sub-valvular apparatus was severely retracted 78%. Pts with high Sc were significantly older and 27% had a previous balloon valvotomy vs 10% in low Sc and 16% in mid Sc ($p < 0.01$). Pre-valvotomy mitral valve area (MVA, cm^2) by planimetry was similar in high Sc (0.88 ± 0.2), in low Sc (0.93 ± 0.22) and mid Sc (0.92 ± 0.2). Number of openings (2 to 4) was similar in the 3 groups and maximal opening size (40 mm) was used in 81% of low Sc, 91% of mid Sc and 87% of high Sc ($p = 0.01$).

The procedure was successful (MVA > 1.5 cm^2 and mitral regurgitation (MR) ≤ 2/4 of Sellers classification) in 97% of low Sc, 96% of mid Sc and 89% of high Sc ($p < 0.05$). Mean absolute increase in MVA (cm^2) was 1.25 ± 0.37 in low Sc, 1.2 ± 0.35 in mid Sc and 1.07 ± 0.36 in high SC ($p < 0.01$). Post-valvotomy MVA was slightly lower in high Sc (1.95 ± 0.38) than in mid Sc (2.12 ± 0.3) and low Sc (2.17 ± 0.33) ($p < 0.0001$). Double commissural splitting was obtained in 88% of low Sc, 83% of mid Sc and 78% of high Sc (ns). Severe MR occurred in 1 Pt with low Sc, 2 Pts with mid Sc and 2 Pts with high Sc (1 valve replacement).

Conclusion: Percutaneous mechanical mitral valvotomy appeared feasible, efficient and safe in Pts with a high echo-score who are usually considered as poor canditates to balloon valvotomy.

236 Haemostatic changes in patients with mitral stenosis: immediate impact of balloon mitral valvuloplasty

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Recent evidence suggests that left atrial coagulation activity may be increased in mitral stenosis (MS). This study was conducted to assess regional right and left atrial hemostatic status in patients with MS and to investigate whether balloon mitral valvuloplasty (BMV) has favorable effects on hemostatic parameters.

Methods: Right and left atrial biochemical markers of platelet [Platelet factor 4 (PF4) and B thromboglobulin (BTG)], coagulation [thrombin-antithrombin III complex (TAT)], and fibrinolytic [D-dimer] systems were measured in 28 patients with MS and no left atrial thrombus before and 30 minutes after BMV. Right atrial levels were also measured in 20 control subjects

Results: Optimal BMV results (mitral valve area > 1.5 cm2, left atrial pressure < 10 mm Hg, and no mitral regurgitation) was reported in 16 patients (gp. I) and good results (mitral valve area > 1.5 cm2, left atrial pressure > 10 mm Hg, and no mitral regurgitation) in 12 patients (gp. II). Right atrial PF4, BTG, TAT and D-dimer levels were significantly higher in patients with MS than controls. Only TAT levels were significantly higher in the left atrium than in the right atrium of patients before BMV 7.01 ± 3.66 Vs 8.35 ± 3.89 ug/L, P < 0.0001). Right atrial levels of PF4, BTG, and TAT showed significant reduction in group I only after BMV than before the procedure (from 33.09 ± 11.16 to 23.18 ± 11.08 IU/ml, p = 0.001; from 212.19 ± 32.30 to 193.13 ± 34.39 IU/ml, p = 0.004; and from 7.98 ± 4.39 to 5.51 ± 1.64 ug/L, p = 0.007 respectively). The left atrial levels showed similar significant decrease after the procedure (from 34.53 ± 8.24 to 26.34 ± 8.74 IU/ml, p = 0.0001; from 224.69 ± 40.84 to 195.94 ± 28.47 IU/ml, p = 0.001; and from 9.51 ± 4.68 to 6.51 ± 1.46 ug/L, p = 0.013, respectively). Left atrial spontaneous echo contrast (LASEC) emerged as the only significant predictor of increased regional left atrial coagulation activity (p = 0.001) on multiple logistic regression analysis.

Conclusions: These data indicate that platelet, coagulation and fibrinolytic markers are increased in patients with MS in the absence of left atrial rombus. Regional left atrial coagulation activity is increased in such patients. Optimal BMV has favorable immediate hemostatic effects.

237 Incidence and types of valve dysplasia in 155 pulmonary valvuloplasty procedures

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Balloon pulmonary valvuloplasty (PV) is the ideal treatment for typical pulmonary valve stenosis. Howewer, the results of PV had been controversial when dysplastic valve stenosis is present. Our purpose is to study this problem in a large series of patients.

The existence of valve dysplasia was evaluated following angiographic criteria. Several degrees were considered. The data obtained were related with PV results. PV was performed in 155 ocasions in patients aged 0.1 to 51 years divided in 3 groups depending on angiographic anatomy. Group I, without dysplasia: 106 patients; group II, slight and moderate dysplasia: 34 patients and group III, severe dysplasia: 15 patients. In group I, pulmonary systolic gradient (PG) droped from 75.4 ± 22.3 to 24.6 ± 14.5 mmHg (P < 0.0001); echo-doppler follow-up showed even more decrease in PG (18.5 ± 10.6 mmHg). In group II, PG was reduced from 79.0 ± 30.7 to 25.5 ± 15.6 mmHg (P < 0.0001); follow-up by echo showed maintenance of similar PG (26.2 ± 16.1 mmHg). Howewer, in group III, reduction in PG was not significant (pre PG = 79.0 ± 28.9 mmHg; post PG = 74.1 ± 29.0 mmHg; echo-doppler PG = 73.2 ± 29.3 mmHg). Balloons were inflated several times at its maximum size and balloon/annulus ratio was 1.3 ± 0.25. In most patients an indentation was seen which was abolished easily in group I, with dificulty in group II, and was persistent in group III. Twelve patients in group III had to be operated on, and severe dysplasia was confirmed by surgeron.

In conclusion, PV is a very effective technique in patients with no or slight dysplasia. Howewer, this procedure has not been succesful in patients with severe grade of valve dysplasia. Severe dysplasia of the pulmonary valve has been stated with the typical morphology with nodular and uneven thickening of th valve, no doming, valve ring hypoplasia and no poststenotic dilatation. But some cases with severe and uneven valve thickening with no leaflets mobility had to be considered as severe types, even with good annulus and pulmonary artery size. The results of PV will be always dependig on the existence and the grade of valve dysplasia.

GENE EXPRESSION IN HEART FAILURE

248 Impaired cardiac function and bioenergetics in old transgenic mice overexpressing bovine growth hormone gene

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Substantial evidence indicates the importance of growth hormone (GH) for cardiac structure and function. The aim of the study was to evaluate cardiac function and myocardial energy status in mice with a long exposure to high levels of GH.

Methods: Female, eight months old transgenic mice (TG), expressing bovine growth hormone (bGH) gene (n = 11) and aged matched controls (n = 11) were used. Cardiac function was evaluated using transthoracic echocardiography. The animals were examined with 31P magnetic resonance spectroscopy to determine the cardiac energy status. The levels of apoptosis were also assessed.

Results: TG had a significantly higher body weight (BW), 53.2 ± 2.4 *vs.* 34.6 ± 3.7 g (p < 0.0001) and increased heart mass in relation to BW (HW/BW) compared to non-transgenic mice (5.6 ± 1.6 *vs.* 2.7 ± 0.2 mg/g, p < 0.01). bGH overexpressing mice were associated with significant decreases in several indexes of systolic function compared with control mice such as shortening fractions (25 ± 3.0% *vs.* 39.9 ± 3.1%), ejection fraction (57 ± 9% *vs.* 77 ± 5%), normalized mean velocity of circumferential shortening (4.7 ± 0.8 *vs* 6.4 ± 1.1 circ/sec), p < 0.01. Creatine phosphate-to-ATP ratio was lower in bGH mice in comparison to normal mice (1.3 ± 0.08 *vs.* 2.1 ± 0.23 p < 0.05). There was no sign of an increased number of apoptotic nuclei in myocytes from TG mice compared to controls.

Conclusions: Although short term treatment with GH may improve cardiac function, long term exposure to high levels of GH leads to increased BW, HW/BW and impaired systolic function. Moreover, these changes are associated with altered myocardial energy metabolism.

249 Decreased expression of insulin-like growth factor mrna in muscle biopsies from patients with chronic heart failure

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Background: Patients with chronic heart failure (CHF) show a reduced exercise capacity at least partially associated with metabolic and structural changes in the skeletal muscle. In CHF, an impairment of the GH/IGF-I axis has been demonstrated but no data are known about peripheral abnormalities in IGF-I mRNA expression. Therefore, the aim of this study was to investigate the local expression of IGF-I mRNA in skeletal muscle in pts. with CHF.

Methods: Skeletal muscle biopsies were obtained from 10 pts. with CHF and 6 normal controls. Total RNA was isolated and a RT-PCR with specific primers for human insulin-like growth factor I was performed. The expression of IGF-I was quantitated by densitometrical analysis of the ethidium bromide stained bands and expressed as ratio IGF-I/GAPDH.

Results: In skeletal muscle biopsies from pts. with CHF (body mass index 27.2 ± 3.0, age 63 ± 4 years, ejection fraction 20 ± 6%), the expression of insulin-like growth factor I mRNA was significantly reduced (0.02 ± 0.02 vs. 0.32 ± 0.4 arbitrary units, p = 0.015 vs. control) as compared to normal controls (body mass index 31.3 ± 5.3, age 54 ± 9 years, ejection fraction 73 ± 8%).

Conclusion: Peripheral expression of IGF-I mRNA is downregulated in pts. with CHF suggesting that a decreased local expression of growth factors might be involved in the loss of muscle bulk and the development of cachexia in CHF.

250 Effect of angiotensin II on extracellular matrix protein synthesis in the human heart

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The pathways by which Ang II induces fibroblast proliferation and extracellular matrix protein synthesis in the human heart are still unknown. We investigated whether Ang II directly alters the synthesis of collagen and fibronectin mRNAs after 4 hrs in isolated human myocardial preparations or after a longer stimulation period of 24 hrs in cardiac fibroblasts and whether the growth factors TGF-β1 and osteopontin are involved in this process.

The effect of 4 h Ang II stimulation on collagen I, TGF-β1, osteopontin, AT1 and AT2 mRNA was measured with quantitative RT-PCR in fresh strips of human atrial myocardium. The viability of the preparations was assessed by their adenine nucleotide content. In addition, the effects of 24 h Ang II or TGF-β on collagen I, III and fibronectin mRNA and on proliferation in isolated human cardiac fibroblasts were determined.

After 4 h, Ang II-stimulated atrial samples gave a significantly higher TGF-β1 mRNA expression (268 $\pm$ 52% of control, $p < 0.02$) and osteopontin mRNA expression (474 $\pm$ 174%, $p < 0.05$) than controls. In contrast, the expression of the collagen I mRNA or the reference gene PDH was not sign. altered. After 4 h AngII, AT1 and AT2 mRNAs were increased to 259 $\pm$ 67% and 247 $\pm$ 63% of con ($p < 0.005$ and $p < 0.05$). In human cardiac fibroblasts Ang II caused a dose-dependent stimulation of proliferation but did not affect collagen I, III or fibronectin mRNA synthesis after 24 h. In contrast, TGF-β1 stimulation sign. increased collagen I and III mRNA expression to 124 $\pm$ 5% and 128 $\pm$ 5% of control ($p < 0.002$).

Ang II does not directly increase collagen gene mRNA in the human heart. However, AngII induces the synthesis of TGF-β1 and osteopontin. Since TGF-β1 induces collagen I and III mRNA in cardiac fibroblasts, it probably mediates the effects of Ang II on collagen gene expression.

251 Myocardial inducible nitric oxide synthase gene expression modulates left ventricular contractile response to β-adrenergic stimulation in transplant recipients and in patients with dilated cardiomyopathy

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Nitric oxide(NO) derived from NO-donor or coronary(Cor) endothelium(Endo), modulates left ventricular(LV) function of the human heart through a LV relaxation hastening effect, which reduces LV end-systolic(ES) pressure(P) without change in LV+dP/dt. Pretreatment with dobutamine(dob) potentiates these effects. In the present study, LV contractile effects of NO produced by myocardial inducible(i) NO Synthase(S) were investigated in pts with non ischemic dilated cardiomyopathy (DCMP) and transplant (Tx) recipients and correlated with iNOS mRNA gene expression in simultaneously procured LV endomyocardial biopsies. Micro-tip LV pressure recordings before and during IV-dob(15 microg/kg/min) and endomyocardial biopsies, on which quantitative RT-PCR of iNOS mRNA was performed, were obtained in 17 patients. Dob-induced changes (D) in LV contractile performance (LVPSP = LV Peak Systolic Pressure; LVEST = LV Electromechanical Systole Time = Time from onset of QRS to LV-dP/Dt) were correlated with iNOS-mRNA molecules/microg total RNA in the endomyocardial biopsies.

iNOS and adrenergic stimulation

	DCMP (n = 9 pts)	Tx (n = 8 pts)
D-LVPSP vs iNOS	p = 0.10; r = −0.62	p = 0.07; r = −0.65
D-LV+dP/dt vs iNOS	p = 0.69; r = −0.17	p = 0.98; r = 0.98
D-LVEST vs iNOS	p = 0.03; r = −0.76	p = 0.52; r = 0.18
(D-LV+dP/dt)/(D-LVEST) vs iNOS	p = 0.01; r = −0.81	p = 0.007; r = −0.86

In DCMP pts iNOS gene expression was inversely correlated with D-LVEST. The inverse relation between iNOS gene expression and the ratio of D-LV+dP/dt divided by D-LVEST in DCMP and Tx pts implies a larger dob-induced abbreviation of LV contraction for a similar dob-induced rise in LV+dPdt at higher iNOS gene expression. This potentiating interaction between iNOS and beta-adrenergic stimulation on the onset of LV relaxation could result from additive effects on myofilamentary calcium sensitivity of a NO-induced rise in cGMP and a beta-agonist induced rise in cAMP.

252 The overexpression of the Na/Ca exchanger compensates for partial inhibition of the sarcoplasmic reticulum Ca ATPase in ventricular myocytes from transgenic mice

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In heart failure a reduced expression of SERCA is often associated with an overexpression of the Na/Ca exchanger. The role of this overexpression in relation to a reduction in SERCA function was investigated in cardiac myocytes from transgenic mice overexpressing the Na/Ca exchanger (TR) and littermates (NON). Cytoplasmic [Ca] was monitored using indo-1. To partially inhibit SERCA, 200 nM thapsigargin (TG) was used. Ca transients were faster in TR compared with NON (time-to-peak + time-to 50% relaxation in TR = 234 $\pm$ 6 ms, n = 14; in NON = 332 $\pm$ 11 ms, n = 24, $p < 0.01$, mean $\pm$ SEM). Application of TG to TR slowed Ca decline until the time course of the Ca transient was equal or slower than the one measured in NON. The degree of inhibition of SR Ca uptake needed to produce an equal rate of Ca decline in the two groups was quantified by calculating Ca flux via SERCA (JSR). This, together with Ca flux mediated by the exchanger (JNa/Ca), was obtained as follows. Stimulation was stopped and Na-free/Ca-free (0/0) solution was applied for 2 s. The same solution containing 10 mM caffeine (0/0+caff) was then applied for 1 s producing an increase in Ca. Returning to 0/0 solution produced a decline in Ca mediated by SERCA. After 10 s, 0/0+caff was again added for 1 s and a second increase in cytoplasmic Ca was observed. Superfusate was then changed to 1 mM Ca +10 mM caffeine solution and maintained for a further 10 s. In this case Na/Ca exchange was responsible for the decline of Ca. In TR myocytes Vmax of JNaCa was 255 $\pm$ 45% (n = 9) of the one measured in NON myocytes. Vmax for JSR in TR had to be reduced to 72.4 $\pm$ 5% (n = 8) by TG application in order to obtain the same duration of the Ca transient measured in NON.

SR Ca content was also calculated as follows. Cells were voltage-clamped at −75 mV, 10 mM caffeine rapidly applied and a transient inward current recorded. The integral of this current allows quantification of Ca released from the SR upon caffeine application. In TR in control conditions the SR Ca content was larger than in NON (SR Ca in TR = 122 $\pm$ 9 μM/l non-mitochondrial volume, n = 15;in NON = 91 $\pm$ 6 μM/l,n = 12, $p < 0.02$). When TG in TR myocytes produced a twitch of similar duration to the one recorded in NON, the SR content was similar to the one recorded in NON (SR Ca in TR in TG = 98.4 $\pm$ 10 μM/l, n = 10; in NON in control = 91.4 $\pm$ 6.3 μM/l, n = 12). In conclusion, a 2.5 fold overexpression of the Na/Ca exchanger allows for ~30% reduction of the SR Ca uptake to take place before the Ca transient is slowed and the effect is accompanied by a return of the SR Ca content to NON myocyte values.

253 Differential gene expression in the systemic and pulmonary myocardium during mouse heart development: the left/right paradigm?

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Differential gene expression among five embryonic cardiac compartments, the inflow tract, atria, atrioventricular canal, ventricles and outflow tract, has been widely demonstrated for several sarcomeric genes. We have previously described differences between left/right sides of the embryonic atria and ventricles in transgenic mice carrying regulatory sequences of myosin light chain (MLC) 1F/3F locus. In these mice, transgene expression becomes confined to the embryonic left ventricle (LV), atrioventricular canal (AVC) and right atrium (RA) just after cardiac looping. MLC3F transgene expression in situs inversus remains confined to the morphological LV, AVC and morphological RA. This data suggests that specification of the left/right ventricular identity is mainly dependent upon anteroposterior positional cues.

In order to get insight into the nature of the regionalization of gene expression in the developing left/right sides of the heart, we have investigated the expression pattern of various sarcomeric genes (MLC isoforms) and transcription factors (dHAND, eHAND, Nkx2.5, pitx-2 and chisel) by means of whole-mount in situ hybridization and radioactive in situ hybridization on tissue sections.

Expression of Nkx2.5 is observed in all myocardial cells of the embryonic heart (E10.5), whereas expression of chisel, a downstream target of Nkx2.5, is confined to the ventricular and atrial working myocardium, but not expressed in the outflow tract (OFT), AVC or the inner curvature connecting both segments. Pitx-2 transcripts are mainly confined to the right ventricle (RV) and left atrium (LA), a pattern complementary to that observed in the MLC3F transgenic mice. Atrial myosin heavy chain and MLC isoforms are firstly expressed throughout the myocardium but, as they become confined to the atria, a transient difference between left/right ventricles is observed.

Taken these data into account, we now report that the "primary myocardium" is characterized by the expression of Nkx2.5 whereas the pattern of chisel expression suggests a role in the development of the working atrial and ventricular myocardium. We further propose that the MLC3F transgene expression domain, i.e. the systemic myocardium, represents the evolutionary-conserved primitive heart, whereas pulmonary heart (LA and RV) is newly added to provide a double- pumping system; the expression of pitx-2 is in line with this notion. We further envisage that temporal differences in right/left ventricular myocardium are due to differences in maturation of the distinct cardiac chambers.

INTRAVASCULAR DIAGNOSIS AND INTERVENTION

254 Diagnostic and predictive intravascular images for successful thromboendoarterectomy in patients with thromboembolic pulmonary hypertension

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Thromboembolic pulmonary hypertension (CTEPH) often leads to a severe disability and fatal outcome. To define the surgical accessibility in patients with CTEPH, bilateral lesions in the proximal (main or lobar) pulmonary arteries(PA) should be accurately assessed. Recent studies have shown that intravascular imaging provides direct evidence of lesions in PA as well as coronary and peripheral arteries. In order to examine whether intravascular images have diagnostic and predictive values for successful surgery in CTEPH, we analyzed the images obtained from 40 patients (25 with CTEPH and 15 with the other conditions which potentially affect the pulmonary circulation such as plexogenic, congenital and valvular diseases). An angioscopy (XPF30AL,Olympus,Tokyo,Japan) with an inflatable balloon on the distal tip and a mechanically rotated intravascular ultrasound (IVUS) system (SSD550, Aloka, Tokyo, Japan) were utilized. Angioscopy was useful in determining the location and extent of organized thrombi and thickened intima, recognized by the deformity of the intima and lumen in CTEPH. In contrast, a relatively smooth and uniform surface of intima and regular and round lumina were seen in the proximal PA in the others. A three layered structure with an intermediate echo-lucent zone was clearly demonstrated in CTEPH compared with a single 0.5 mm- to 1.0 mm-thick echogenic layer in the others by IVUS images. In addition, a thickening of the intima-media complex more than 1.0 mm in the proximal PA was the reliable predictor for complete thromboendarterectomy in CTEPH. In conclusion, direct visualization with intravascular imaging could disclose the diagnostic features in PA and lead to successful surgical treatment in CTEPH.

255 Intravascular ultrasound as a new approach for the anatomic and functional evaluation of primary pulmonary hypertension

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The use of intravascular ultrasound (IVUS) for the study of pulmonary vessels has been limited to the evaluation of secondary pulmonary hypertension and pulmonary embolism. The purpose of our study was to analyze by IVUS the structural and functional characteristics of pulmonary vessels in the setting of primary pulmonary hypertension (PPH). In 11 patients with PPH (8 female, mean age of 37 years) we performed heart catheterization and simultaneous IVUS of pulmonary artery branches at baseline and after infusion of epoprostenol (EPO). By IVUS, two pulmonary lobes per patient were studied and the following parameters analyzed: presence of intima + media thickening (>0.2 mm), vessel diameter, mean wall thickness (WT), wall area (WA), area circumscribed by the external elastic membrane (EEM), lumen area in systole (LAs) and dyastole (LAd). Vessel distensibility (Dist) was calculated as: LAs-LAd/LAd. At baseline pulmonary resistance (PR) was 1709 $\pm$ 817 dyn.sec.cm^{-5}, with a mean pulmonary artery pressure (PAP) of 72 $\pm$ 21 mmHg and a cardiac index (CI) of 2.1 $\pm$ 0.7 L/min/m^2. Mean vessel diameter was 4.0 $\pm$ 0.8 mm and the presence of intima + media thickening was observed in all cases, being eccentric in 73% of them; with WT = 0.48 $\pm$ 0.1 mm, WA = 4.4 $\pm$ 1.2 mm2, WA/EEM = 36 $\pm$ 6%, and Dist = 15 $\pm$ 6%. With EPO infusion, PR decreased by 31% ($p < 0.001$), CI increased by 53% ($p < 0.001$) and there was no change in PAP (75 $\pm$ 34 mmHg). Dist had a mean increase of 88% ($p = 0.01$), irrespective of PAP changes. The severity of morphological findings did not correlate with haemodynamic variables at baseline or with changes induced by EPO.

In conclusion, IVUS demonstrates an intima + media thickening in all cases of PPH, predominantly eccentric, with >30% narrowing of the vessel lumen. However, the severity of these changes did not correlate with haemodynamic variables. The increase in vessel distensibility by epoprostenol as determined by IVUS suggests another beneficial effect of this drug in PPH.

256 Relation between pulmonary artery compliance and pulmonary artery pulsatility assessed by IVUS in primary pulmonary hypertension patients

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The non-invasive estimation of Pulmonary Artery Compliance, C (SV/Pulse pressure, ml/mmHg) correlates well with pulmonary vascular resistances in pacients with primary pulmonary hypertension (PPH) that undergo an acute vasodilator test by the intravenous infusion of epoprostenol. The aim of the study was to investigate the relationship of pulmonary artery compliance (C) and pulmonary artery pulsatility assessed by changes in luminal area measured by intravascular ultrasound (IVUS) during the performance of a vasodilator test with epoprostenol in PPH patients.

Methods: eleven patients with PPH underwent an acute vasodilator test with epoprostenol. During right-heart catheterization oxymetric samples were obtained and calculations of cardiac output (CO), stroke volume (SV), systemic vascular resistances (SVR), pulmonary vascular resistances (PVR) were performed at every increasing dose of the drug. Compliance was estimated by the ratio between SV/Pulse Pressure. Pulmonary intraluminal area was measured in 2 to 4 mm diameter vessels by IVUS (Endosonics®, vision-five cahteter), performed at baseline and at the end of the test (maximal tolerated drug dose or achievement of a 30% reduction in PVR), and pulsatility was calculated (sistolic area-diastolic area/diastolic area).

Results: Compliance increased from a baseline value of 0.75 $\pm$ 0.5 to 1.18 $\pm$ 0.77. Arterial pulsatility increased from 0.14 $\pm$ 0.06 to 0.23 $\pm$ 0.063. No correlation was found between C and Pulsatility at baseline (R 0.29 $\pm$ 0.50, p = 0.37 (ANOVA)) nor at the end of the test (R 0.128 $\pm$ 0.80, p = 0.70). We did not found correlation between proportional changes in C and Pulsatility either (R 0.50 $\pm$ 0.52, p = 0.117).

Conclusions: In PPH patients that underwent a vasodilator test, no correlation was found between pulmonary arterial pulsatility assessed by IVUS and compliance estimated by hemodinamic parameters. This may be explained by the heterogeneous distribution of the disease, by the fact that the non-invasive estimation of C explains the behaviour of the pulmonary arterial tree as a whole, whereas IVUS measurements are focused only in small arteries, and because the degree of pulsatility could be preserved with increased pressure (low compliance) or with normal pressure (high complicance).

257 Prognostic role of temporary caval filters in patients with acute major pulmonary embolism

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Background The aim of this study was to assess the prognostic role of implantation of temporary vena cava filters in patients with acute major pulmonary embolism.

Methods and Results We present the clinical course of 115 consecutive patients with acute major pulmonary embolism presenting with hypotension (systolic aortic pressure $\leq$ 90 mmHg) or shock and diagnosed by pulmonary angiography between January 1987 and December 1998. In all patients, baseline therapy consisted of Heparin and thrombolysis (if not contraindicated), 7 patients were treated with pulmonary thrombectomy. Since its first use in 1991, an increasing number of patients additionally received temporary vena cava filters, which were systematically used in all patients since January 1995.

In patients treated between 1987 and 1990 (group I: no use of caval filters; n = 39), in hospital mortality was 38.5% (15/39 patients). Mortality of resuscitated patients was 71.4% (10/14 patients). During the first 6 days of treatment, recurrent pulmonary embolism was observed in 17.9% (7/39 patients), which directly caused death in 2 patients.

In 36 patients treated between 1991 and 1994 (group II: sporadic [n = 12] use of temporary caval filters), in hospital mortality was 38.8% (14/36), and early recurrent embolism occurred in 11.1% (4/36 patients; all of them no caval filter) leading to death in 2 patients.

In patients treated between 1995 and 1998 (group III: use of caval filters in all patients; n = 40), in hospital mortality was 30.0% (12 of 40 patients) [vs. 38.5% in group I, $P = 0.46$], and no patient suffered recurrent pulmonary embolism during the first 6 days of treatment with caval filters in place. In group III, mortality of resuscitated patients was 45% (9/20) [vs. 71.4% in group I, $P = 0.13$].

In the total of 115 patients with acute major pulmonary embolism, mortality was 42.9% (27/63) in patients with no use of temporary caval filters, but 26.9% (14/52) in patients treated with temporary caval filters ($P < 0.05$).

Conclusions: These results suggest that use of temporary V. cava filters may reduce the rate of recurrent pulmonary embolism and may favorably affect the clinical outcome in patients with major pulmonary embolism, especially in resuscitated patients.

258 Clinical evaluation of the pathophysiology of acute and chronic pulmonary thromboembolism by observing with intravascular ultrasound and angioscopy

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Purpose: By observing with intravascular ultrasound(IVUS) and angioscopy(AS) pulmonary artery thrombi and parietal lesions in patients with acute and chronic pulmonary thromboembolism(APTE,CPTE), we investigated the differences in the pathophysiology of the two entities.

Material and Methods: At the time of right heart catheterization IVUS and AS were performed in 15 patients with pulmonary thromboembolism (PTE)(mean age 58 $\pm$ 18 years old, APTE n = 5, CPTE n = 10).

Results: In APTE without underlying disease no intimal thickening was noted and good pulsality was shown. On AS red thrombi could be directly observed, the surface was white-colored and smooth, and no parietal thrombi were found. In CPTE, the cases could be classified into the three groups: (1) Poor extensibility of the vessel wall and intimal thickening were noted on IVUS, while on AS relatively fresh parietal thrombi consisting of a mixture of red blood cell and fibrin, and spider web-like thrombi were found. (2) On IVUS, crescentic parietal thrombi and wall irregularity were seen, while on AS probably organized thrombi with a mixture of red and white surface were seen. (3) On IVUS, marked and echo-rich intimal thickening and poor extensibility were noted, while on AS intimal surface irregularities and yellowish changes were observed. All of the acutely deteriorating cases in the chronic phase belonged to (1), (2).

Conclusion: 1) IVUS and AS are useful in characterizing the thrombi and related pulmonary artery lesions in pulmonary thromboembolism. 2) The pulmonary artery intima and thrombus differ between APTE and CPTE, and among CPTE cases. 3) Unstable pulmonary artery lesions might be present and lead to acute deterioration.

259 Diagnose of pulmonary hypertension reversibility degree using transvascular pulmonary puncture-biopsy (by a new invented method registered in Romania)

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It is well known that in the congenital heart diseases that develop high pressures and increased blood volumes in pulmonary circulation, the results of surgical treatment are correlated with the reversibility degree of pulmonary circulation alteration. To estimate this reversibility degree, the most accurate method is the histologic examination of the pulmonary tissue, but the intraoperatory or percutaneous pulmonary biopsy presents a high risk. The aim of our study was to elaborate a repeatable method for prelevating pulmonary tissue, without the risks and the complications of the other methods.

Methods: We experimented the method on 35 dogs and 20 corpses, using a biopsy catheter specially create by us for this purpose. For this biopsy-catheter and for the method, the Romanian Office for Inventions and Marks conferred us in 1990 the invention patent nr. 100812. Using the right cardiac catheterization way, after we fixed the catheter in a ram of pulmonary artery, we prelevated samples of pulmonary tissue. The animals were hemodyamicaly monitored.

Results: In all cases, we obtained samples of pulmonary tissue with 3–5 mm. length (average 3.8 mm) and 2–3 mm height (average 2.4 mm), among 3 and 5 samples in each case. The samples were large enough for microscopic examinations, which permitted to distinguish constitutive elements of pulmonary structures. After performing biopsies, we effectuated a segmentotomy of the punctured lobe together with the catheter and we examined this macro- and microscopic. We did not find any significant traumatical injuries at the site of the puncture.

In conclusion, transvascular pulmonary biopsy can be a very useful method to follow the modifications of pulmonary circulation in cardiac diseases and to diagnose the reversibility degree of pulmonary hypertension. This method presents the advantages that it can be repeated and implicates no risks, and can be extended in future in other fields of medicine, for instance in pulmonary tumours.

PATIENT EDUCATION IN HEART FAILURE AND OTHER CARDIAC PATIENTS

275 Study of nursing intervention in practice

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Background: A number of initiatives have employed nurses in roles traditionally associated with the medical profession but few have been formally evaluated. We have tested the performance of a Nurse Practitioner (NP) trained to prepare patients for diagnostic cardiac catheterisation.

Method: This was a prospective randomised study. Consecutive patients attending pre-admission clinic for daycase cardiac catheter were screened. Consenting patients scheduled for elective cardiac angiogram were randomised to preparation by either the NP or medical house officer (HO). The principal outcome measure was the combined rate of in-hospital major adverse clinical events (death, MI, emergency cardiac surgery, emergency interventional procedure, CVA, vascular surgery). Secondary outcome measures included (i) combined rates of in-hospital minor adverse clinical events (ii) senior angiographic operator (SAO) assessment of patient preparation and (iii) patient satisfaction.

Results: During April 1997 to May 1998 a total of 355 patients were screened, of these 347 patients were eligible. A total of 339 patients consented to participate and were randomised to NP group (n = 161, age mean $\pm$ SD 62.6 $\pm$ 10.2, male 73%) or HO group (n = 175, age mean $\pm$ SD 60.8 $\pm$ 10.5, male 71%). The rate of major adverse events was lower in the NP group compared to the HO group (NP 0.0% v's HO 1.2%, risk difference −1.2% upper limit of 90% CI +2.0%). The rate of minor adverse evnts was higher in the NP compared to the HO (NP 2.3% v's HO 0.6%, risk difference +1.7% upper limit of 90% CI = +6.2%). The SAO assessment of patient preparation was similar in both groups. Overall patients were satisfied but the proportion of patients grading their care as "very satisfied" was higher in the NP group (NP 94.3% vs HO 86.8% p = 0.02).

Table 1: Results from the SNIP Study

	NP	HO	Risk diff	UL 90% CI	P
Major adverse events	0.0%	1.2%	−1.2%	+2.0%	0.23
Minor adverse events	2.3%	0.6%	+1.7%	+6.2%	0.37
Patient satisfaction	94.3%	86.8%	–	–	0.02

Risk diff = risk difference, UL 90% CI = upper limit of 90% confidence interval

Conclusions: A trained NP can safely prepare patients for cardiac catheterisation. Patients have a higher level of satisfaction with the NP.

276 Nurse-led heart failure clinics in Sweden

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Nurse-led heart failure clinics have been proven cost-effective and improving the patient's quality of life. The aim of this study was to describe the nurse-led heart failure care in Sweden.

Methods: A questionnaire was sent to all 86 hospitals in Sweden, treating heart failure patients. All hospitals completed the questionnaire, which contained questions about presence of heart failure nurses, their education and delegation, how patient education was provided, presence of a heart failure clinic and if so, how it was organised.

Results: Fifty-nine hospitals (69% of all hospitals) had nurses specially trained to take care of heart failure patients, in total 148 heart failure nurses. The nurses were involved in patient education. In all hospitals the heart failure patients were given both oral and written information. The patients were additionally shown a video about heart failure in 24 hospitals, and in 23 hospitals the patients had access to an interactive computer based information. Seven hospitals had group information. Fifty-seven hospitals (66% of all hospitals) had nurse-led heart failure clinics. The clinics provided follow up after hospitalisation, telephone counselling and drug titration. In 40 hospitals the heart failure nurses had a delegation for making protocol led changes in medications such as ACE-inhibitors, β-blockers, stop medication with interactive drugs usually potassium sparing drugs and decrease or increase the dose of diuretics. The majority of the clinics registered the number of visits to the clinic, and the largest clinic had up to 1000 visits annually. Some of the clinics also evaluated their clinic in concern of patient satisfaction, quality of life and the number of readmissions to hospital.

In conclusion, the first nurse-led heart failure clinic started in Sweden in 1990 and since then the concept has been spread to two thirds of the Swedish hospitals.

277 Cardiac patients perceived education and use of sub-lingual glyceryl trinitrate upon commencement of outpatient cardiac rehabilitation

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Purpose: Patients leaving hospital with a discharge diagnosis of myocardial infarction (MI) or angina will be on a variety of cardiac medications. As glyceryl tri-nitrate (GTN) is in the front line of treatment with which cardiac patients can self-medicate with, the question arises as to the education and practical use of this drug amongst angina sufferers. This study was designed to assess patients use of sub-lingual GTN and to discover how they came by this knowledge prior to attendance at outpatient cardiac rehabilitation.

Methodology: Upon attending their first visit to the cardiac rehabilitation outpatient clinic 50 successive patients with a diagnosis of (MI) or angina were interviewed using a closed questionnaire. All patients consented verbally to participate.

Results: Of the 50 patients questioned 35 (70%) complained of post discharge angina. (34%) of this group did not receive a prescription upon discharge. Only 14 patients remember receiving any advice or information about sl-GTN. Patients who had suffered angina while an in-patient were more likely to receive a prescription for GTN pre-discharge (21 out of 22). However this did not necessarily mean receiving education as only 13 remembered receiving any advice as to the correct use of this medication.

Conclusions: The findings of this study suggest that cardiac patients do not know enough about SL GTN and require more education if they are to manage their own health. As cardiology nurse specialists education of the cardiac patient begins with admission and should encompass medication advice alongside that given by medical and pharmacy staff.

278 Cardiac rehabilitation in an outpatient clinic managed by nurses quality assured by computers, doctors and patients

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Purpose: To establish a method for cardiac rehabilitation that makes it possible to reduce the modifiable risk factors for development of ischemic heart disease and at the same time follow the efficacy of the treatment.

Methods: The nurses make use of a computer programme and a detailed manual for all procedures in the clinic.

Based on the values for blood cholesterol, blood pressure, body weight and smoking habits the computer programme generates instantly at each consultation a patient report. The patient report graphically depicts all previous and present values as well as the target values for the treatment on a single sheet given to the patient. The patient report is used as a basis for the consultation with the nurse, who focuses on lifestyle changes as well as drug treatment.

In addition the computer generates automatically an updated clinic report.

The clinic report graphically depicts the effect of the treatment on the modifiable risk factors for the entire population of patients. The clinic report also depicts the number of consultations per month, the average time between the visits as well as the total patient time below the individualised targets for the blood cholesterol level.

The manual describes in details the logistic and all the procedures in the clinic.

After the treatment goals have been achieved the treatment is continued by the general practitioner. It is possible for the general practitioner to continue the patient report containing values both from the hospital and from the general practitioner.

Results: The system has been in use for 1 year. One nurse (34 hours per week) has seen 300 patients with established ischemic heart disease and compiled 100 treatment years. The mortality has been 6%. The LDL-cholesterol has decreased by 15%, the HDL-cholesterol has increased by 15%. There has been a 20% reduction in total risk score for the development of ischemic heart disease.

Conclusion: We have developed a nurse-managed system with automatic quality assessment. One nurse has treated and monitored 300 patients with 1.000 consultations in 1 year with a significant reduction in the patients risk profile.

279 Effects of a multidisciplinary, home-based intervention on unplanned readmissions and survival among chronic congestive heart failure patients: a randomized controlled study

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Hospital admissions among individuals with congestive heart failure (CHF) represent a costly burden to the health-care system. We evaluated a post-discharge, multidisciplinary, home-based intervention (HBI)specifically designed to identify and address the precipitants of clinical deterioration among such patients (pts) in order to reduce the frequency of unplanned readmission.

Methods: Hospitalised CHF pts were randomised to either usual care (UC: n = 100) or to HBI (n = 100) and followed-up for a minimum of 6 months. The primary end-point of the study was frequency of unplanned readmission plus out-of-hospital death within 6 months. Secondary end-points included duration of event-free survival and survival alone, frequency of multiple readmissions, cost of hospital-based care and quality of life.

Results: During 6 months follow-up the major end-point occurred more frequently in the UC group (129 vs. 77 primary events; P = 0.02). More HBI pts remained event-free (38 vs. 51; P = 0.04) and had accumulated fewer unplanned readmissions (68 vs. 118; P = 0.03) and associated days of hospitalisation (460 vs. 1173; P = 0.02). Hospital-based health-care costs for the HBI group were approximately half those of UC ($A490,300 vs. $A922,600; P = 0.16). The mean cost of HBI was $A350 per patient, whilst other community-based health care costs were similar for both groups. The overall distribution of unplanned readmissions was significantly different for the two groups (P = 0.04) with fewer HBI pts being readmitted (42 vs. 54) and requiring 3 or more readmissions (5 vs. 19). In a subgroup of 68 pts, heart failure-specific (P = 0.04) and general quality of life scores (P = 0.01) at 3 months were most improved among HBI pts. Assignment to HBI was both an independent predictor of event-free survival (RR 0.66; P = 0.03) and survival at 6 months (RR 0.54; P = 0.046).

Conclusions: In this controlled study, among a cohort of previously hospitalised CHF pts, a relatively inexpensive HBI was associated with reduced frequency of unplanned readmission plus out-of-hospital death, more prolonged event-free survival, fewer health-care costs and improved quality of life.

280 Comprehensive medical and nursing management decreases hospital care of heart failure

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The number of patients with congestive heart failure (CHF) is increasing rapidly. Due to financial constraints, means of reducing hospital care are of prime importance. A program of intensified outpatient care, comprising systematic patient instruction and follow-up by a specialized nurse and dedicated outpatient department has been proposed as a means to decrease hospital care of CHF. Accordingly, we investigated the effect of institution of such a program in our department on hospital admissions. Since 1998, a nurse and cardiologist specialized in protocolized care of CHF collaborate within the framework of a dedicated outpatient clinic in our hospital, with a reference area of 200.000 people. We compared data regarding admissions and readmission rate from 1998 to historical data from 1995–1997. Clinical characteristics were unchanged over these years (age 73 ± 12, 56% male, LVEF 40 ± 16%). Results are presented in the Table. There was no change in the number of first admissions, but the readmission rate was dramatically reduced.

	1995	1996	1997	1998
First admission	324	349	338	316
Readmission	80	78	106	53

Thus, our results suggest that in the face of an unchanged incidence of CHF in our catchment area (unchanged number of first admissions), our program was succesful at decreasing hospital care of congestive heart failure (decreased number of readmissions).

TREATMENT OF IN-STENT RESTENOSIS

281 Randomized trial of rotational atherectomy vs. balloon angioplasty for in-stent restenosis (ROSTER): interim analysis of 150 cases

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Based on our preliminary experience with rotational atherectomy (RA) for treatment of diffuse in-stent restenosis (ISR), a randomized trial comparing RA versus high pressure (12–16 atm) balloon angioplasty (BA) with IVUS guidance was started in 11/96.

Results: Baseline variables were compared between the two groups. RA group: burr size 2.2 mm, burr number 2.2, burr-to-artery ratio 0.72 & mean post dilatation balloon pressure 4.8 atm. BA group: mean balloon size 3.4 mm & mean inflation pressure 13 ± 4 atm. IVUS data revealed larger post-procedure lumen area gain after RA vs. BA (4.2 ± 1.8 vs. 3.6 ± 1.9 mm^2: p = 0.02) with predominant contribution by plaque debulking in the RA group (54%) vs. plaque compression/extrusion in the BA group (62%). There was no major procedural or clinical complications and 8% in the RA group and 36% in the BA group required re-stenting (p < 0.01). At a mean follow-up of 12 ± 4 months there has been one death & two CABG in each group. Clinical restenosis, defined as angiographic restenosis, target vessel revascularization or recurrent angina class III-IV, has occurred in 20% in the RA group and 43% in the BA group (p = 0.01).

Interim analysis of ROSTER trial

Variable	RA (n = 75)	BA (n = 75)	p
Ref vessel diam (mm)	3.1 ± 0.4	3.1 ± 0.3	NS
MLD Pre (mm)	0.8 ± 0.2	0.9 ± 0.4	NS
MLD Post (mm)	2.8 ± 0.4	2.5 ± 0.3	0.03
Clinical restenosis (%)	20	43	0.01

Conclusion: In the ROSTER trial for ISR, RA resulted in better luminal gain, lower incidence of stent use and lower clinical restenosis compared to PTCA. Thus RA appears to have an advantage over BA for the treatment of diffuse ISR.

282 In-stent restenosis: excimer-laser angioplasty, rotational atherectomy or conventional balloon angioplasty?

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Background: Conventional balloon angioplasty (PTCA) for treatment of in-stent restenosis results in high re-restenosis rates after 6 months. Tissue debulking with excimer-laserangioplastie (ELCA) or rotational atherectomy (PTRA) may be more efficious than PTCA alone. Therefore, the present study evaluates the acute and long-term results after ELCA, PTRA or PTCA for in-stent restenosis.

Methods: 314 lesions (L) with in-stent restenosis were treated with ELCA (124 L), PTRA (124 L) or PTCA (238 L), respectively. After tissue debulking with ELCA or PTRA, additional PTCA was performed to achieve optimal acute procedural results. Coronary angiogramms were analyzed by quantitative angiography (QCA).

Results: QCA data are given in the table.

	Acute intervention				Long-term results	
	n	MLD before intervention	MLD after debulking	MLD after intervention	n	MLD at follow-up (6 months)
ELCA	124	0.93 ± 0.48	1.74 ± 0.42	2.60 ± 0.72	72	1.21 ± 0.86
PTRA	124	0.92 ± 0.55	1.75 ± 0.42	2.57 ± 0.54	75	1.51 ± 0.86*
PTCA	238	0.84 ± 0.51	-	2.31 ± 0.58	118	1.30 ± 0.75

MLD: minimal lumen diameter (mm), *: p < 0.05 for PTRA vs ELCA or PTCA, respectively

Conclusions: ELCA and PTRA for in-stent restenosis result in significant ablation of restenotic tissue. After 6 months, MLD was greater after PTRA than after ELCA or PTCA, respectively

283 Treatment of diffuse in-stent restenoses with the "cutting" balloon: acute angiographic and clinical results

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At present, the treatment of diffuse (>10 mm) in-stent restenosis by established procedures such as balloon angioplasty, laser angioplasty or rotablation is unsatisfactory. Use of the "cutting" balloon (CB) promises an improvement of acute and long-term results.

Between 3/98 and 10/98, we treated 111 diffuse in-stent restenoses (50 LAD, 41 RCA, 18 LCx, 2 ACVB) in 105 patients (78 m, 26 f; 61 ± 10 years) with the CB. The procedure was performed within a median of 6.4 months of stent implantation; in 31 lesions (28%), it had been preceded by at least 1 angioplasty, while no intervention had preceded the CB approach in the other lesions.

Results: Intervention with the CB was angiographically successful in all cases (visual estimation of residual stenosis <20%). Additional stent implantation was required in 22 lesions because of a dissection (n = 14) or a significant residual stenosis (n = 8). One patient in whom LAD and LCx had been treated with the CB in close vicinity to the main stem and another vessel had been dilated conventionally, died in cardiogenic shock within 8 hours of the procedure. There were no more acute complications. To date, follow-up angiography within 6 months had been performed in 35 patients (33%); a diameter stenosis ≥ 50% was found in 14 (40%).

Conclusions: Treatment of diffuse in-stent restenoses with the CB results in the majority of patients in an excellent acute angiographic outcome. The safety of the procedure in lesions located close to the main stem needs to be established. Final data on the late angiographic outcome are forthcoming.

284 Long-term clinical and angiographic follow-up of coronary stenting for patients with in-stent restenosis

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Background: Restenosis (RE) of a previously implanted stent (ST) constitutes a therapeutic challenge affecting a growing number of patients (P). Conventional angioplasty (PTCA) and new debulking devices are currently used in this setting. However, the role of a new ST implantation (ST intra ST) remains unclear.

Methods: Of 361 consecutive P requiring intervention for in-ST RE, 65 P (18%) (mean age 62 ± 11 years, 12 female) underwent repeat ST implantation (42 elective, 23 unplanned). In-ST RE was diffuse (>10 mm) in 60% of P.

Results: Angiographic success was obtained in all P. During hospitalization 1 P died (refractory heart failure) and 2 had non-Q-wave myocardial infarctions (1 side-branch occlusion, 1 subacute ST thrombosis treated with PTCA). At follow-up (mean 17 ± 11 months) 1 P died (noncardiac death) and 9 (14%) required target vessel revascularization (5 PTCA, 4 surgery). Kaplan-Meier event-free survival (from death, myocardial infarction or target vessel revascularization) at 1 year was 84%. With Cox analysis, P with unstable symptoms, shorter time to repeat ST, non-elective ST, and B2-C lesions, tended to have poorer prognosis. However, after adjustment, only non-elective ST was associated (RR 2.9, 95% CI 0.82–10.3, p = 0.09) with adverse outcome. On quantitative angiography (centralized cor lab) RE was found in 13 (30%) of 43 P (75% of those eligible). Logistic regression analysis identify 2 factors: RE length (RR 1.43, 95% CI 1.04–2.14, p = 0.04) and time to RE (RR 0.67, 95%CI 0.47–0.94, p = 0.01) as the only independent predictors of RE.

Conclusions: 1) In P with in-ST RE, both elective and unplanned stenting provide excellent initial results. 2) The long-term clinical and angiographic outcome of P treated with this new strategy (ST intra ST) also appears favorable.

285 β-radiation for the treatment of recurrent in-stent restenosis

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Introduction: Recurrent in-stent restenosis after balloon angioplasty (BA) poses a serious management problem. Previously γ-radiation has been shown to be effective in this subgroup, however the role of β-radiation (β-rad) remains undefined. We studied the feasibility, safety and efficacy of β-rad in patients with recurrent in-stent restenosis.

Methods and Results: From May 1997 until December 1998, 12 male and 6 female patients (mean age 63 years, range 44–75) were treated with either (BA) or laser debulking (L) followed by β-rad. Quantitative coronary angiography (QCA) was performed post procedure (Post) and at 6 month follow-up (FU). Vessels treated were as follows: Left Anterior Descending: (n = 5), Circumflex: (n = 4), Right Coronary Artery: (n = 6), Saphenous Vein Graft: (n = 3). Frequency of previous restenosis were as follows: 2nd restenosis = 10, 3rd restenosis = 7, 4th restenosis = 1. The average time interval for recurrence of symptoms was 3 months (range 1–12). The mean lesion length was 16 mm and mean stent-length was 25 mm (range 9–39 mm). Eleven lesions were diffuse. Patients were treated with BA (n = 8) or L (n = 10), followed by intracoronary β-rad at a prescribed dose of 16 Gray, using the Betacath™ System (Novoste Co. USA). Two treatment failures occurred secondary to myocardial infarction and uncovered distal dissection, both complications of L. Six-month FU has been completed in 14 patients to date: mean minimum lumen diameter (mm) (pre = 0.80 ± 0.38, post = 1.86 ± 0.33, FU = 1.41 ± 0.66), late loss index = 0.36. Restenosis (> 50% DS) was seen in 6 patients (43%). Target lesion revascularisation was performed in 5 patients.

Conclusion: Intracoronary β-radiation for recurrent in stent restenosis in long lesions appears to be a safe and feasible management strategy in a difficult treatment group.

286 Intravascular ultrasound for the selection of patients at risk of recurrent restenosis after repeat intervention for in-stent restenosis

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Background: Adjunctive therapy, like coronary radiation after repeat angioplasty for in stent restenosis seems promising, mainly for pts at risk of recurrent restenosis or clinical adverse event after repeat intervention. Selection criteria for this high risk population are needed.

Population: Clinical, angiographic and intravascular Ultrasound data were recorded before and after repeat angioplasty in 70 pts to determine predictors of one year event free survival (EFS). Forty pts with focal lesion were treated by balloon angioplasty and 30 by combination of rotablator and balloon for diffuse lesion. Clinical event were defined as death, myocardial infarction or need for lesion revascularization.

Results: Clinical event occurred in 14 pts. Lesion length, elapsed time between stent implantation and repeat angioplasty, or severity of the restenosis were not different in the group with vs. without event. Conversely, the lumen cross sectional area (L-CSA) and the percent of neo intimal tissue within the stent after repeat angioplasty were univariate predictors of EFS. By multivariate analysis, only the L-CSA was independent predictor of EFS; the odds ratio was 4.5 (95% confidence interval = [1.1; 18], p = 0.03) per additional mm^2. The cut-point determined by discriminant analysis was set at 4.7 mm^2. EFS of pts with L-CSA < 4.7 mm^2 was 69 ± 15% vs. 91 ± 8% in pts with L-CSA > 4.7 mm^2 (p = 0.008 by Mantel-Cox test), whatever the treatment strategy used.

Conclusion: L-CSA assessed after repeat angioplasty for in-stent restenosis, was the only independent predictor of EFS. Pts with L-CSA < 4.7 mm^2 have high probability of adverse clinical event within one year and may be good candidates for brachytherapy.

CORONARY DISSECTION: TO STENT OR NOT TO STENT

287 Short and long-term evolution of unstented non-occlusive coronary dissection after coronary angioplasty

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We assessed the short and long term clinical and angiographic outcome of non occlusive unstented dissection after coronary angioplasty (PTCA) and its correlation with restenosis. We studied 129 consecutive patients (103 male, mean age 55 ± 11 yrs) undergoing elective PTCA (147 lesions, 66 LAD, 49 CX, 32 DX). All underwent coronary angiography 24 hours and 6 months after PTCA. Lesions were measured by QCA and coronary dissection was graded using the NHLBI classification (type A–D; Huber Am J Cardiol 1991; 68: 467). Study subiects were matched with 60 other patients in whom elective stenting was performed for the presence of dissection. In the first "unstented group" mean stenosis was 85 ± 11% before and 20 ± 7% immediately after PTCA (p < 0.001). Residual stenosis was not significantly different at the 24 hrs restudy (24 ± 5%). Non occlusive coronary dissection (flow TIMI grade 3 in all pts) was seen in 49/147 lesions (33%) and evolved as follows:

Dissection (grade)	Immediate 49 (33%)	24 hrs 41 (28%)	6 months 18 (12%)
A	33	27	10
B	10	8	5
C	4	4	2
D	2	2	1

At follow-up, restenosis was seen in 51/147 dilatation sites (34%), of which 5/41 (12%) occurred in dissected lesions, while 46/106 (43%) were present in vessels with no obviuos dissection (p < 0.001). B, C, and D dissection grade occurred respectively in 56, 32 and 12% of the "stented" patients. In this group restenosis rate was 25% (15/60). In both groups no cardiovascular events or recurrence of symptoms were recorded in the absence of restenosis.

Conclusions: 1) non occlusive dissection after PTCA usually improves after 6 months; 2) in the absence of flow impairment and ischemia this complication does not require any further interventiuon; 3) non occlusive dissection is not associated with increased incidence of restenosis.

288 Clinical outcome after balloon-induced vessel dissection without protective stent implantation

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IVUS guided PTCA results in the use of larger diameter balloons. This technique is associated with a higher luminal gain, a lower restenosis rate and a higher incidence of dissections. Aim of this study was to evaluate the clinical effects of not flow limiting dissections on the acute- and longterm outcome. In our trial the only indication for stent implantation were severe dissections resulting in persisting limitation of antegrade flow.

Methods: 252 patients with 271 lesions underwent IVUS guided PTCA in our lab. In 189 of these patients dissections were detected by IVUS postinterventionally. All dissections were classified in mild (n = 30), medium (n = 36) and severe (n = 123) by IVUS criteria. In 4 patients only additional stent implantation due to flow limitation was necessary. MACE were defined as cardiac death, CABG, RePTCA and Q wave MI in the target vessel.

Results: Acute MACE in hospital occurred in 5 (2%) patients. One patient with medium and one patient with severe dissection had a total occlusion which could be managed successfully by repeated PTCA followed by stent implantation. 3 other patients had had an acute MI without showing evidence of vessel wall dissection. One of them underwent emergency CAGB and died subsequently.

All patients had a clinical follow up after 12 month. During this period MACE occurred in 2 (8%) patients with mild, 3 (8%) patients with medium and 5 (4%) patients with severe dissections, 10 (13%) MACE's were observed in 82 patients without dissections (p = 0.02).

Conclusion: The high incidence of dissections in our patient population did not lead to an increase of acute events. The low rate of longterm events suggests that substantial dissections and an altered remodeling provides a favorable clinical longterm result, most probably due to a "beneficial" remodeling process.

289 A plea for plain old balloon angioplasty with a low rate of provisional stenting: an unselected consecutive group of 1058 patients

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Background: In most PTCA trials selected groups of patients are studied. We prospectively studied the 1-year results of all consecutive patients referred for PTCA of a native coronary artery. A policy of provisional stenting was used. Events were death, myocardial infarction and reintervention.

Results: A total of 1058 patients underwent PTCA between March 1996 and November 1997. Baseline characteristics: mean age 60 ± 10, male sex 78%, diabetes 9%, hypertension 21%, hypercholesterolemia 74%, smoking 31%, previous myocardial infarction 39%, previous PTCA 15%, angina class III or IV (CCS) 69%, multi-vessel disease 33%, EF < 50 percent 18%, LAD lesion 46%, calcified lesion 24%, angulation > 45 degrees 21%, total occlusion 9%, mean lesion length 12 ± 6 mm. In 369 (35%) patients a stent was placed. The stents were placed for dissection in 72% of these patients of which 24% were bail-out situations. The events in all 1058 patients were:

Events – No. (%)	In-hospital	Total at 1 year
Death	3 (0.3)	12 (1.1)
Myocardial Infarction	35 (3.3)	35 (3.3)
Q-wave	11 (0.9)	11 (0.9)
Non-Q-wave	24 (2.3)	24 (2.3)
Coronary bypass surgery	3 (0.3)	22 (2.1)
Target lesion angioplasty	35 (3.3)	148 (14.0)
Target lesion revascularization	38 (3.6)	163 (15.4)
Any event	48 (4.5)	193 (18.2)

Conclusion: The strategy of Plain Old Balloon Angioplasty with a low rate of provisional stenting yields excellent results for all comers.

290 Is "bail-out" stenting the effective option? The widest trial

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Three hundred patients needing a single vessel angioplasty for stable angina were randomised, 146 to undergo angioplasty alone (POBA) and 154, angioplasty plus stent (STENT) in a European multi-centre study. There were no significant differences in the baseline variables between the 2 groups. Two POBA patients received no treatment because of regression of the lesion and 44 (30%) crossed over to stenting, 37 because of some degree of lesion dissection and 7 for a 'suboptimal' result. The procedure failed in 5 (3.4%). 146 (94.8%) of the STENT patients had the stent successfully implanted. There were 5 (3.2%) failures and 3 (1.9%) crossovers. There were severe adverse events (death, MI, vessel occlusion, CABG and repeat angioplasty) in 3.4% in POBA patients and 3.9% in STENT at the initial procedure. The only death was in the POBA group. The post procedure drug management was decided by the patient's physician and included anticoagulation in some of the early cases but more frequently was ticlopidine and aspirin.

The event rate at 1 year was POBA 19.2% and STENT 20.8%, not significantly different. 92.9% (263) of available patients underwent repeat angiography and quantitative analyses performed by an independent core laboratory were available for comparison in 213 (81%) of these. As expected the acute gain in minimum lumen diameter (MLD) was significantly greater in the STENT group (1.68 mm vs 1.3 mm). A similar gain of 1.72 mm was seen in the PTCA crossovers compared to 1.1 mm in the remainder of that group.

Restenosis (more then 50% diameter stenosis at follow-up angiography) rates were not significantly different (17.3%, POBA vs 21.6% STENT)

Conclusions: The outcomes in this study in terms of acute complications, 1 year event and restenosis rates are similar to other published studies. The crossover rate of 30% in the POBA patients was however higher reflecting clinicians attitudes to the perceived value of stenting during the period of randomisation. The final result suggests that adopting a policy of stenting when the initial angioplasty result is not thought to be satisfactory is as effective as stenting all patients for de novo lesions. This approach would have a marked effect on stent implantation rates and thus the cost of intervention. It would also reduce the incidence of in-stent restenosis and 'imprisonment' of branches both of which have no satisfactory treatment at present.

291 "Real-world" in the PTCA-cathlab: high stent-rates and only little differences between the follow-up restenosis rates of stent- and lone-balloon angioplasty

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Recently, rather high restenosis rates in stented Non-Benestent/Stress-lesions were reported. In order to scrutinize these preliminary data, we performed an blind interims analysis of the ongoing multicentre PTCA-Restenosis VESPA-Trial (VESPA = Verapamil high dose Early administration Slow release for Prevention of major cardiovascular events and restenosis after Angioplasty). Up to 1999 January 520 of 700 patients were randomised and in 261 of these follow-up angiography had been already performed (6 months after PTCA). The stentrate in the 5 centres varies between 60% and 92% (average 81%). The stentrates in the different lesion-types were: A: 56%; B1: 80%; B2: 84% and C: 81%. Only 9.6% were A-lesions. The QCA-evaluation of 261 Verum- and Placebo-patients (blind) showed the following data for minimum lumen diameter (MLD) and %-stenoses immediately post PTCA and at follow-up for the balloon- and stent-treated patients:

	Balloon-PTCA (n = 53)	Stent-PTCA (n = 208)	
MLD (mm):			
Post PTCA	2.10 ± 0.05	2.70 ± 0.03	p = 0.0000
Follow-up	1.65 ± 0.11	1.81 ± 0.05	n.s.
Lumen loss	0.45 ± 0.10	0.89 ± 0.05	p = 0.0001
Reference	2.89 ± 0.07	3.11 ± 0.04	p = 0.01
%-Stenose:			
Post PTCA	26.2 ± 1.80	12.2 ± 0.97	p = 0.0000
Follow-up	43.2 ± 3.45	41.1 ± 1.58	n.s.

Conclusion: In daily routine, the follow-up results of the balloon- and stent-treated patients differ far less than reported in the randomised trials. Reasons are the selection of good balloon-results (PTCA-technique not randomized) and the frequent stent-use especially in more complex Non-Benestent/Stress-lesions, which are more proness to renarrow.

292 Decrease in target lesion revascularization after PTCA: due to more liberal stenting?

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A reduction of restenotic events after primary stent implantation has been proved in selected study populations. The impact of stenting in clinical outcome is less well documented in routine practice. We therefore assessed three different groups of consecutive patients undergoing PTCA for a first de novo lesion. Stents were used only for correction of suboptimal results.

Methods:

Group I (1996): 375 patients – 430 segments
Group II (1997): 410 patients – 499 segments
Group III (1998): 224 patients – 266 segments

Demographic and clinical variables and pre-PTCA angiographic data (DS (%), MLD, reference diameter) were similar in the 3 groups. The use of stents increased markedly overtime. In-hospital major cardiac events (MACE: death, CABG, infarction and repeat PTCA) and target lesion revascularization (TLR) procedures during a follow-up of 7 months were assessed.

Results:

	Group I (1996)	Group II (1997)	Group III (1998)	Trend
% Stents/segment	22	46	53	
MLD post (mm)	2.42 ± 0.82	2.57 ± 0.76**	2.74 ± 0.71**	
DS post (%)	17 ± 15	14 ± 13***	12 ± 12*	
In-hospital MACE (%)	13.6	10.0	5.8	p < 0.01
TLR (%)	12.5	9.8	6.7	p < 0.05

Group II vs I – Group III vs II: *p < 0.05; **p < 0.01; ***p < 0.001

On the basis of this study performed in an unselected patient population, we conclude that liberal stenting in the case of suboptimal results improves immediate angiographic results and reduces significantly in-hospital and restenotic events. This strategy permits to reduce the need for repeat procedures to an unexpectely low level even in routine practice.

CARDIOVASCULAR EFFECTS OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTORS BLOCKERS

329 Angiotensin II type 1 receptor gene polymorphism predicts left ventricular function in healthy adults

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Angiotensin II acts as a potent vasoconstrictor and a modulator of myocardial growth and contractility exerting most of its cellular actions through type 1 receptor (AT1R). The cytosine (C) over adenosine (A) allele predominance in the 1166 position of AT1R gene has been implicated as a risk factor for coronary events and hypertension, and there is some evidence that it may also predict left ventricular (LV) hypertrophy and decreased systolic function.

We evaluated the association of AT1R A1166C polymorphism with LV structure and function in a random sample of population (n = 83, 39 men) aged 36 to 37 years free of heart disease. LV diameters, mass and systolic function were measured by M-mode echocardiography. Doppler velocimetry of transmitral flow was used to assess LV diastolic function. AT1R polymorphism was determined by restriction enzyme digestion of PCR products. Subjects genotyped as AC or CC were compared as one group (n = 23) with the AA group (n = 60). Statistical analyses were made with Students t-test and multiple linear regression.

The presence of C allele was associated with longer mean (SD) end-systolic LV diameter, 35.1(4.0) vs 32.6(4.5) mm (P = 0.022), lower peak diameter shortening rate, 79(11) vs 84(12) mm/s (P = 0.048) and lower fractional shortening 30.9(5) vs 33.8(4.5)% (P = 0.016). The differences were independent of sex, body mass index, regular physical activity, smoking, ethanol consumption and sodium intake. Heart rate, blood pressure, Doppler indices of LV filling or LV mass [130(23) g vs 134(33) g, P = 0.59] did not differ between subjects with and without C allele.

We conclude that AT1R A1166C polymorphism predicts variation of LV systolic function in healthy adults. The mechanism remains unknown but the known contraction-promoting effects of AT II on the vasculature and myocardium may play a role.

330 Preventing the effects of angiotensin II in human arteries: angiotensin-converting enzyme inhibition or angiotensin II–AT1 antagonism?

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Background: We recently demonstrated a non-ACE angiotensin (Ang) II forming pathway in human internal mammary arteries. This implicates differential Ang inhibitory effects of ACE-inhibition and Ang II–AT1 receptor antagonism.

Aim and Methods: The aim of the present study was to compare effects of an ACE-inhibitor (captopril (CAP) 1 mM to 10 μM) and an Ang II-AT1 receptor antagonist (irbesartan (IRB) 0.1 nM to 0.1 μM) on the contraction responses to increasing doses Ang I (1 nM–1 μM), in internal mammary arteries from 25 patients undergoing coronary bypass surgery. In addition, a chymase inhibitor was used (1 μM soybean trypsin inhibitor, STI). Responses were expressed as the percentage of a control response to 10 μM phenylephrine.

Results: Organ bath experiments showed that CAP did not change the maximum response to Ang I (control: 46.3 ± 6.3%, CAP: 43.0 ± 4.6%). In contrast, 0.1 μM IRB competely blocked the response to Ang I (from 45.8 ± 6.7% to 1.9 ± 1.9%, $p < 0.001$). Although maximum responses did not change, 100 μM CAP shifted the −logEC50 from 7.50 ± 0.10 to 7.01 ± 0.09. However, addition of STI to CAP more effectively shifted −logEC50 than CAP alone (0.47 ± 0.06 vs. 0.91 ± 0.13, p = 0.01).

Conclusion: Ang I mediated effects are much more effectively inhibited by Ang II-antagonism than by ACE-inhibition. The incomplete effects of CAP on the inhibition of Ang II formation are caused by alternative Ang II forming enzyme(s), as was demonstrated by the additional effects when STI was added to CAP.

331 Attenuated coronary vasoconstrictive effect of angiotensin II and enhanced vasodilatory effect of ACE inhibitor in chronic heart failure

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Background: Increased angiotensin II (Ang II) would modulate coronary circulation in chronic heart failure (CHF), however, the effect has not been directly examined. We investigated the effect of Ang II on coronary circulation in CHF induced by rapid pacing, using Ang II, Ang type 1 (AT1) or type 2 (AT2) receptor blocker and ACE inhibitor.

Methods: Seven Beagle dogs were used. A Doppler flow probe was implanted around the left anterior descending coronary artery, and the atrioventricular node was permanently blocked by formaldehyde injection. Before (baseline study) and 3 weeks after pacing at 240 beats/min, hemodynamic measurements were performed under anesthesia. Coronary flow dynamics were evaluated by coronary pressure-flow relationships (PF·R) during long diastole by transient pacing-off state, before (basal state) and after intracoronary injection of Ang II (10 ng/kg), AT1 blocker (L158809, 0.1 mg/kg), or AT2 blocker (PD123319, 0.2 mg/kg), and ACE inhibitor (enalaprilat, 0.2 mg/kg). The slope of linear regression line of P-F·R, and perfusion pressure at which coronary blood flow ceased (Pf = 0) were evaluated.

Results: After rapid pacing, cardiac output decreased (1.54 ± 0.12 to 0.75 ± 0.07 L/min, $p < 0.05$) and plasma AngII levels increased (28 ± 10 to 318 ± 178 pg/ml, $p < 0.05$). In baseline study, Ang II significantly reduced the slope of PF·R (1.17 ± 0.13 to 0.81 ± 0.11 mL/min/100 g/mmHg, $p < 0.05$) and increased Pf = 0 (27 ± 1 to 31 ± 1 mmHg, $p < 0.05$), while L158809, PD123319, or enalaprilat did not change them. After rapid pacing, the slope of PF·R did not change (1.17 ± 0.13 to 1.20 ± 0.08, N.S.) and Pf = 0 increased (27 ± 1 to 31 ± 1, $p < 0.05$) in basal state. Ang II changed neither the slope of P-F·R (1.20 ± 0.08 to 1.18 ± 0.07, N.S.) nor Pf = 0 (31 ± 1 to 32 ± 1, N.S.) in contrast to the response in baseline study. On the other hand, enalaprilat significantly increased the slope of PF·R (1.25 ± 0.09 to 1.46 ± 0.08, $p < 0.05$) and decreased Pf = 0 (32 ± 1 to 29 ± 1, $p < 0.05$), while neither L158809 nor PD123319 changed them.

Conclusion: The vasoconstrictive effect of Ang II on coronary circulation would be significantly attenuated, vice versa, the vasodilatory effect of the ACE inhibitor presumably via bradykinin would be augmented in CHF.

332 Bradykinin and the vasodilator effects of enalapril compared with losartan in patients with heart failure

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Angiotensin converting enzyme (ACE) inhibitors have been shown to potentiate the effects of exogenous bradykinin (BK) by inhibition of its breakdown. Despite this there is little evidence that inhibition of endogenous BK breakdown actually contributes to the effects of ACE inhibitors, or indeed other inhibitors of the renin-angiotensin-system such as angiotensin II receptor (AT1) antagonists, and no evidence at all that it does so in patients with heart failure.

Methods: 12 patients with heart failure (11 male, 1 female, ages 59 to 81 years) were randomised to double-blind crossover treatment with enalapril 10 mg bd followed by losartan 25 mg bd, each for 5 weeks, or the reverse. At the end of each treatment period, forearm blood flow was measured by venous occlusion plethysmography during an intra-brachial infusion of BK before and after an intra-brachial infusion of Hoe-140 (a potent, selective and long-acting BK antagonist).

Results:

	Enalapril	Losartan
Vasodilatation to BK	357 ± 67%	230 ± 46%
Vasoconstriction to Hoe-140	4 ± 2%	−4 ±6%
Vasodilatation to BK after Hoe-140	192 ± 35%	66 ± 13%

Conclusions: Inhibition of endogenous BK breakdown does not appear to contribute significantly to the effects of ACE inhibition or AT1 antagonism in the forearm of patients with heart failure at rest, despite the marked effect of ACE inhibition compared with A2 antagonism on exogenous BK breakdown.

333 Effects of ACEI and calcium antagonists on minute-to-minute sympathetic nerve traffic variability in heart failure

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Purpose: It has been previously shown that congestive heart failure (CHF) is characterized by a marked increase in muscle sympathetic nerve traffic (MSNA) and by a reduction in its min-to-min spontaneous oscillations. It is unknown, however, whether this impaired MSNA variability is irreversible or it can be favourably affected by drugs commonly employed in CHF treatment.

Methods: In 16 CHF patients treated with diuretics and/or digitalis (NYHA class II–III; age: 64.3 ± 1.8 yrs, mean ± SEM), we measured mean arterial pressure (MAP, Finapres), heart rate (HR, EKG) and MSNA (microneurography at a peroneal nerve) during a 20 min resting period. MSNA was calculated as bursts incidence over time (bursts/min) and as min-to-min variability, expressed as variation coefficient (VC). In 8 patients measurements were repeated after a 2 month benazepril (10 mg/die) administration while in the other 8 after a 2 month amlodipine (10 mg/die) administration.

Results: In the control condition, MAP and HR were 96.5 ± 2.0 mmHg and 74.9 ± 4.0 b/min, respectively, while absolute MSNA values amounted to 59.4 ± 4.2 bs/min and VC of MSNA was 5.3 ± 2.1%. Benazepril caused slight and not significant MAP and HR decreases (−5.8 ± 2.3 mmHg and −3.3 ± 1.1. b/min), which were accompanied by a marked and significant ($p < 0.01$) reduction in absolute MSNA values (−28.4 ± 3.1%) and by a significant increase ($p < 0.05$) in MSNA-VC (+41.2 ± 5.0%). In contrast amlodipine, although causing similar MAP and HR effects did not significantly affect absolute MSNA values (−4.3 ± 3%) and VC (+5.3 ± 4%).

Conclusions: These data provide evidence that the impaired MSNA variability characterizing CHF can be reversed by drug treatment. They also show, however, that only drugs, such as ACEI, capable to exert sympathoinhibitory effects, allow to improve the abnormal pattern of sympathetic nerve traffic oscillation.

334 Acute effects of intravenous enalaprilat and perindoprilat in patients with ischaemic heart disease

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The relative contribution of kinin and angiotensin peptides to the intracardiac effects of angiotensin converting enzyme (ACE) inhibitors and their cardioprotective and anti-ischaemic properties remain controversial. We investigated the acute effects of perindoprilat (P) and enalaprilat (E) on coronary haemodynamics and metabolism, and levels of angiotensin (A), and bradykinin (BK) peptides, in 22 patients undergoing non-emergent cardiac catheterisation for the investigation of chest pain. A coronary sinus (CS) catheter was positioned to enable atrial pacing, determination of CS flow and serial sampling of CS blood. All measures were performed both at rest and during pacing induced tachycardia (at 60.5 ± 1.4% of baseline cycle length). Patients received either P 1.25 mg or E 2.5 mg, in a non-randomised, unblinded fashion, as a rapid intravenous bolus injection. Response to tachycardia (T) induction was re-examined 14 ± 1 minutes following drug administration.

Results: Both P and E abruptly and virtually completely suppressed serum ACE activity, the effects on A and BK peptides, just prior to T induction, being displayed below. T was associated with a 35 ± 14 and 44 ± 11% increase in CS flow pre and post P respectively and 58 ± 17 and 26 ± 9% increase pre and post E respectively ($p < 0.05$ for P vs E effect). P reduced myocardial lactate production and increased oxygen extraction during T, whereas E did not ($p < 0.05$ for P vs E effect).

Results: Peptide levels

	Perindoprilat (n = 12)		Enalaprilat (n = 10)	
	Femoral Artery	Coronary Sinus	Femoral Artery	Coronary Sinus
ΔAI (fmol/ml)	3.0 ± 1.1*	3.2 ± 1.5	3.7 ± 1.1*	2.7 ± 0.8*
ΔAII (fmol/ml)	−1.0 ± 0.3*	−0.7 ± 0.3	−1.6 ± 0.6*	−0.8 ± 0.5
ΔAII/AI	−0.6 ± 0.2*	−1.1 ± 0.7	−2.7 ± 1.1*	−1.3 ± 0.8*
ΔBK-1-9 (fmol/ml)	2.9 ± 1.6	−2.3 ± 1.1*	2.0 ± 0.2*	−2.6 ± 3.7
ΔBK-1-7 (fmol/ml)	0.7 ± 1.0	−6.7 ± 3.4	0.7 ± 0.7	−2.1 ± 1.1
ΔBK-1-7/BK-1-9	−1.9 ± 1.9	−0.6 ± 0.2*	−3.0 ± 0.9*	−0.3 ± 0.3

*$p < 0.05$

Conclusions: Despite similar inhibition of plasma ACE activity, acute administration of P, in contrast to E, exerted greater effects on transcardiac BK peptide levels. Acute effects of ACE inhibitors may depend on extent of inhibition of intracardiac ACE activity.

UPDATE ON TREATMENT OF HEART FAILURE

335 Antithrombotic therapy is associated with better survival in patients with severe heart failure

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Background: The effects of long term antiplatelet or anticoagulant therapy on survival in patients with congestive heart failure (CHF) have not been investigated in prospective controlled trials. Moreover, it has been suggested that the benefit form ACE inhibitor therapy may be decreased in patients concomitantly treated with aspirin. The aim of this work was to identify the interaction between cardiovascular drug therapy, with special reference to antithrombotic agents, and survival, in patients with advanced CHF.

Methods: The observational prospective community based study, EPICAL (EPidémiologie de l'Insuffisance Cardiaque Avancée en Lorraine) has identified 417 patients with advanced CHF. Inclusion criteria were: age 20–80 years, at least one hospitalization for CHF with NYHA III/IV, hypotension and/or peripheral and/or pulmonary oedema and ejection fraction < 30%. Average follow up was 18 months. Cardiovascular drugs used at hospital discharge were tested in a multivariate Cox model adjusted for other known predictive factors (clinical and biological baseline characteristics). Association between variables and survival was expressed as RR (relative risk of death) and corresponding 95% CI (confidence interval).

Results: ACE inhibitors were used in 312 pts (75%), nitrates in 170 (41%), aspirin in 129 (31%) and oral anticoagulants in 128 (28%). Duration of disease, history of renal failure and/or serum creatinine>180 mmol/d, low serum sodium, serious comorbidity and age above 65 were independently associated with a lower survival. Use of nitrates (RR = 0.6, 95% CI = 0.5–0.7), aspirin (RR = 0.5 65% CI = 0.4–0.7) and oral anticoagulants (RR = 0.5, 95% CI = 0.4–0.7) were independently associated with better survival. Interaction between aspirin and the ACE inhibitor therapy was not significative.

Conclusion: Aspirin or oral anticoagulant therapy was associated with better long term survival (death risk was decreased twice) in patients with advanced CHF. These results support the conduct of a clinical trial investigating the effects of long term antithrombotic therapy in patients with heart failure.

336 Binding properties of β-adrenoceptor antagonists used in heart failure at recombinant β1, β2 and β3-adrenoceptors

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A large body of evidence indicates a benficial effect of β-adrenoceptor (β-AR) antagonists on symptoms and survival of patients with coronary heart disease and heart failure. Human myocardium contains at least four distinct β-AR subtypes, three of which have been cloned from different tissues. β1- and β2-AR are well characterized and stimulate adenylyl cyclase (AC) via stimulatory Gs proteins. β3-AR couple to inhibitory Gi proteins and thus inhibit cAMP formation by AC. The identity of a fourth β-AR subpopulation is not yet thoroughly characterized.

The present study investigates the binding properties of the widely used β-AR antagonists metoprolol (M), atenolol (A), bisoprolol (B) and carvedilol (C) at β1-, β2- and β3-AR, respectively. For this purpose, COS-7 cells were transfected with the cDNAs of the respective β-AR and radioligand binding experiments using [^{125}I]cyanopindolol were performed in membrane preparations of transfected cells. The table includes Ki-values in nM.

β-AR antagonist	β1-AR	β2-AR	β3-AR
Metoprolol (M)	69 ± 26	286 ± 73	331 ± 83
Atenolol (A)	556 ± 168	3052 ± 1348	3168 ± 772
Bisoprolol (B)	15.6 ± 2.7	235 ± 73	484 ± 198
Carvedilol (C)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1

These data suggest that carvedilol is nonselective for any β-AR, while A and M exhibit a 5-fold selectivity for β1 versus β2- and β3-AR. B is 15-fold selective for β1 versus β2- and 31-fold selective for β1- versus β3-AR.

In conclusion, binding properties of β-AR antagonists on distinct β-AR differ and have to be taken into account with respect to therapeutic and adverse effects of these drugs.

337 Effect of endothelin on myocardial fibrosis in response to chronic administration of angiotensin II or aldosterone

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Background: Elevations of circulating angiotensin II (AII) and/or aldosterone (Ald) leads to myocardial fibrosis. Several studies have demonstrated that AII and Ald may stimulate endothelin (ET) expression while some experiments suggest ET may stimulate AII and Ald production. Other studies demonstrated ET, per se, is responsible for increased collagen synthesis. Objective: We hypothesized that ET could contribute to cardiac fibrosis through a complex mechanism involving AII or Ald.

Methods: We used bosentan (B), an endothelin ET_A and ET_B receptor antagonist, to treat Sprague-Dawley rats. Five groups were studied (14 rats in each group): 1) untreated age-sex matched controls; 2) intact rats receiving AII (75 ng/min subcutaneous); 3) intact rats receiving AII and B (100 mg/kg/day po); 4) uninephrectomized rats receiving Ald (0.75 μg/h subcutaneous) and high salt diet; 5) uninephrectomized rats receiving Ald plus high salt diet and B. Cross sections of the heart were stained with collagen specific picrosirius red and videodensitometry was then used to quantify the interstitial and perivascular collagen volume fraction (ICVF, PCVF) of the right and left ventricles (RV, LV).

Results: Table below (**p < 0.05 vs. Control and *p < 0.05 vs. Ald or AII).

Table

		Cont	AII	AII + B	Ald	Ald + B
ICVF (%)	LV	0.61	1.16**	0.70*	1.32**	0.80*
	RV	0.80	1.92**	1.33*	3.50**	2.23*
PCVF (%)	LV	1.20	5.35**	0.96*	3.63**	1.50*
	RV	1.14	4.40**	1.00*	1.71**	1.51*

Conclusion: Bosentan prevents fibrosis in both the normotensive, nonhypertrophied right ventricle and in the hypertensive, hypertrophied left ventricle. These findings suggest that endothelin plays an important role in fibrous tissue formation stimulated by AII or Ald.

338 Intra-aortic balloon counterpulsation in patients with cardiogenic shock complicating acute myocardial infarction – duration of shock to cardiac assist is an independent predictor of short-term outcome

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Aims. The aim of this study was to identify clinical and procedural variables as predictors of survival in patients with cardiogenic shock complicating acute myocardial infarction supported by intraaortic balloon counterpulsation (IABP).

Methods and results. Out of 427 consecutive patients treated with counterpulsation between 1977 and 1996 at our catheterization laboratory and/or medical intensive care unit, we analyzed all 286 patients presenting with cardiogenic shock related to acute myocardial infarction. Mean duration of shock before IABP-insertion was: 9.2 ± 18.7 hours (range: 0.5 to 28 hours). Early reperfusion-procedures (thrombolysis; angioplasty; coronary artery bypass grafting) were performed in 209 patients (73%) with successfull revascularization in 149 patients (71.3%; TIMI II or III-flow). Another 13 patients had spontaneous reperfusion with open infarct-related artery at the time of IABP-placement.

In hospital mortality was 56.3% (161/286) in the total group of shock-patients, but was significantly decreased in patients in whom counterpulsation was initiated within 4 hours after onset of shock-symptoms (47.9% vs. 67.8%; P < 0.001).)

Multivariate logistic regression analysis identified early IABP-support with duration of shock to IABP-treatment of ≤4 hours (odds ratio 0.3), hyperlipidemia (odds ratio 0.3), nicotine use (odds ratio 0.4), and early revascularization with open infarct related artery within 4 hours after onset of shock (odds ratio 0.4) as independent predictors of survival. Mortality was independently elevated in patients with bundle branch block (OR 2.7), CABG-patients with graft-occlusion (OR 2.5) and in patients resuscitated before insertion of IABP (OR 2.0).

When considering patients with reopened infarct-related artery (162 patients), mortality was 39.6% in patients with duration of shock to IABP-treatment ≤ 4 hours and 62.5% in patients with duration of shock > 4 hours (42/106 vs. 35/56 pts; P < 0.01). Patients with persistent coronary occlusion (124 patients) as well had lower mortality when counterpulsation had been initiated within 4 hours (62.7% vs. 72.3%; not significant).

Conclusion. Early treatment with both revascularization and IABP-support is the most effective therapy in cardiogenic shock complicating acute myocardial infarction. In these patients, early IABP-support is an independent prognostic factor and, per se, leads to a decrease in mortality.

339 Progressive cardiac dysfunction and effects of growth hormone on cardiac function and myocardial gene expression in genetic murine dilated cardiomyopathy

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Recombinant human growth hormone (rhGH) after myocardial infarction in rats has beneficial effects on cardiac function, and physiological rather than pathological hypertrophy has been suggested as a possible mechanism for this. Disruption of the muscle LIM protein (MLP), an essential regulator of myogenesis, gene in mice is associated with dilated cardiomyopathy (DCM) closely similar to human DCM. However, the effects of GH on cardiomyopathic heart are unknown. The present study was designed to determine whether cardiac dysfunction in the MLP knockout (KO) mice was progressive and to assess the effects of GH on cardiac function and myocardial gene expression in these mice. Serial echocardiographic studies were performed in 8 week old MLP KO mice (n = 31). Most of these animals exhibited increasing left ventricular (LV) chamber size and/or decreasing LV systolic function during 5 to 9 month follow-up period. Twenty-two animals showing both LV dilatation and reduced LV systolic function were randomized to vehicle (Control, n = 10) or rhGH (8 mg/kg, bid, SC) (GH group, n = 12) for 2 weeks. In the GH group, LV % fractional shortening and wall thickness were significantly increased, the LV dP/dt max was elevated, and relaxation (tau) was improved. The LV expression of many genes was altered in the MLP KO mice compared to the wild type animals, and GH reduced elevated mRNA levels for atrial and brain natriuretic peptides (p < 0.05 for each). Thus, the cardiomyopathy of the MLP KO mice was associated with progressive LV dilatation and dysfunction, and short-term rhGH treatment improved LV function and reduced elavated LV mRNA expression of members of the embryonic gene program related to pathological hypertrophy in this genetic murine DCM.

340 Bioengineered grafts to repair the infarcted myocardium

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The persistent shortage in donor hearts stimulates the search for alternative strategies to treat end-stage heart failure. Tissue engineering is a promising strategy that offers the potential to create replacement tissues from autologous cells and three-dimensional polymeric scaffolds. We present a novel approach to tissue-engineered "myocardial tissue".

Methods and Results: We developed a method to grow cardiomyocytes and fibroblasts in three-dimensional compatible alginate scaffolds. The scaffolds are engineered to be highly porous to accommodate a large number of cells, and to be biodegradable. The alginate scaffold temporarily provides the biomechanical and structural characteristics for the replacement of the infarcted myocardium until the engrafted cells produce their own extracellular matrix. Fetal cardiomyocytes were seeded into these novel alginate scaffolds. The cells were cultured for 7 d to verify viability and morphology. The cellular constructs (10x5 mm, dxh) were surgically implanted into myocardial scar of rats (1–3 for each rat), 7 days after myocardial infarction. Two months later, the grafts were studied histologically. The engineered grafts consisted of confluent cell layer mixed with collagen fibers. The specimens showed almost complete disappearance of the scaffold polymer. Prominent blood vessels grew into the tissue-engineered graft from the surrounding coronary network. The overall appearance of the graft suggested integration into the host.

Conclusions: Cardiac cells can grow in polymeric scaffolds. The cells form a viable graft tissue, survive at least 2 months in the infarcted myocardium and stimulate neovascularization. This bioengineered tissue may be used for regeneration and healing of the infarcted myocardium. It can be used for attenuation of infarct expansion and left ventricular dilatation, for prevention of heart failure progression and to allow cell-based gene therapy into the infarcted myocardium.

CARDIOGENIC SHOCK: INTERVENTIONAL THERAPY

347 Primary stenting of left main coronary artery improves immediate and late outcome in patients admitted for acute myocardial infarction with cardiogenic shock

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Objectives: The purpose of this retrospective study was to investigate immediate and late outcome in patients (pts) with AMI and cardiogenic shock (CS) due to acute left main coronary artery (LMCA) occlusion or critical narrowing who underwent LMCA primary stenting compared to pts treated with LMCA conventional PTCA.

Background: In AMI, occlusion of LMCA is a rare angiographic finding resulting most often in CS or sudden death. Only few data are available about LMCA stenting in AMI with CS and acute LMCA occlusion.

Methods: From 08/88 to 08/98, we reviewed 17 consecutive pts (13 men, mean age 58 yrs) admitted for AMI with CS and occlusion (TIMI 0) (n = 14) or critical narrowing (TIMI 1) (n = 3) of LMCA. From 08/88 to 01/95, PTCA was performed in 9 pts, referred for primary (n = 5) or rescue PTCA (n = 4) after failed thrombolysis. From 01/95 to 08/98, primary stenting was performed in 8 pts (6 unprotected and 2 protected LMCA). Time delay between onset symptoms and procedure was 4 ± 1.3 hrs.

Results: Angiographic success was achieved in 14 pts, providing 2 procedural death and 1 emergency CABG. Clinical outcome was available in all pts (mean follow-up 2 yrs, range 1 to 10). Table shows immediate and late clinical events in conventional PTCA and stent groups. Overall, 6/17 pts (35%) were alive and 3/6 (50%) surviving pts were event-free.

	PTCA Group (n = 9)	Stent Group (n = 8)
Procedural success.	6 (68%)	8 (100%)
In-hospital mortality	7 (78%)	3 (37%)
2-year follow up		
Mortality	1	–
Repeat PTCA	–	1
CABG	–	1
Transplantation	1	–
Overall mortality	8 (89%)	3 (37%)

Conclusion: Primary stenting is an effective treatment for AMI with CS due to acute occlusion or critical narrowing of LMCA and improves immediate and long term survival in these critically ill patients.

348 Coronary stenting in acute myocardial infarction with cardiogenic shock. Should we dilate also the non-culprit lesions?

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Background. Cardiogenic shock in acute MI remains associated with a high in-hospital mortality even after successful PTCA, stenting and IABP. In pts with multivessel disease, shock may be related not only to the culprit lesion but also to other severe lesions with no compensation of the non-infarct territory.

Methods. For this reason, we decided to evaluate in those pts a new strategy of multivessel PTCA with coronary stenting (Multivessel) and compare this strategy to the reference one i.e. treatment of the culprit vessel only (Culprit). The 2 strategies were not randomized but left to the operator's decision.

Results. Out of 884 AMI pts admitted directly to the Cathlab within 24 hours (1995–1998), 112 (12.9%) had cardiogenic shock. The main characteristics and results of the 2 shock groups are summarized below:

	Culprit	Multivessel
Patients (n)	89	23
Age (years)	71.9 ± 14.2	62.0 ± 13.6
Onset to admission (min;)	328 ± 237	509 ± 469
CPR before admission (%)	19	39
Triple vessel disease (%)	33	70
Left main disease (%)	22	23
Procedural success (%)	89	96
Coronary stenting (%)	83	96
IABP (%)	69	91
In-hospital death (%)	51	35

Conclusion. Coronary stenting in AMI with cardiogenic shock is feasible in the majority of cases. Procedural success rate is acceptable but mortality remains high. PTCA and stenting of other major vessels does not seem to increase the risk when performed by experienced operators and may be of particular interest in selected pts. This strategy should be assessed in a randomized trial.

349 Transport to primary PTCA in acute myocardial infarction complicated by acute heart failure. Results from the Prague study (national multicenter randomized study)

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The aim of the study was to prove the safety of interhospital transport for primary PTCA in patients with acute myocardial infarction complicated by acute heart failure. Their prognosis was compared with a group treated by thrombolysis in the community hospital.

In total, 259 patients were randomised into 3 groups: A (thrombolysis in the community hospital, no transport), B (thrombolysis during transport), C (transport to primary PTCA without thrombolysis)

Results:

	Group A	Group B	Group C
n =	87	86	86
Pts. with Killip II–IV on admission, n =	22	15	23
Mortality during transport or 30′ after	N.A.	0	0
30-days mortality of pts. Killip II–IV	36%	20%	9%

Conclusion: The transport of patients with acute myocardial infarction complicated by acute heart failure is safe and primary PTCA after transport seems to improve their mortality prognosis.

350 Should we emergently revascularize occluded coronaries for cardiogenic shock? An international randomized trial of emergency PTCA/CABG: results of the SHOCK trial

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The NHLBI funded SHOCK Trial was testing the hypothesis that, in patients (pts) with cardiogenic shock (CS) due to acute myocardial infarction (MI), a direct invasive strategy with early revascularization (ERV) reduces 30-day Mortality by an absolute 20% when compared to initial medical stabilization (IMS), including Thrombolysis, IABP, and possible revascularization after 48 hours. Thirty centers randomized 302 pts from 4/93–11/98 among 1492 pts with suspected CS. Non-randomized pts failed to meet strict CS criteria (43%), had clinical exclusion (45%), were outside time window (5%), or were eligible but not randomized (7%). Coronary angiograms pre and post angioplasty, and 2D echocardiograms were analyzed at core facilities. Trial demography: Mean age was 66 ± 10 years, 32% were women, 33% had prior MI, 46% prior hypertension, and 31% diabetes. Index MI was anterior in 60% with diagnosis of CS early after MI onset (median 5.6 hours). The hemodynamic profile at randomization was: pulmonary capillary wedge pr. 24 ± 7 mmHg, Cardiac Index 1.8 ± 0.6 l/min/m2 often recorded on support measures, systolic BP 88 ± 20 mmHg. Thrombolytic was administrated in 56%, IABP was utilized in 86%, ventilator in 83% and 55% of pts were transferred to tertiary care SHOCK center. The crossover rate from IMS to ERV was very low (<4%). Median times to PTCA and CABG in the ERV group were 0.9 and 3.0 hours after randomization, respectively.

Final analysis of the primary endpoint, 30-day all cause mortality will be presented for the two trial arms.

351 Long-term survival after invasive treatment of cardiogenic shock

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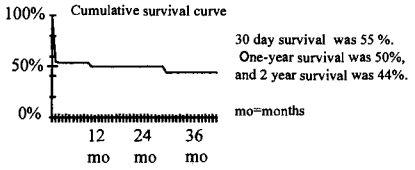
Patients with acute myocardial infarction (AMI) and cardiogenic shock have a poor prognosis with only limited benefit on mortality rates by thrombolytic therapy. Treatment with Emergency PTCA or CABG seems to improve outcome. Information of the long term survival of these patients is scarce.

Methods: Patients were deemed to have cardiogenic shock if the systolic blood pressure was less than 80 mmHg without inotropic support, or 90 mmHg with inotropic support, and clinical signs of cardiogenic shock were present (oliguria/anuria, reduced peripheral circulation). In a consecutive series of 47 patients (mean age 64 years) with cardiogenic shock caused by AMI (not due to mechanical causes) treated with PTCA and/or CABG during 1995–1998 we analysed the long term survival. All patients were included on the "intention to treat" basis. Mean follow up time was 22 months.

Results: 4 patients died prior to treatment. 43 patients were treated with PTCA. 4 patients were treated with initial PTCA and then immediately with CABG. 32 patients were treated with IABP.



In **conclusion,** Patients with cardiogenic shock due to AMI have high initial rates of mortality despite treatment with PTCA and/or CABG, but those who survive the first thirty days seem to have a good long term outcome.

352 Long-term survival of patients undergoing coronary stent placement in cardiogenic shock after acute myocardial infarction

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Background: Myocardial infarction (MI) complicated by cardiogenic shock is asscociated with a very high mortality. Previous studies have shown the advantages of reperfusion strategies in these patients. Comprehensive studies on the role of coronary stenting are not available.

Methods: Starting in January 1995, coronary stent placement has been the primary goal in the treatment of these patients referred to our institution. This intention-to-treat analysis provides a complete one-year clinical follow-up of all patients with cardiogenic shock referred to us after January 95.

Results: Of 108 patients admitted to our institution, one patient was treated conservatively, 107 underwent coranary angioplasty and 100 were treated with additional stent placement. These procedures were successful in 96.3% During the first 30 days, 38.9% died, 2.8% had a repeat nonfatal MI, and 2.8% needed a repeat intervention (overall adverse event rate 41.7%). After one year, 45.4% had died, 4.6% had a repeat nonfatal MI, and 8.3% required a repeat intervention (overall adverse event rate 51.9%).

Conclusions: This analysis suggest that coronary stent placement in myocardial infarction complicated by cardiogenic shock is feasible and can be achieved with a high primary success rate. Major adverse events occur mainly during the first 30 days. Patients surviving this early critical phase experience a very favorable longterm follow-up.

DIRECT ANGIOPLASTY: INTERNATIONAL EXPERIENCE

353 Twelve-month follow-up of the Stent PAMI trial

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The Stent PAMI trial randomized 900 pts with AMI < 12 hours at 62 centers worldwide to either primary PTCA with balloon alone or elective stenting with heparin coated Palmaz Schatz stent. Primary endpoint was combined death, recurrent MI, disabling stroke or ischemia driven target vessel revascularization at 6 months (MACE). Mace at 12 months was a secondary endpoint as well as restenosis rate by QCA analysis on a 6-month angio.

Results: Baseline demographics were well matched in stent (n = 452) and PTCA (n = 448) arms except for age (60.9 stent group vs 59.2 balloon group, p = 0.05). A heparin-coated stent was deployed in 97.6% of cases and a bail-out stent was necessary for 67 (15.0%) pts. Acute angiographic success was similar between stent and PTCA group (99.8% vs 99.1%) but minimal lumen diameter post procedure was larger in the stent group (2.56 vs 2.12 mm, p < 0.0001). At 30 days outcome was similar in the two groups except for ischemic target vessel revascularization favoring the stent (1.3% vs 3.8%, p = 0.02) but at 6-month follow-up occurrence of MACE was lower (12.6% in the stent group, 20.1% in the balloon group, p < 0.01) 12-month follow-up is as follows:

	Stent%	Balloon%	p value
Death	5.5	3.1	NS
Reinfarction	2.9	2.7	NS
Disabling stroke	0.4	0.4	NS
Ischemic TVR	10.6	21	<0.0001
MACE	16.8	24.8	<0.01

In conclusion, primary stenting with heparin-coated stent achieved a superior clinical outcome as compared to balloon angioplasty with bail-out stenting at 6-month-follow-up. This superiority remains at 12 months.

354 In-hospital mortality of 865 patients with ptca for myocardial infarction complicated by cardiogenic shock. Results of the PTCA-registry of the ALKK

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This study reports on the results of PTCA within 24 hours after onset of symptoms in 865 consecutive patients with acute myocardial infarction (AMI) complicated by cardiogenic shock.

Between July 1994 and October 1998 865 consecutive patients with cardiogenic shock were treated in 62 centres participating in the direct PTCA in AMI registry of the ALKK. Mean Age was 63.6 ± 11.8 yrs and 68.1% were male. The time from start of symptoms to PTCA was 284 ± 271 min and 25.8% received thrombolysis before PTCA. One-, two- and three-vessel disease was observed in 36%, 27% and 37% of the patients, respectively. A patent infarct vessel after PTCA was observed in 86% of the patients, with TIMI 3 flow in 76.5% and TIMI 2 flow in 9.5%. The total in-hospital mortality was 49.4% and was highest in the group with TIMI 0/1 flow (80.4%), somewhat lower in patients with TIMI 2 flow (64.6%) and lowest in the group with TIMI 3 flow (40.4%).

Mortality in the 335 patients with additional stent implantation was 45.1%, compared to 52.5% in patients without stent (p = 0.051). Of note, mortality in patients with TIMI 3 flow was similar (40.6 vs. 40.1) in the groups with and without stent implantation.

An intraaortic balloon pump was inserted in 94 (10.9%) of the patients, of these patients 58 (61.7%) died. An acute bypass sugery was done in 29 patients, the in-hospital mortality in this group was 38%.

Conclusion: In-hospital mortality in patients with AMI complicated by cardiogenic shock remains high, even with direct PTCA. Outcome is dependent of TIMI flow after the intervention. Stent implantation in patients with TIMI 3 flow does not appear to improve prognosis.

355 Improving survival in acute myocardial infarction treated with primary percutaneous coronary intervention: the Mayo Clinic experience

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Background: The approach to treatment of acute myocardial infarction (AMI) by catheter-based techniques has evolved over recent years. Improvements in balloon and stent technology, and technical expertise have occurred. In addition, newer adjuvant antiplatelet therapies are now widely utilized. The totality of impact of these factors on outcomes has not been clearly defined.

Methods: We analyzed our PTCA registry database and identified all patients (n = 1066) who underwent primary PTCA (no thrombolytics) within 24 hours of AMI at Mayo Clinic, from 1991 to 1997 and characterized the clinical factors, procedural changes and subsequent results.

Results: The number of patients treated for AMI by primary PTCA increased from 118 in 1991 to 192 in 1997. Overall baseline clinical and angiographic characteristics were similar over the time period studied. Intracoronary stent use increased from 1991 to 1997 (1.7% vs. 62.5%, $p < 0.05$). This coincided with an increase in ticlopidine use from 1994 to 1997 (3.4% vs. 60.9%, $p < 0.05$) and abciximab use from 1995 to 1997 (2.9% vs. 63.0%, $p < 0.05$). An increase in beta-blocker (54.2% vs. 74.0%, $p < 0.05$) and ACE-inhibitor (27.7% vs. 39.1%, $p < 0.05$) use occurred with a decrease in calcium channel antagonist use (29.7% vs. 8.3%, $p < 0.05$) on discharge. Overall from 1991 to 1997, there was an increase in successful procedures (78.0% to 90.1%, $p < 0.05$) and successful lesion dilatation (83.6% to 95.1%, $p < 0.05$) with a decrease in emergency CABG (3.4% to 0.5%, $p < 0.05$), in-hospital mortality (9.3% to 4.7%,$p < 0.05$), and 1-year mortality (13.6% to 8.9%, $p < 0.05$). The incidence of stroke was very low.

Conclusions: The success rates, hospital survival and long-term survival have improved dramatically for patients with AMI treated with primary PTCA. These improvements may reflect a combination of increasing operator experience, improvement in equipment, increased use of stents, better antiplatelet therapies, and increasing use of beta-blockers and ACE-inhibitors.

356 Thrombolysis vs. PTCA vs. both in patients with acute myocardial infarction (Prague trial): narography findings and PTCA results

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The Prague trial compares the effect of 3 treatment strategies in 240 patients with acute myocardial infarction (AMI) admitted to the hospitals without PTCA centre: thrombolysis in the general hospital (group A); thrombolysis + immediate transport to the PTCA centre (group B); bolus 10,000 U of Heparin + Aspegic 500 mg i.v. + immediate transport for direct PTCA (group C).

Coronarography and PTCA results:

	Group B	Group C
Number of pts	79	80
IRA LAD	62.5%	59.1%
RCA	37.4%	30.3%
RCx	3.1%	13.6%
TIMI flow before PTCA 0+I	58.37%	66.7%
II+III	41.8%	33.3%
TIMI flow after PTCA 0+I	5.2%	5.4%
II+III	94.7%	94.5%
No of stents per pts	0.8 (0–2)	0.8 (0–2)
30 days mortality (group A 14.5%)	16.6%	8.4%
Reinfarction	9.7%	0%
Stroke in 30 days	4.1%	0%

IRA = infarction related artery.

Preliminary results: We conclude, that the administration of Heparin 10,000 U + Aspegic 500 mg i.v. is very effective before direct PTCA. This medication reopened the IRA only 8.5% less frequently (33.3% v.s. 41.8%)in comparison with the group of patients treated with streptokinasis up to one hour after admission. Direct PTCA (group C) seems to be the optimal treatment strategy for AMI (primary success 94.5%), if the transport is not longer than 1 hour.

357 Primary angioplasty versus thrombolysis in acute myocardial infarction: long-term follow-up

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Background: Several studies demonstrate a better outcome after primary angioplasty, compared to thrombolysis for acute myocardial infarction. However, until now only short-term follow-up has been presented.

Design: Long-term follow-up of a randomised trial of primary angioplasty compared to thrombolysis.

Patients and Methods: 395 patients with acute myocardial infarction were randomised to either primary angioplasty or thrombolytic therapy. Primary end points were death or recurrent myocardial infarction.

Results: Median follow-up period was 70 months in the primary angioplasty group and 67 months in the thrombolysis group. Of the 194 patients treated with angioplasty, during the follow-up period 27 patients died (14%), compared to 47 of the 201 patients (23%) treated with thrombolysis ($p < 0.05$). Adjusted for age, gender, Multi Vessel Disease (MVD) and Left Ventricular Ejection Fraction (LVEF), patients treated with thrombolysis had a relative risk of long-term mortality of 1.3 (95% CI 0.78 – 2.30) compared to those treated with primary angioplasty. Recurrent myocardial infarction during the follow-up period was observed in 12 patients (6%) treated with primary angioplasty and 44 patients (22%) treated with thrombolysis ($p < 0.05$). Adjusted for differences in age, gender, MVD and LVEF, those treated with thrombolysis had a relative risk of 2.3 (95% CI 1.5 – 3.5) on either death or recurrent infarction compared to those treated with primary angioplasty.

Conclusions: Our results show a beneficial effect of primary angioplasty on mortality and recurrent infarction, not only after short-term but also after long-term follow-up.

358 Predictors of poor outcome in a non-selected population of patients with acute myocardial infarction treated with primary angioplasty

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The objective of this study was to identify clinical and angiographic predictors of in-hospital mortality in a non-selected population of patients with AMI treated with primary PTCA.

Methods: The study population is constituted by 713 patients (64 ± 13 yrs, 80% male) with AMI treated with PTCA within the first 12 hours after the onset of symptoms. A univariate and multivariate analysis were performed considering multiple clinical and angiographic variables, in order to identify predictors of in-hospital death.

Results: The mortality rate was 13.9% in the entire population and 7.6% after excluding patients in cardiogenic shock (3.2%, 18.2%, 25.0% and 69.4% in patients in Killip class I, II, III and IV). The following characteristics were associated with a higher in-hospital mortality in the univariate analysis: >65 years (19.9% vs. 8.5%, $p < 0.0001$), female gender (20.1% vs. 12.1%, $p = 0.0170$), multivessel disease (21.5% vs. 5.3%, $p < 0.0001$), angiographic unsuccessful result (49.0% vs. 10.7%, $p < 0.0001$), proximal vessel occlusion (17.6% vs. 7.4%, $p = 0.0001$), Killip class III–IV (52.6% vs. 5.0%, $p < 0.0001$), anterior location or left bundle branch block (17.1% vs. 7.8%, $p = 0.0004$), non smoking (20.9% vs. 8.9%, $p < 0.0001$), absence of hypercholesterolemia (17.4% vs. 7.5%, $p = 0.0001$), diabetes mellitus (20.9% vs. 11.8%, $p = 0.0048$) and hypertension (16.3% vs. 10.9%, $p = 0.0371$). The following were independent risk factors of in-hospital mortality in the multivariate analysis: angiographic unsuccessful result (OR 4.3; $p = 0.0012$), multivessel disease (OR 2.9; $p = 0.0025$), Killip class III–IV (OR 11.3; $p < 0.0001$), anterior location of left bundle branch block (OR 2.6; $p = 0.0208$) and absence of hypercholesterolemia (OR 2.2; $p = 0.0453$).

Conclusion: The presence of multivessel disease, an angiographic unsuccessful result, anterior location or left bundle branch block and absence of hypercholesterolemia are associated with a higher in-hospital mortality after primary angioplasty for acute myocardial infarction.

MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY: PERFUSION AND REPERFUSION

359 Does colour-blooming limitate assessment of myocardial perfusion using harmonic power Doppler?

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Background: It has been shown that visualisation of myocardial perfusion (MP) is feasible using Harmonic-Power Doppler Imaging (H-PDI) in combination with modern intravenous ultrasound contrast agents. However, it is unknown whether low intensity signals in the subendocardial myocardium are due to blooming from the high intensity signals in the cavity or reflect real perfusion.

Objective: to evaluate in a pulsatile flow phantom, whether and at which distance low intensity signals in small vessels could be visualized next to a cavity with high intensity contrast signals.

Methods: 10 small silicon tubes (diam. 0.5 mm) were fixed close to a perfused balloon (diam. 1.7 cm) at various distances (0.25–9.25 mm). Single or simultaneous perfusion of the tubes and the balloon was performed using 3 ml of the ultrasound contrast agent SH-U 563 A (Schering AG, Berlin, Germany). The recordings were performed by means of an ATL HDI-5000 ultrasound system (ATL, Bothell, WA, USA) in the intermittent Harmonic-Power-Doppler-mode (HPD) at variable receive gain (60%, 71% and 81%). The lateral and axial diameter of the tubes and of the balloon as well as their mean signal-intensity was measured off-line using a new developed imaging software.

Results: The diameter of the ballon was overestimated using the H-PDI recordings: 1.7 mm (9.9%; SD = ± 1.6%) for the highest gain setting and 0.35 mm (2%; SD = ± 1.2%)for the lowest receive-gain setting. Tubes 1.25 mm and more distant from the balloon could be delineated with all receive-gain settings.

Conclusions: Only the immediate border area of about 1 mm between a cavity with high intensity signals and a adjacant tissue with small vessels is influenced by blooming with adequate gain setting. Outside this area H-PDI signals represent real intramyocardial contrast.

360 Triggered multiple-frame loss of correlation Doppler energy imaging produces non-uniform microbubble destruction: a quantitative videointensity analysis

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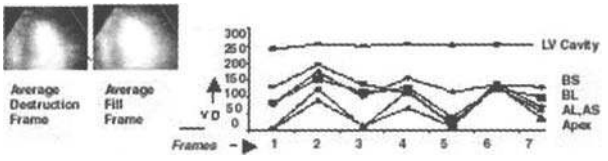
Background: Loss of correlation (LOC) at high mechanical indices (MI) causes microbubble destruction. Doppler Energy imaging detects the consequent acoustic emission. We combined this method with rapid multiple-frame triggering (MFT) to delineate myocardial opacification in patients (pts) with no previous history of myocardial infarction.

Methods: An apical 4-chamber view was obtained in 8 pts using an Acuson Sequoia system. IV infusion of 3 mL of Optison at a rate of 0.5 mL/minute was used. MFT was performed at 1:4 cardiac cycles with an average frame interval of 40 msec. Data were analyzed by video densitometry (VD) using background-subtraction (averaged fill frames minus averaged destruction frames) in five regions of interest (ROI) located in the basal septum (BS), apical septum (AS), apex, apical lateral wall (AL), and basal lateral wall (BL).

Results: The difference in VD between the averaged fill frames and destruction frames was greatest in the apex (up to 90%, SD 2%). Differences in other proximal field ROIs were: AS (up to 48%, SD 5%) and AL (up to 35%, SD 46%). Changes in distal field ROIs were: BS (up to 35%, SD 20%) and BL (up to 42%,SD 29%). In the LV cavity the difference was up to 15%, SD 3%. An example is shown below (figure). Thus, the proximal field showed efficient and reproducible effect of MFT. Substantial changes in the distal field were offset by large variations.



Conclusions: Rapid MFT combined with Doppler Energy LOC imaging produces efficient but non-uniform microbubble destruction across the imaging field. This has implications for interpretation of myocardial perfusion patterns when using this MCE technique.

361 Viable myocardium can be detected by harmonic power doppler imaging in combination with SHU 563A, a new air-filled contrast agent: a contrast echocardiographic study in a canine model of acute coronary occlusion and reperfusion

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To assess whether harmonic power Doppler [HPD] imaging in conjunction with the transvenous contrast agent SHU 563A would be useful in detecting stunned but viable myocardium, we created 2–3 hr coronary occlusion [CO] followed by reperfusion [REP] in 10 dogs. Besides continuous imaging for wall motion analysis, we employed HPD in triggered mode to assess myocardial perfusion during CO and REP. TTC staining was performed postmortem to determine the presence and size of infarction. Wall motion abnormalities (WMA), perfusion defects and TTC data were compared to each other.

Results: All 10 dogs showed WMA during CO. In 8/10 HPD detected perfusion defects. The concordance rate (by segmental analysis) between WMA and perfusion defect was 86%. After REP, the extent of WMA (%LV slice) was larger than the area of perfusion defect (% slice) (WMA 30 ± 13% vs. PD 9 ± 8%, $p < 0.01$). Eventual infarct size was only 6 ± 7%. Thus, the extent of WMA was greater than the size of perfusion defect and eventual infarct indicating the presence of stunned, but viable myocardium.

Conclusion: HPD imaging in conjunction with agent SHU 563A can demonstrate the efficacy of reperfusion, identify necrotic regions and aid in the recognition of stunned but viable myocardium. This approach could be useful clinically in patients with acute myocardial infarction undergoing reperfusion therapy.

362 Assessment of myocardial reperfusion after acute myocardial infarction using harmonic power Doppler and Levovist®: intravenous versus intracoronary contrast injection

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Myocardial contrast echocardiography (MCE) (intracoronary application) has emerged as accurate method to detect "no-reflow phenomenon" after acute myocardial infarction (AMI). In order to investigate the diagnostic value of harmonic power Doppler (HPD) after intravenous infusion of Levovist®, both intracoronary (IC) and intravenous (IV) contrast injections were performed in a group of patients with AMI.

Methods: Seventeen patients (mean age 50 ± 10) underwent MCE using HPD (HP Sonos 5500, ATL HDI 5000) with Levovist® (400 mg/ml, intravenous pump infusion, trigger intervals 1:4) and sonicated albumin (0.5–1, ml intracoronary bolus) within 7 days after their first AMI successfully reperfused (within 6 h from symptoms onset) by primary PTCA or IV r-TPA. Myocardial perfusion was assessed as present or absent using a 12 segment model (4-2-chamber apical views). A wall motion analysis was performed in the corresponding segments.

Results: Of a total of 204 segments, 37 were not analyzed after IVMCE and 43 after ICMCE because of artifacts. ICMCE showed perfusion defect in 31 segments (19%), whereas IVMCE in 33 (19%) with a concordance of 71% for the detection of no-reflow segments. Concordance in anteroseptal segments was 78%, and inferoseptal segments 66%. Using ICMCE as the standard, IVMCE had a sensitivity of 71% and a specificity of 92% for diagnosing contrast deficits. The extent of no-reflow after IVMCE was 18 ± 19 and after ICMCE was 21 ± 17 (ns). A perfusion defect was observed in 38% of akinetic segments and in 72% of dyskinetic segments with both methods.

Conclusion: IVMCE with Levovist® reliably identifies no-reflow phenomenon after successful reperfusion especially in anteroseptal AMI.

363 Contrast echocardiographic evaluation of myocardial salvage after reperfusion therapy in acute myocardial infarction

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In the experimental setting, venous myocardial contrast echocardiography (VMCE) has been shown to accurately delineate risk area during coronary occlusion and infarct size after reperfusion. We therefore hypothesized that in patients with acute myocardial infarction (AMI), myocardial salvage after reperfusion therapy can be assessed using this technique.

15 patients with AMI underwent both rest Tc 99m Sestamibi SPECT imaging (SI; pre reperfusion injection, post reperfusion imaging) and VMCE (venous infusion of Optison, intermittent harmonic imaging, off-line digital image processing with background subtraction, grey scale expansion and color coding) before reperfusion therapy (stenting n = 12, PTCA n = 3). SI, VMCE and coronary angiography follow up was performed after 14 days. Vertical and horizontal long axis views (SI) were compared with 4- and 2- chamber views (VMCE) respectively. Separate observers determined the localization of perfusion defects on SI and VMCE pre-reperfusion and categorized pre- and post-reperfusion images as demonstrating complete (2), partial (1) or no (0) myocardial reperfusion.

14/15 infarct related arteries (LAD n = 7, LCX n = 4, RCA n = 4) could be revascularized without residual stenosis (TIMI III flow). All patients had identical angiographic results at 14 days follow up. On SI, initial perfusion defect localization was anterior (n = 7), inferior (n = 5) and lateral (n = 3). Myocardial reperfusion was categorized as 2 (n = 7), as 1 (n = 5) and as 0 (n = 3). On VMCE, in 14/15 patients initial perfusion defects were localized in concordance with SI; myocardial salvage was categorized in concordance with SI in all patients.

We therefore conclude, that VMCE is a promising clinical tool for the evaluation of myocardial salvage achieved by reperfusion therapy in patients with AMI.

364 Demonstration of collateral-derived myocardial perfusion using quantitative myocardial contrast echocardiography

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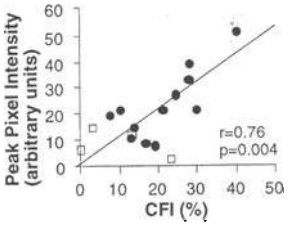
Background: Coronary collaterals supply myocardium at risk for infarction. In humans, this blood supply has never been assessed quantitatively at the perfusion level using contrast echocardiography.

Methods: In 16 patients (pts) undergoing coronary angioplasty, a collateral flow index (CFI) was determined using intracoronary wedge pressure measurements distal to the stenosis to be dilated. During ballon occlusion, echo contrast (Levovist®, Schering) was injected directly into the contralateral coronary arteries. Transthoracic echocardiography in the view best visualizing the myocardial area at risk was performed using harmonic imaging with high dynamic range. Pixel intensities (PI, units 0–255) were measured placing a hand-traced region of interest within the area at risk. Perfusion parameters were obtained from a fitted gamma-variate curve.

Results: The mean CFI was 18 ± 11%. The size of the regions of interest was 727 ± 193 pixels. In 12 pts, a significant background-subtracted peak of the gamma curve (peak) was observed (defined as peak > mean background + 2× standard deviation of background). Background-subtracted peak pixel intensity was linearly related to CFI in all pts (r = 0.68, p < 0.004.) and in the subgroup with significant peak (r = 0.76, p = 0.004).



Conclusions: A collateral-derived perfusion of a myocardial area at risk for infarction can be demonstrated using contralateral intracoronary echo contrast injections. The peak echo contrast effect is directly related to the magnitude of collateral flow.

IMAGING IN ISCHAEMIC HEART FAILURE

365 Tc-99m sestamibi and Thallium-201 retention in failing human hearts excised at transplantation

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Different mechanisms underlie cellular retention of Tc-99m-sestamibi (MIBI) and Thallium-201 by the myocardium: Thallium-201 enters the myocell via the Na^+/K^+ ATPase, while MIBI is sequestered within the mitochondrial inner matrix. We evaluated the distribution of both tracers in failing human hearts with idiopathic dilated cardiomyopathy (IDC) and ischemic heart disease (IHD) excised at transplantation, in order to assess differences in tracer uptakes as a possible expression of distinct disease mechanisms.

Methods: Six transplant candidates, 3 IDC and 3 IHD, mean age 59 ± 3 yrs, mean LVEF 18 ± 3% were injected with MIBI 15 mCi and Thallium-201 1 mCi, 1 and 3 hours before surgery, respectively. One cm-thick slices from the excised heart were imaged on a gammacamera immediately after surgery and 30 hours afterwards, to allow radioisotope cross-talk correction. MIBI and Thallium-201 retention from 16 automatically defined regions were expressed as percent of each tracer maximum regional activity. Myocardial fibrosis was assessed in samples from the same regions as percent of histologic slide area.

Results: Out of 96 myocardial segments, 75 (29 IHD, 46 IDC) showed normal uptake (>75%) of both tracers and <5% myocardial fibrosis. MIBI activity averaged 87 ± 8% in IHD vs 89 ± 8% in IDC (ns), mean Thallium-201 activity was 86 ± 10% in IHD vs 91 ± 5% in IDC (p = 0.002); mean differential activity (Thallium-201 minus MIBI) was −1 ± 7 in IHD vs 3 ± 8 in IDC (p = 0.02). Furthermore Thallium-201 and MIBI activities were linearly related in IHD (r = 0.71, p = 0.0001) but not in IDC (r = 0.25, p = 0.08).

In conclusion, a different myocardial handling of Thallium-201 and MIBI is observed in failing hearts of IDC vs IHD; this behaviour might express either increased regional Na^+/K^+ ATPase activity or altered mitochondrial function in the failing IDC heart.

366 The magnitude of improvement of LVEF post-revascularization is determined by the extent of viable tissue

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The extent of viable myocardium, needed to result in improvement of *global* LV function is unknown. We assessed the relation between the extent of viable tissue (and scar tissue) and the magnitude of improvement of LVEF post-revascularization (post-REV).

Methods: Patients (n = 32) were studied with FDG SPECT and early thallium-201 SPECT (to assess perfusion). Data were analyzed using polar maps (13-segment model). Dysfunctional segments showing normal perfusion or mismatch were considered viable. LVEF was assessed before and 3 months post-REV. Improvement of LVEF > 5% was considered significant. The optimal cutoff level (number of viable segments) to establish improvement of LVEF post-REV was determined by ROC curve analysis.

Results: A significant relation existed between the number of viable segments on FDG SPECT and the magnitude of improvement of LVEF post-REV: y = 1.5* × −0.98 (r = 0–.70, P < 0.01). No relation existed between the extent of scar tissue and the change in LVEF. ROC curve analysis results to predict significant improvement of LVEF post-REV:

Viable segments	Sensitivity (%)	Specificity (%)
≥2	100	63
≥3	94	81
≥4	75	88
≥5	44	94

Conclusion: the extent of viable tissue is closely related to the magnitude of improvement of LVEF post-REV. Considering an improvement in LVEF > 5% significant, optimal sensitivity and specificity were obtained when ≥ 3 segments were viable on SPECT.

367 Relationship between global left ventricular function and incidence of ischaemia in viable, dysfunctioning myocardium

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In patients with coronary artery disease, the progression of left ventricular (LV) dysfunction is often associated with the reduction of anginal symptoms. However, it is still to be defined whether this phenomenon actually parallels a reduction of stress-induced ischemia. This study aimed to assess the prevalence of ischemia, defined as reversibility of stress perfusion defects, in patients with significant impairment of LV function. Thallium-201 stress reinjection scintigraphy was performed in 124 patients (112 male, mean age 60 ± 9 years) with angiographically documented CAD, mean ejection fraction 0.33 ± 0.09 and previous myocardial infarction. Out of 990 segments supplied by a stenotic coronary artery 763 (77%) were scored viable. Stress (exercise or dipyridamole) imaging showed reversible defects indicative of transient ischemia in only 189 (25%) of the viable segments. To explore the relationship between incidence of ischemia and degree of dysfunction, patients were divided into two groups (with (n = 39) or without (n = 85) severe functional impairment (LVEF < 0.26). Compared with the remaining 85, the 39 patients with severe functional impairment showed a higher prevalence of NYHA III-IV dyspnea (60% vs 40%, $p < 0.05$), a lower prevalence of angina (31% vs 69%, $p < 0.05$) and a lower prevalence of ischemia in the dysfunctioning viable segments downstream from a stenotic coronary artery (18% vs 28%, $p < 0.05$). This paradoxical phenomenon was less evident when only segments with normal wall motion, supplied by stenotic arteries were considered (18% vs 22%, respetively, ns). These data confirm that reversible ischemia is relatively uncommon in patients with advanced left ventricular dysfunction, suggesting that viability rather than reversibility should guide the choice of medical treatment or revascularization. The observed low incidence of stress ischemia correlates with the dominance of heart failure symptoms and probably reflects the efficiency of the hibernation process at higher degree of LV dysfunction.

368 Enhanced diagnostic accuracy to predict improvement of LVEF post-revascularization by sequential thallium-201 imaging and dobutamine echocardiography

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Tl-201 imaging and low-dose dobutamine echo (LDDE) can predict functional outcome after revascularization (REV). While Tl-201 exhibits a relatively low specificity (Spec), LDDE shows a lower sensitivity (Sens). The aim of this study was to develop an optimal testing strategy for prediction of post-REV functional outcome.

Methods: 66 patients (LVEF 33 ± 8%) underwent LDDE and Tl-201 SPECT (rest-redistribution or 4-hour delayed imaging) prior to REV. Dysfunctional segments (Segs) with Tl-201 activity ≥ 50% or with contractile reserve were considered viable. LVEF was assessed before and 3 months post-REV.

Results: ROC curve analysis showed that the optimum criteria to predict improvement (≥5%) in LVEF after REV were ≥ 6 viable dysfunctional Segs (16-Segs model) on Tl-201 and ≥ 4 Segs on LDDE. Sens and Spec for Tl-201 were 83% and 65% and for LDDE 69% and 84%. Change of Tl-201 criteria to improve Spec to 78% (≥8 Segs) yielded a low Sens of 41% and change of LDDE criteria to improve Sens to 83% (≥2 Segs) lowered Spec to 57%. To achieve optimal Sens and Spec, 2 sequential testing strategies were explored. In strategy# 1, 27/66 (41%) patients with an intermediate (58%) likelihood of viability by Tl-201 (5–8 viable Segs) underwent LDDE study. In strategy#2, 26/66 (39%) patients with an intermediate (42%) likelihood of viability by LDDE (2–4 viable Segs) underwent Tl-201 study. Sens and Spec for strategy#1 were 88% and 81% and for strategy#2 79% and 82%.

Conclusion: Sequential testing by Tl-201 and LDDE in a subgroup of patients with an intermediate likelihood of viability by either test optimizes prediction of post-REV improvement of LVEF.

369 Prognostic value of the amount of dysfunctional but viable myocardium using Tl-201/I-123 BMIPP dual SPECT in revascularized patients with 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 severe left ventricular dysfunction using Tl-201/I-123 BMIPP dual SPECT. 76 patients with LVEF < 40% underwent dual SPECT. They were revascularized using euther CABG or PTCA and entered this study. To quantify the amount of dysfunctional but viable myocardium, both tracers uptake were scored using a 4-point system in 18-segment model. Dysfunctional but viable myocardium were defined if they exhibited the mismatch segment by at least one grade with dual SPECT images. The patients were followed up for a mean period 32 months for cardiac mortality and nonfatal cardiac events. Standard folloe-up of left ventriculography was performed 6 to 12 months after revascularization. 32 patients exhibited a large amount of dysfunctional but viable myocardium (>6 segments, group A), 28 patients had a small amount of dysfunctional but viable myocardium (2 to 6 segmaents, group B) and 16 patients were found to have irreversible damage to the myocardium (group C). Similar prerevascularization LVEF of 35 ± 5%, 34 ± 8%, 36 ± 6%, in group A, B, and C increased to 46 ± 6% ($p < 0.01$), to 40 ± 6% ($p < 0.05$), and to 36 ± 8% (n.s), respectively after revascularization. The greatest functional improvement after revascularization of group A was accompanied by a loe rate of cardiac events during follow-up and better cardiac event free survival as judged by the Kaplan-Meier survival cuirve ($p < 0.05$, vs group Band C).

In revascularized patients wuth severe LV dysfunction, the presence of a large amount of dysfunctional but viable myocardium evaluated by Tl-201/I-123 BMIPP dual SPECT identifies patients with the best prognosis.

370 Skeletal muscle I-123-metaiodobenzylguanidine scintigraphy in patients with chronic heart failure

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To determine the abnormality of the systemic autonomic nervous system caused by the chronic heart failure(HF), we assessed 123 I-metaiodobenzylguanidine (MIBG) uptake in femoral muscle.

Methods: Sixteen HF patients without diabetes (13 men and 3 women, mean age 64 ± 14 years, mean LV ejection fraction 40 ± 14%, NYHA classification... I:2, II: 8, III: 3, IV: 4) and seven healthy control subjects (5 men and 2 women, mean age 59 ± 4 years) underwent whole body scintigraphy immediately after injection of 123 I-MIBG (111 MB), and measured the planar imaging of femoral muscle 20 minutes and 4 hours after injection. After femoral muscle scanning, myocardial scintigraphy was performed, and calculated the H/M ratio-early (H/M-E) and H/M ratio-delay (H/M-D). Then, mean counts in a region of interest (ROI) surrounding the both femoral muscle was calculated 20 minutes and 4 hours after injection (FM-E, FM-D), and further, total ROI counts was expressed as a percentage of whole body counts (%FM-E,%FM-D).

Results: There was no correlation between LV ejection fraction and FM-E, FM-D, while FM-E correlated positively to H/M-E ($r = 0.56$), H/M-D ($r = 0.50$), and FM-D correlated positively to H/M-E ($r = 0.68$), H/M-D ($r = 0.64$). HF patients had lower uptake than the control group in FM-D ($p < 0.01$). Similarly, percentage of the whole body counts in HF patients was significantly lower than that in control group (%FM-E: 2.4 ± 0.5% vs 3.7 ± 1.3%, $p < 0.005$ %FM-D: 2.3 ± 0.5% vs 4.1 ± 1.3%, $p = 0.0003$).

Conclusion: Compared with the control group, HF patients had lower uptake of 123 I-MIBG in skeletal muscle, and uptake in skeletal muscle and myocardium correlated closely in patients with HF. These results suggest that patients with chronic heart failure had the abnormality of the autonomic nervous system not only myocardium but also skeletal muscle.

COMPUTER DEMONSTRATIONS

D386 Low-cost computer system for analysis of digital diagnostic coronary angiograms in view of coronary flow measurements

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Absolute coronary flow and coronary flow reserve measurements are useful for determining the functional status of coronary artery. Until recently these measurements have required an invasive techniques but in the last years some noninvasive methods like e.g. MRI are used for the assessment of coronary flow. Presented method utilises the dynamics of coronary angiograms and is based on the analysis of mean brightness curve constructed for these parts of image which present whole coronary artery or its part in motion – Mean Brightness Method (MBM). The contractual measure of blood flow – Coronary Flow Index (CFI) is percent change of mean brightness of coronary artery in unit of time (%/cycle, %/sec).

System software enables review and analysis of digital coronary images in DICOM standard from CD-R as well as from cinefilm after digitisation via cinefilm projector, video camera and framegrabber into 512 × 512 × 8 matrix. Images, digitised from cinefilm can be next archive in DICOM standard for further review and analysis. The possible speed of dynamic reviewing is from 0.5 to 30 frames per sec (in loop; forward and reverse). In view of coronary flow assessment software defines cardiac cycles, generates subtracted images of coronary arteries, normalised mean brightness curves and calculates CFI.

System software enables off-line analysis of conventional coronary angiograms, is user-friendly, requires typical PC hardware (optimal parameters: processor Pentium ≥ 350 MHz, RAM ≥ 128 MB), environments supported include Windows95, Windows98, WindowsNT.

MBM and CFI were validated with positive result in group of patients with angiographically normal coronary arteries and in patients undergoing PTCA procedure by comparing with intracoronary Doppler measurements.

In conclusion: System provides accurate assessment of coronary flow by means of digital analysis of diagnostic coronary angiograms and CFI calculation; thereby might be a promising alternative to invasive coronary flow measurements.

D387 Heart vectorcardiographical monitoring and arterial hypertension: new clinico-electrocardiologic aspects

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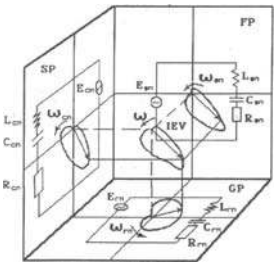
Purpose: To design simultaneous computer analysis of linear and phase electrocardiography (ECG) and integrated vectorcardiography (VCG) for monitoring of electrical remodeling (MER) of left ventricular (LV) of the heart in patients with arterial hypertension (AH).

Patients and methods: 34 healthy volunteers (17 men and 17 women) and 170 patients (85 men and 85 women) with mild AH were examined. VCG computer MER LV of hearts were carried out according to the following scheme: on admission (before treatment); after 21 days of hospitalization; on follow-up visits to the out-patient department every 3rd month within one year.

The designed spatial – volumetric 3D biophysical model of dipole electric generator of the heart is a new fundamental aspect of VCG monitoring (fig.).



New monitored ECG parameters are the following: R duration on isoelectric line, average electrosystole Q-factor of "electrical heart", de- and repolarization Q-factors.

Conclusion: Simultaneous spatial-volumetric analysis of VCG and ECG with introduction of new standard controlled parameters is fundamental modern computer technique in electrocardiology for MER LV of the heart, optimal treatment and forecast in patients with hypertension.

PEPTIDES IN VASOMOTION AND VENTRICULAR FUNCTION

P388 Adrenomedullin selectively inhibits angiotensin II stimulated aldosterone production in healthy humans

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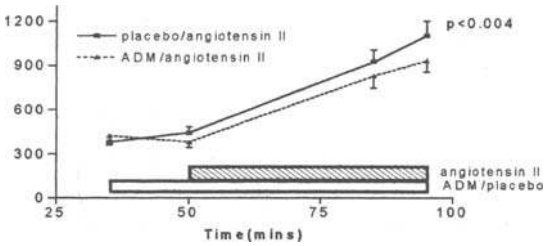
Background: Adrenomedullin (ADM) inhibits angiotensin II (AII) stimulated aldosterone production *in vitro* in experimental animals. We investigated the effect of ADM on AII and adrenocorticotrophic hormone (ACTH) stimulated aldosterone production *in vivo* in healthy humans.

Methods: 7 volunteers were studied in a quiet, temperature controlled laboratory. After 35 minutes, an infusion (placebo or ADM [3 pmol/kg/min]) was given over 60 minutes. 15 minutes after starting this first infusion, AII (10 pg/kg/min) was co-infused and continued for 45 minutes.

Results: ADM caused a small but highly significant inhibition of AII stimulated aldosterone production ($p < 0.004$). ADM did not inhibit ACTH stimulated aldosterone or cortisol release. Data are presented as mean ± SEM.



Conclusion: ADM selectively inhibits angiotensin II stimulated aldosterone production. ADM may be an important regulator of the renin angiotensin aldosterone system in health and disease.

P389 Endothelin-1-induced ventricular arrhythmias are effectively suppressed by LU135.252, the selective endothelin A-receptor antagonist

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Background: Endothelin-1 (ET-1) is the most potent vasoconstrictor peptide, which may have a direct arrhythmogenic effect, as well. The aim of our study was to investigate the role of the selective ET_A-receptor antagonist LU135.252 (LU) in protecting the heart from ET-1 induced ventricular arrhythmias.

Methods: Eighteen Na-pentobarbital anesthetized open-chest mongrel dogs were divided into two groups. In group A (n = 10) a bolus injection of 5 mg/kg LU was administered intravenously. The 30 min intracoronary (i.c.) ET-1 infusion was started 20 min after the LU bolus at a rate of 3 pmol/kg/min. In group B (n = 8) the 30 min ic. ET-1 was administered at a rate of 2 pmol/kg/min. Left anterior descending coronary artery flow (CBF), cardiac output (CO), ECG and arterial blood pressure (BP) were monitored. Two monophasic action potential (MAP) catheters were placed onto the left ventricular epicardium (LVEPI) and into the right ventricular endocardium (RVENDO) to follow electrophysiologic changes.

Results: Neither BP (0 min vs. 30 min: group A: 99 ± 4 vs. 90 ± 5 Hgmm; group B: 109 ± 7 vs. 105 ± 7 Hgmm), nor CO (0 min vs. 30 min: group A: 3.5 ± 0.7 vs. 3.2 ± 0.8 l/min; group B: 3.7 ± 0.3 vs. 3.1 ± 0.8 l/min) changed significantly, whereas a significant decrease was observed in CBF (DCBF30MIN: group A: 28 ± 2%, $p < 0.05$; group B: 35 ± 2% $p < 0.05$).

In group A ventricular fibrillation (VF) occurred once. Ventricular premature contractions and short, non-sustained ventricular tachycardic (VT) episodes were observed in 7 cases. Two animals exhibited sustained VT, moreover six died of VF in group B. The changes of MAP duration 90% (MAPD90) are presented in Table 1.

Table 1

Change of MAPD90	Control	ET 0 min	ET 30 min	p
Group A				
LVEPI	263 ± 7 ms	241 ± 11 ms	260 ± 14 ms	NS
RVENDO	242 ± 6 ms	233 ± 5 ms	239 ± 8 ms	NS
Group B				
LVEPI	190 ± 3 ms	188 ± 5 ms	208 ± 8 ms *	* <0.05
RVENDO	187 ± 6 ms	189 ± 5 ms	207 ± 10 ms *	* <0.05

Conclusion: Our results suggest, that a single bolus injection of LU effectively protects the heart from ET-1 induced malignant ventricular arrhythmias, but only partly inhibits ET-1 mediated vasoconstriction.

P390 Analogies of human and swine endothelin receptors in ventricular cardiomyocytes

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Studies are in progress to use pigs for cardiac xenotransplantation and endothelin-1 (ET-1) is potentially involved in graft rejection. The present study aimed to compare ET-1 receptor characteristics between human and swine cardiomyocytes. [125I]-ET-1 binding studies were performed with freshly isolated cardiomyocytes obtained by enzymatic digestion from left ventricles of five healthy donors, whose hearts were *not* suitable for transplatation for non cardiac reasons, and of five adult farm pigs. ETA (PD-155080) and ETB (BQ-788) selective and *non*-selective (PD-145080) receptor antagonists were used to characterize ET-1 receptor subtypes. In situ hybridization studies with specific cDNA probes (ETA, American Type Culture Collection, ATCC 105194 and ETB, ATCC 1250426) investigated the "ex vivo" cell distribution of mRNA for ETA and ETB receptors in left ventricular sections.

In both human and swine hearts [125I]-ET-1 binding reached equilibrium in about 120 min (Kobs = 0.051 and 0.049 min^{-1} respectively) and was only partially displaceable by the addition of a large excess of ET-1. In equilibrium binding studies [125I]-ET-1 had a Kd of 0.43 ± 0.08 and of 0.24 ± 0.09 nM and maximum binding (Bmax) of 42.8 ± 6.6 and of 38.5 ± 9.2 fmol/mg protein for human and swine respectively. ETA and ETB receptors are both represented in human and swine cardiomyocytes with a 85:15 ratio as indicated by the biphasic pattern of competition of both PD-155080 and BQ-788. In situ hybridization studies confirmed the prevalence of ETA at mRNA level both in human and swine left ventricular myocytes. These results showed that ET-1 binds with high affinity and poor reversibility to specific receptors, in both human and swine isolated ventricular cardiomyocytes, without significant species differences.

P391 Adrenomedullin and atrial natriuretic peptide interaction in humans

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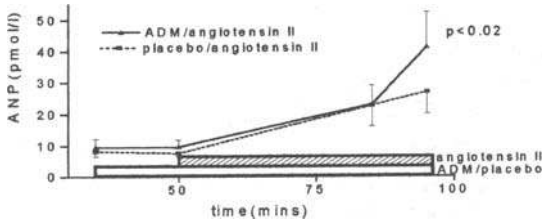
Background: Adrenomedullin (ADM) and atrial natriuretic peptide (ANP) appear to interact. In experimental heart failure infusion of ADM results in increased ANP concentrations. Conversely, systemic infusion of ANP in healthy humans increases ADM concentrations. We have investigated the effect of ADM on angiotensin II (AII) stimulated ANP in healthy humans.

Methods: 7 volunteers were studied in a quiet, temperature controlled laboratory. After 35 minutes, an infusion (placebo or ADM [3 pmol/kg/min]) was given over 60 minutes. 15 minutes after starting this first infusion, AII (10 pg/kg/min) was co-infused and continued for 45 minutes. Plasma ANP was measured at 35 (baseline), 50, 85, 95 and 105 minutes.

Results: ADM significantly augmented AII stimulated ANP production ($p < 0.02$). Data are presented as mean ± SEM.



Conclusion: Despite its vasodilator and natriuretic action, ADM significantly augmented AII-stimulated ANP concentrations in healthy humans in this study. This provides further evidence of a synergistic interaction between ADM and ANP.

P392 Omapatrilat, a vasopeptidase inhibitor, enhances baroreflex gain in spontaneously hypertensive rats

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This study sought to determine the effects of omapatrilat on basal sympathetic nervous system activity and baroreflex function in conscious spontaneously hypertensive rats (SHR) and control normotensive Wistar-Kyoto (WKY) and Sprague-Dawley (SD) rats. Omapatrilat, a vasopeptidase inhibitor, is a single molecule that inhibits neutral endopeptidase (NEP) and ACE.

Methods: Recording electrodes were surgically secured to the lumbar nerve. After 24 hr, reflex changes in lumbar sympathetic nerve activity (LSNA) that occurred during phenylephrine- and nitroprusside-induced increases or decreases in blood pressure were measured both before and during omapatrilat exposure.

Results: Baseline mean arterial pressure (MAP) was 97 ± 4 (SD, n = 6), 101 ± 3 (WKY, n = 7), and 122 ± 2 (SHR, n = 7) mm Hg, and heart rate was 428 ± 22 (SD), 356 ± 13 (WKY), and 409 ± 25 (SHR) bpm. Table shows logistic curve-fitting values in LSNA during omapatrilat exposure (mean ± SE).

		Minimum SNA	Midpoint MAP	Maximal slope (gain)
SD	Pretherapy	23 ± 6	104 ± 2	−1.29 ± 0.10
(n = 6)	Omapatrilat	21 ± 9	85 ± 3*	−1.34 ± 0.14
WKY	Pretherapy	22 ± 5	99 ± 4	−1.54 ± 0.10
(n = 7)	Omapatrilat	19 ± 5	92 ± 3	−1.69 ± 0.20
SHR	Pretherapy	27 ± 4	124 ± 3††	−1.06 ± 0.14
(n = 7)	Omapatrilat	17 ± 4	99 ± 3*†	−1.37 ± 0.11*

*$p < 0.05$ vs pretherapy; †$p < 0.05$ vs SD rats; SNA = sympathetic nerve activity; Midpoint MAP = MAP at baroreflex curve midpoint; Maximum slope = maximal slope of the baroreflex curve.

In conclusion, therapy with omapatrilat significantly increased baroreflex gain in SHR but not in SD rats, which may contribute to its antihypertensive activity. Further study is needed to assess the relative contributions of ACE vs NEP inhibitory pathways to this response.

P393 Increasing secretion of A-type natriuretic peptide induced by annexin V in the primary culture of atrial cardiocytes

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Annexin V is one of the proteins binding phospholipid calcium-ion dependently, and reported to be distributed in both the myocytes and non-myocytes of the rat heart. On the other hand, A-type (atrial) natriuretic peptide (ANP) and endothelin (ET) which are secreted by atrial myocytes and by such non-myocytes as vascular endothelial cells, respectively, have been reported to play essential roles in the control of local circulation of the heart. However, the functional significance between annexin V and those peptides still remains unknown. We, therefore, aimed to examine whether annexin V is associated with the secretion of ANP and ET in the context of the control of local circulation of the heart.

Methods: Atrial cardiocytes were dissociated from neonatal Wistar rats 5 days of age, and processed for the primary-culture. Cultured cells were divided into 2 groups as follows: (Group1) Human recombinant annexin V (rAxV) at 1 to 1,000 ng/ml or anti-annexin V antiserum (anti-AxV) were administered into the culture medium at 2 days after the dissociation, (Group 2) Anti-ET antiserum or cytosine b-D-arabino-furanoside were applied to the medium to block the function of ET, or to prevent the proliferation of *non*-myocytes, respectively, prior to the administration of rAxV as in group 1. In both groups, the amounts of ANP secreted into the culture medium were measured by radioimmunoassay at 0 to 48 hr after the administration of rAxV. In addition, ANP-immunopositive areas were examined immunohistochemically, measured morphometrically and analyzed statistically in the cultured cells.

Results: The administration of rAxV increased the secretion of ANP dose-dependently, but that of anti-AxV induced no difference in the amount of ANP secretion in group 1. In group 2, however, the administration of rAxV caused no change in the amount of secreted ANP. These results suggest that rAxV induce the increase of ANP secretion in the close relationship with non-myocytes. Immunohistochemical studies revealed that the amount of intracellular ANP was maintained at constant level, suggesting that the ANP synthesis was accelerated when the secretion of ANP was increased by the administration of rAxV to result in the constant amount of intracellular ANP.

Conclusion: Since annexin V was reported to be secreted from cultured fibroblasts, the present results suggest that annexin V is synthesized in the myocytes and/or in non-myocytes, secreted into extracellular space, and increases the synthesis and secretion of ANP from the myocytes under the influence of ET by autocrine or paracrine manner.

P394 Efficient transcription of human angiotensin II type 2 receptor gene depends on intronic sequence elements

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The angiotensin II receptor type 2 (AT2) is the predominant angiotensin II (Ang II) receptor in the human heart. AT2 probably mediates anti-proliferative and anti-hypertensive Ang II effects and its expression is upregulated in cardiac and vascular remodeling. We therefore analyzed the mechanisms that regulate the transcription of the human AT2 (hAT2) gene. For this purpose, we functionally characterized the hAT2 promoter using luciferase reporter gene assays in PC12W cells and Electrophoretic mobility shift assays. The downstream region of the hAT2 gene (exon 1 and 2, intron 1 and 2) was included into the analysis, since this region may also comprise *cis*-active DNA elements.

The hAT2 promoter region from −1417 through +100 exhibited only weak promoter activity in PC12W cells. Inclusion of the 152-bp intron 1 of the hAT2 gene in a luciferase construct containing the hAT2 core promoter (−271/+100) increased reporter gene expression 6.7 ± 1.65-fold (n = 4; p < 01). When intron 1, exon 2, and the 1.2-kb intron 2 were integrated in the promoter construct, luciferase activity was increased 11.6 ± 1.7-fold (n = 4; p < 0.01). In contrast, fusion of the spliced 5′untranslated regions of the hAT2 cDNAs to the promoter did not alter luciferase expression, which indicated that intronic sequence elements were responsible for the observed effect. Mapping of intron 1 revealed a 12-bp region, which mediated the increase in promoter activity. In gelshift assays, we identified PC12W cell nuclear proteins binding to the 12-bp sequence. Further reporter gene assays showed that intron 1 is *by itself* able to direct luciferase expression. This suggests that intron 1 may function as an alternative promoter perhaps under specific (patho)physiological circumstances.

In conclusion, intronic sequence elements are necessary for efficient hAT2 gene expression. In particular, the first intron represents a region with high regulatory potency.

STRUCTURE AND FUNCTION OF VESSEL'S WALL

P395 The biological activity of amide linked angiotensin II cyclic analogues confirms the ring clustering and charge relay bioactive conformation of all

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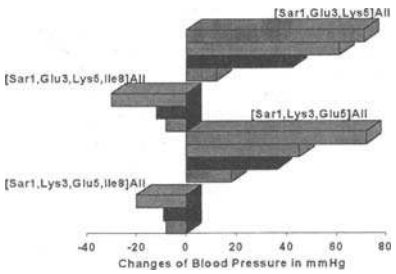
We have recently suggested that Tyr-Ile-His bend, a His-Pro trans amide bond configuration and a side chain aromatic ring cluster of the key aminoacids Tyr, His, Phe are important characteristics in the bioactive conformation of AII (J Biol Chem 269: 5303; 1994, J Med Chem 38: 4660; 1995).

Methods: To test this hypothesis novel amide linked AII-cyclic analogues with the Tyr, His, Phe ring cluster, [Sar^1, Glu^3, Lys^5] – AII and [Sar^1, Lys^3, Glu^5] – AII or without this important conformational property [Sar^1, Glu^3, Lys^5, Ile^8] – AII and [Sar^1, Lys^3, Glu^5, Ile^8] AII, were designed and synthesized by connecting the Lys amino and Glu carboxyl groups at positions 3 and 5. These analogues were then tested and compared for biological activity with the parent molecule (AII) in anesthetized rabbits under continuous blood pressure monitoring and the results are summarized in the following Figure.



Conclusion: The dose-dependent agonistic or antagonistic activity of the synthesized cyclic AII-analogues is associated with their conformational properties, as proposed in our model and provides further evidence on the importance of the charge relay system and ring clustering for AII to exert its biological activity.

P396 Inhibiton of human vascular smooth muscle cell proliferation by cyclic-adenosine monophosphate and cylcic guanosine monophosphate – an in vitro comparison of anti-proliferative signal-transduction

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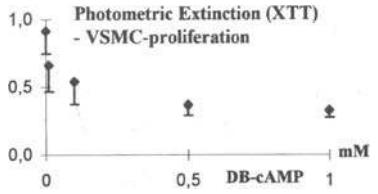
Background: Intracellular signal transduction of multiple receptors and substances in vascular smooth muscle cells (VSMC) are mediated through the activation of adenosine-and guanosine-cyclases resulting in an increase of cellular cyclic adenosine-monophosphate (cAMP) or cyclic guanosine monophosphate (cGMP). This signal transduction is also involved in the regulation of cellular proliferation and the activation of protein kinases.

Methods: VSMC were cultivated by explantation from human iliac artery and aorta. Proliferation was assessed by determination of bromodeoxyuridine (pyrimidine analogue) incorporation in DNA (BrdU), by cell number and through a terazolium-formazan assay measuring mitochondrial dehydrogenase activity (XTT).

Results: The cyclic monophosphate analogues 8-Br-cGMP and Dibutyryl-cAMP (DB-cAMP) as well as the phosphodiesterase inhibitor isobutyl-methyl-xanthine (IBMX) were incubated over different periods of time with proliferating human VSMC. DB-cAMP decreased growth to 35.6% (1.0 mM, p < 0.001), 8-Br-cGMP to 49.1% (1.0 mM, p < 0.001) and IBMX to 34.2% (1.0 mM, p < 0.001). Results from other methods (BrdU, cell count) parallel the given results.



Conclusion: Cyclic monophosphates show a time- and dose-dependent growth inhibitory effect on human VSMC in vitro, while cAMP is more effective than cGMP. This common pathway of receptor-mediated signal transduction might allow the treatment of hyperproliferative VSMC reactions in processes such as postinterventional restenosis and post-transplant vasculopathy.

P397 Homocysteine induces tissue inhibitor of metalloproteinase-1 expression in vascular smooth muscle cells

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Abnormally high levels of plasma homocysteine (HCys) have been associated with an increased risk of cardiovascular disease, although the mechanism of action is not known yet. Vascular smooth muscle cells (VSMC) have a key role in the atherosclerotic process and could be a potential target for HCys action. This study was performed to look for genes whose expression could be specifically changed by HCys in VSMC.

Primary cultures of VSMC, established from human mammary artery (h-VSMC and porcine aorta (p-VSMC), were treated or not with HCys (100 μM) and their RNA extracted. Differential display technique was used, and bands corresponding to differentially expressed genes were identified by cloning and sequencing. The specificity of the induction was confirmed by *northern blot*, with RNAs from h-VSMC and p-VSMC, treated or not with HCys.

Differential display showed a 0.9 Kb band with higher expression in h-VSMC treated with HCys. After cloning and sequencing, the fragment was identified as tissue inhibitor of metalloproteinases-1 (TIMP-1). HCys treatment induced an increase in the expression of proliferating cell nuclear antigen in quiescent VSMC. A dose-dependent increase in TIMP-1 mRNA expression after HCys treatment was observed in h-VSMC and p-VSMC.

Homocysteine induces specifically the expression of TIMP-1 invascular smooth muscle cells through an unknown mechanism. TIMP-1 induction, causing collagen and extracellular matrix accumulation, could be the key to the better understanding of the mechanisms responsible for the action of HCys as cardiovascular risk factor.

P398 Vitamin C reduces oxidative stress induced by maximal exercise and improves arterial distensibility in healthy subjects

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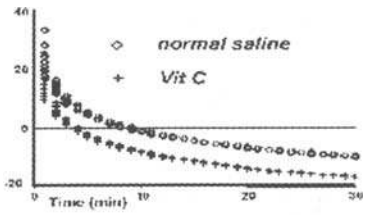
Maximal exercise induces oxidative stress. We hypothesised that this may reduce large artery distensibility (via reduced NO bio-availability) with potential adverse effects on cardiovascular efficiency – changes that may be prevented by the free radical scavenger Vitamin C (Vit C).

Methods: 8 healthy male volunteers performed exhaustive bicycle exercise on 2 occasions, randomly assigned to either intravenous Vit C (2 g) or normal saline (placebo). For 15 minutes pre and 30 minutes post exercise we measured 1) pulse wave velocity (PWV, inversely related to arterial distensibility) in the upper limb using oscillometry (QVLTM, SciMed, UK) from transit times of pressure waveforms between 2 cuffs for 15 seconds every minute and 2) blood pressure (BP – Finapres, Ohmeda) continuously. Lipid-derived free radicals (FR) were measured ex vivo pre and post exercise by electron paramagnetic resonance spectroscopy.

Results: PWV was increased immediately after exercise but fell below baseline levels by 10 minutes following placebo, describing a curve as shown in the figure. Vit C shifted the curve downwards (mean difference ± SEM, 10 ± 3.5%, 95% CI: 1.9–18.2, p = 0.02) without changing BP pre, during or post exercise compared to placebo. FR increased after exercise with placebo (50 ± 17% rise, p < 0.05) and Vit C abolished this increase.



% changes in PWV cf. rest.

Conclusions: Arterial distensibility is transiently reduced following maximal exercise and increases later in the recovery period. Pre-treatment with Vitamin C reduces the exercise-induced oxidative stress and improves arterial distensibility. In cardiovascular disease states where oxidative stress is increased, these adverse effects seen in health may be exaggerated, suggesting a potentially important role for antioxidant therapy.

P399 The insertion/deletion polymorphism within the angiotensin converting enzyme and reactivity of isolated resistance arteries

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An insertion-deletion polymorphism within the angiotensin converting enzyme (ACE) gene is associated with a 26% increase in risk of myocardial infarction. The aim of this was to determine whether the ACE polymorphism produced function differences in local resistance arterial reactivity.

Method: 242 resistance arterioles were excised from the margin of colonic specimens resected for adencarcinoma from 70 patients (mean age 64 ± 2 years). Vessels were loaded onto a small vessel wire myograph at a resting tension equivalent to 100 mgHg mean arterial pressure. Vessel viability was assessed by contraction >0.5 mN mm to KCl (100 mM) and >50% relaxation to acetylcholine (0.1 μM). The ACE I/D polymorphism was assayed by PCR amplification.

Results: 27 subjects were DD, 28 ID, and 15 II. Vessel contraction to angiotensin I (0.1 nM–0.1 μM) was not altered by ACE genotype (Emax DD 4.4 ± 0.6 mN/mm: ID/II 4.4 ± 0.7 mN/mm, p = 0.99). Contraction to angiotensin II (0.1 nM–0.1 μM) did not depend upon genotype (Emax DD 4.5 ± 0.5 mN/mm, p = 0.66). In order to exclude the possibility that non-ACE conversion of A I in the isolated arteries was concealing a difference between ACE polymorphisms, contraction to the ACE-specific substrate, proline10 angiotensin I (1 nM–0.1 μM) was assessed. No difference was seen (Emax DD 2.6 ± 0.3 mN/mm; Emax ID/II 2.1 ± 0.3 mN/mm, p = 0.21). Specificity of proline10 A I for ACE confirmed by abolition of contraction in the presence of the inhibitor captopril 1 mmol/L (2.04 ± 0.3 mN/mm v 0.007 ± 0.12 mN/mm, p = 0.0001). Chymostatin-sensitive A II generating enzyme was not found to be an important ACE-independent source of A II in the arteries used, since chymostatin did not reduce maximum contraction to A I (Emax 2.1 ± 0.3 mN/mm v 1.8 ± 0.4 mN/mm, p = 0.5). As expected ACE genotype was a predictor of serum ACE levels, with the highest occurring in association with the D allele. However, there was no correlation between the serum level of ACE and the EC50 for A I (r = 0.08, p > 0.2), A II (r = 0.08, p > 0.2), nor proline10 A I (r = 0.09, p > 0.2).

Conclusion: The I/D polymorphism within the ACE gene is not associated with a difference in arterial contractility despite differences in level of serum ACE. No difference in contractility is found even after exclusion of non-ACE conversion of AI.

P400 The importance of endocardial endothelium on the effects of db-cAMP on the calcium content in the isolated right ventricle of rat heart

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The specific functional morphological features of the endocardial endothelium suggest the possibility that this adjustable physicochemical barrier may selectively regulate the exchange of substances and ions

Methods: Experiments were performed on the isolated right ventricle of the rat heart with the intact and without endocardial endothelium. Endocardial endothelium was damaged by brief immersion of right ventricle in 1% dilute detergent solution of Triton X-100 in Krebs-Ringer. Immediately after preparation, the ventricle was suspended in a bath for isolated organs with Tyrode's solution that was bubbled with 95% O_2/5% CO_2. Contractions were induced with square wave impulses of twice the diastolic threshold and a duration of 5 ms at a frequency of 1 Hz. After the stabilization period db-cAMP (Sigma, USA) in a concentration of 3×10^{-4} moll/l, was added into the bath and contractions were registrated for another 30 minutes. After that, the ventricle was removed from the bath and the lower part of the ventricle was taken, minced and dried at 105°C to constant weight, and then the tissue was extracted. Calcium was determined by the atomic absorber, from the appropriate dilutions of the extracted tissue,

Results: The obtained results show that the control values of the calcium content in the myocardium of the right ventricle with the intact endocardial endothelium was 35 mmoll/l while in the myocardium without endocardial endothelium it was 125 mmoll/l. Db-cAMP, in the applied concentration, in the experimental group, in the presence of endocardial endothelium caused mild increase (39 mmoll/l, p > 0.05), but in the group without endocardial endothelium significant decrease (54 mmoll/l, p < 0.05) of the content of myocardial calcium, in comparison with the control group.

Conclusion: The effects of db-cAMP on the content of myocardial calcium are different depending on the presence of endocardial endothelium.

P401 Calcitonin gene-related peptide-induced vasodilation does not depend on the activation of potassium channels in man

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Aims: *In vitro* experiments suggest that potassium channels (K-channels) contribute to CGRP-induced vasodilation. It was investigated in man whether ATP sensitive K-channels (K_{ATP}-channels) or calcium sensitive K-channels (K_{Ca}-channels) are involved in the vasodilation induced by CGRP.

Methods: Venous occlusion plethysmography was used to measure the forearm blood flow (FBF) response to increasing infusion rates of CGRP (3-10-30 ng/min/dl forearm) into the brachial artery of 24 healthy subjects. Dose-response curves were constructed before and during the co-infusion of placebo (NaCl 0.9%, n = 8), the K_{ATP}-channel blocker glibenclamide (2 μg/min/dl forearm, n = 8) and the K_{Ca}-channel blocker tetra-ethyl-ammonium chloride (TEA, 0.1 mg/min/dl forearm, n = 8). Forearm vascular resistance (FVR) was calculated (FVR = mean arterial pressure/FBF) and presented as percentage change from baseline in FVR (ΔFVR). Dose-response curves were compared using ANOVA with repeated measures and Wilcoxon's matched-pairs signed-rank tests. Data are presented as mean ± SEM.

Results: CGRP (n = 24) increased FBF from 2.4 ± 0.2 at baseline to 4.9 ± 0.4, 8.0 ± 0.7 and 12.2 ± 1.1 ml/min/dl forearm, respectively (p < 0.001). ΔFVR during the first co-infusion of CGRP and placebo (−51 ± 4, −66 ± 5 and −75 ± 5%) did not differ from ΔFVR during the second co-infusion of CGRP and placebo (−43 ± 5, −68 ± 4 and −80 ± 3%). ΔFVR during co-infusion of CGRP with glibenclamide (−36 ± 3, −61 ± 3 and −81 ± 2%) or TEA (−37 ± 2, −64 ± 3, −82 ± 2%) was comparable to ΔFVR during CGRP with placebo.

Conclusions: The intra-brachial infusion of CGRP results in a dose-dependent and repeatable increase in FBF. In contrast to *in vitro* experiments, CGRP-induced vasodilation *in vivo* seems not to be mediated by ATP sensitive or calcium sensitive potassium channels in man.

P402 Abnormal vascular function in patients with pre-dialysis renal failure

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Patients with chronic renal failure (CRF) are at 10- to 20-fold increased risk of cardiac death and mortality when compared to matched non-uraemic controls. Endothelial dysfunction plays a key early role in the development of atherosclerotic vascular disease (AVD). The vascular response to nitrates, independent of the endothelium, is also abnormal in patients with atheroma.

Methods: We studied 80 patients (mean ± SD age 61.9 ± 12.2 years, 58 men) with non-diabetic renal failure (serum creatinine, SCr, range 136 to 747 umol/L) and 26 healthy age and sex-matched controls (mean ± SD age 59.9 ± 14.0 years, 17 men). Endothelial function was assessed using high-resolution ultrasonography to measure flow-mediated endothelium-dependent dilatation (EDD,% change) of the brachial artery following reactive hyperaemia. Endothelial independent dilatation (EID,% change) was also assessed following sublingual glyceryl trinitrate. The patients were divided into those with and without clinically apparent AVD.

Results: Although CRF patients had significantly impaired EDD compared to controls, there was no difference between CRF patients with and without AVD. Within the CRF group, EDD was not significantly different in patients in the upper and lower quartiles of calculated GFR (2.8 ± 2.6% v 3.5 ± 3.7%). EID was also reduced in CRF suggesting impaired smooth muscle response to nitric oxide.

Results

	Control	CRF No AVD	CRF Overt AVD	All CRF
N	26	51	29	80
SCr (umol/L)	97 ± 12	279 ± 124	273 ± 130	277 ± 125
GFR (ml/min)	77 ± 21	31 ± 15	30 ± 12	31 ± 14
EDD (%)	6.7 ± 2.8	3.5 ± 3.1***	1.9 ± 2.8***	2.9 ± 3.1***
EID (%)	14.8 ± 4.8	11.0 ± 4.5**	10.3 ± 4.7**	10.8 ± 4.5***

mean ± sd ** $p < 0.01$ *** $p < 0.001$ vs. controls

Conclusions: Vascular function is abnormal in CRF, even in patients with biochemically mild renal insufficiency and patients without AVD, suggesting that subclinical AVD is present early in the development of renal failure.

P403 Angiotensin II increases superoxide production in human internal mammary artery but not saphenous vein

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Purpose of study: In experimental animals angiotensin II (AII) exerts some of its vascular actions by stimulating NAD(P)H oxidase mediated superoxide ($^{\bullet}O_2^-$) production. We have determined whether AII increases $^{\bullet}O_2^-$ production in human blood vessels.

Methods: Human internal mammary artery (IMA) and saphenous vein (SV) were obtained during coronary artery bypass surgery. They were divided into 0.5–1 cm segments and incubated at 37 °C in hepes buffer in the absence (control (CTRL)) and presence of AII (10^{-6} M, 10^{-9} M, 10^{-12} M) for 4 hours and for different time periods (15 mins, 1 and 4 hours) with AII 10^{-6} M. Norepinephrine (NE) was used as a positive control. $^{\bullet}O_2^-$ production was quantified using lucigenin chemiluminescence in a liquid scintillation counter.

Results: Mean ± SEM superoxide production (pmol/mg/min)

	IMA (n = 29)		IMA (n = 11)		IMA (n = 14)
CTRL	927 ± 114	CTRL	1360 ± 293	CTRL	1550 ± 346
AII	1591 ± 210	AII	2285 ± 502	AII	2060 ± 384
10^{-6} M	$p < 0.002$	10^{-9} M	$p < 0.0065$	10^{-12} M	$p < 0.1$

Time	15 min (n = 11)	1 hour (n = 10)	4 hour (n = 29)
CTRL	1173 ± 239	1331 ± 232	927 ± 114
AII	918 ± 170	2572 ± 708	1591 ± 210
10^{-6} M	$p < 0.2$	$p < 0.05$	$p < 0.002$

There was no increase in $^{\bullet}O_2^-$ production in either SV (n = 8) incubated with AII 10^{-6} M, or IMA (n = 8) incubated with NE 10^{-6} M for 4 hours.

Conclusion: These results show, for the first time in human arteries, that AII increases $^{\bullet}O_2^-$ production. Diseases states associated with increased AII production, such as heart failure, may be associated with increased free radical production and vascular oxidative stress.

P404 Impact of medium-term balloon inflation during active coronary perfusion on endothelial morphology and endothelin-1 metabolism

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Background: Coronary restenosis after PTCA plays a crucial role in clinical routine. One candidate for the induction of restenosis is endothelin 1 (ET1) with subsequent proliferation of coronary media and intima. This study evaluated the impact of low pressure balloon inflation on coronary morphology and ET1-metabolism.

Methods: In 12 landrace pigs a perfusion balloon-catheter (2.5 mm diameter) was introduced in the left anterior descending coronary artery (LAD) and inflated with 1.2 bar. After active perfusion over 30 min. the balloon was withdrawn. Pre, during and 30 min. after the end of perfusion blood samples were taken from the ascending aorta and the great cardiac vein. After 3 months the pigs were sacrificed and the LAD segments with prior contact to the balloons (LADB) and a reference segment, taken from the right coronary artery (RCA), were analysed with a selective ET1-PCR for ET1-mRNA expression. From the histologic samples the area of coronary media and intima/neointima was assessed.

Results: In 8 pigs intimal proliferation in the LADB could be detected (0.1 ± 0.06 mm^2 vs 0 mm^2; $p < 0.0004$ compared to RCA), the media/lumen-area ratio remained unaltered in those segments. There was no difference between ET1 concentration in the great cardiac vein and the aortic root pre, during and after 30 min. of perfusion. ET1-PCR (light-cycler) showed no significant difference in mRNA transcript-level between LADB and RCA.

Conclusion: Low pressure balloon inflation can induce coronary intima-proliferation without evidence of increased ET1-metabolism. However, the clinical relevance of this finding is uncertain.

P405 Hypoxia induces heat shock protein expression in human coronary artery bypass grafts

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Background: Heat Shock Proteins (HSPs), present in the vascular wall, are molecular chaperones which are essential for cell survival. Heat shock and hypoxia markedly increase the expression of several HSPs, especially the inducible Hsp70 isoforms. In our study, we investigated whether HSPs are in principle inducible in human coronary artery bypass grafts.

Method: We used remnants of the saphenous vein (SV) and the internal mammary artery (IMA) from 29 patients undergoing coronary artery bypass surgery. Each vessel was devided into segments, one for control conditions at 37°C (5% CO_2/95% air), the remaining ones for thermal (30 min at 42°C) or hypoxic treatment (6 h oxygen deprivation with nitrogen). The expression of Hsp60, Hsp72 and Hsp73 was investigated by immunohistochemistry and western-blot analysis.

Results: Immunohistochemically, segments of the SV undergoing a 30 minutes heat shock at 42°C showed significantly increased expression of Hsp72 in the intima ($p = 0.0354$) and Hsp73 in the media ($p = 0.0033$). In the IMA, Hsp72 and Hsp73 were both expressed in the intima at significantly higher levels ($p = 0.0416$ each). The results were further confirmed by western-blot analysis in a representative vein (7.5fold increase of Hsp72 and a 2.3fold increase of Hsp73 expression). A 6 hour oxygen deprivation resulted in elevated levels of Hsp60 (media: $p = 0.0478$), Hsp73 (intima: $p = 0.0294$) and Hsp72 (intima: $p = 0.0002$ and media: $p = 0.0038$) in the SV (western-blot analysis of Hsp72: 2fold, 1.5fold and 3.5fold increased, on average 2.3fold). Hypoxia enhanced Hsp73 expression in the intima of the IMA ($p = 0.0478$).

Conclusion: Our results clearly demonstrate that hypoxia strongly increases HSPs expression in human coronary artery bypass grafts. The marked increase of the inducible form of the Hsp70 family in the saphenous vein was most striking. Heat treatment was an effective inducer of Hsp72 and Hsp73 expression in both, saphenous vein and internal mammary artery.

P406 Homocysteine-induced endothelial superoxide anion production is associated with upregulation of superoxide dismutase activity

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Elevated plasma levels of homocysteine (HC) are associated with endothelial dysfunction, the induction of oxidative stress by HC having been postulated as a causative mechanism in this process. We have therefore studied the effect of HC on cultured porcine aortic endothelial cell (PAE) superoxide anion (O_2^-) production as a marker of oxidative stress, and the ability of the PAE to control their natural anti-oxidant defences in response to this pathological insult.

Methods: Confluent PAE monolayers (first passage) were incubated at 37°C for 24, 48 and 72 hours in the absence or presence of HC (1 mM), fresh HC being added to the appropriate cells every 24 hours. Following incubation, some cells were trypsin (0.05% w/v)-digested and harvested for the measurement of O_2^- production by lucigenin-chemiluminescence in the presence of triton X-100. The integral of each response represents the total O_2^- produced and is expressed as mV.s/million cells. Superoxide dismutase (SOD) activity was then measured spectrophotometrically in lysates from the rest of the cells using a method based on the ability of the enzyme to inhibit the auto-oxidation of pyrogallol. All data is expressed as mean ± s.e.m. and n = 5 or greater.

Results: In the absence of HC, baseline O_2^- production did not alter with time (19.4 ± 2.2, 19.2 ± 2.3 & 16.7 ± 0.7 mV.s/million cells after 24, 48 and 72 hours respectively). Exposure to HC resulted in a significant ($p < 0.001$) increase in O_2^- production after 24 hours (65.8 ± 4.0 mV.s/million cells), which although still significant ($p < 0.001$) declined after 48 hours (42.0 ± 2.3 mV.s/million cells). After 72 hours, even in the presence of HC, O_2^- production returned to baseline levels (18.9 ± 1.6 mV.s/million cells). Again, in the absence of HC, baseline SOD activity did not alter with time (3.4 ± 0.7, 4.0 ± 0.8 & 2.7 ± 0.4 U/mg protein after 24, 48 and 72 hours respectively). However, SOD activity was significantly elevated ($p < 0.001$) following exposure to HC for 72 hours (8.9 ± 1.3 U/mg protein).

In conclusion, these data demonstrate that exposure to HC induces significant, and time-dependent increases in endothelial O_2^- production that are accompanied by an increase in SOD activity. Endothelial cells are therefore capable of acutely upregulating their natural antioxidant defences in response to the induction of oxidative stress.

P407 Has transforming growth factor beta I cytoprotective properties in heavy smokers with intact endothelial function?

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Some patients do not exhibit atherosclerosis despite cardiovascular risk factors. An effect of transforming growth factor beta 1 (TGF-β1) on endothelial NO-synthase (eNOS) and in the development of atherosclerosis has been suggested. In the present study, we used our new human in-vivo model to assess NO-mediated endothelial function (EF) of lower extremities, a vascular bed more relevant to atherosclerosis than the commonly examined forearm vessels.

In 44 clinically healthy individuals (21 to 59 years), 20 smokers and 24 controls, matched for age and sex, EF was assessed by reactive hyperaemia (peak flow (PF) and late hyperaemic reaction (LHR)) with venous occlusion plethysmography (VOP) (in ml/100 ml tissue/min), and by intraarterial stimulation with the endothelium-dependent NO-stimulator acetylcholine (A). Concentrations of TGF-β1 were measured from citrate plasma with an ELISA taken from the femoral vein.

Overall, smokers showed a 32% lower PF in VOP in response to A (10.8 vs. 15.9, $p < 0.05$), as well as 58% lower LHR (2.8 vs. 4.8, $p < 0.05$). A decline of PF with age was seen in controls ($r = -0.5$, $p < 0.05$). The *older* subgroup (>45 years) of smokers presented with nearly double high PF (14.9 vs. 8.4, $p < 0.05$) than age-matched controls, and with a higher LHR than younger smokers (6.2 vs. 2.1, $p < 0.01$). Even a positive correlation between pack-years and LHR was found ($r = 0.62$, $p < 0.005$). Similar TGF-β1 concentrations were found comparing all smokers and controls (3.2 vs. 2.5 ng/ml). However, smokers with preserved EF showed higher TGF-β1 than those with impaired EF (3.7 vs. 1.2 ng/ml, $p < 0.0005$). There was even a strong correlation of TGF with EF in smokers ($r = 0.77$, $p < 0.0005$), but not in controls. TGF-β1 did not correlate with age in either group.

Our new method confirmed age- and risk factor-related endothelial dysfunction. Stringent inclusion criteria promoted a selection of a subgroup of smokers with an unexpectedly intact endothelium, superior to age- and sex-matched controls as to younger smokers. A strong correlation of TGF-β1 with endothelial function was found only in smokers, suggesting this cytokine to actively maintain normal physiological function of endothelial cells. Since control individuals lack this correlation, a *direct* influence of TGF-β1 on availability of NO under physiological conditions seems unlikely. Identification of individuals with intact endothelium despite risk factors provides a new approach of our understanding of atherosclerosis.

P408 Homocysteine-induced endothelial superoxide anion production is inhibited by tetrahydrobiopterin and folate

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Increased oxidative stress and the inactivation of nitric oxide (NO) have been postulated as causative mechanisms in homocysteine (HC)-induced endothelial dysfunction. A reduction in essential co-factors for NO synthesis secondary to the induction of oxidative stress may lead to impaired NO activity. We have therefore studied the effect of co-factor supplementation on HC-induced superoxide anion (O_2^-) production by cultured porcine aortic endothelial cells (PAE).

Methods: PAE were incubated at 37°C for 24 hours in the absence or presence of either HC, cysteine (CYS) or glutathione (GT, all 1 mM) or HC with either tetrahydrobiopterin (BH4, 0.5 mM, an essential co-factor for NO production), methyltetrahydrofolate (MTHF, 0.5 mM, the active circulating form of folate, also involved in intracellular BH4 regeneration) or folic acid (FA, 0.5 mM, involved in HC metabolism). Following incubation, the cells were trypsin (0.05% w/v)-digested and then harvested for the measurement of O_2^- production by lucigenin-chemiluminescence in the presence of 1% (v/v) triton X-100. The integral of each response represents the total O_2^- produced and is expressed as mV.s/million cells, and all data is expressed as mean ± s.e.m., n = 8 or greater.

Results: In the absence of any intervention, baseline O_2^- production was 21.0 ± 2.4 mV.s/million cells. This level was unaffected by incubation with either CYS or GT. However, exposure to HC resulted in a significant ($p < 0.001$) increase in O_2^- production (53.4 ± 2.9 mV.s/million cells). Furthermore, this HC-induced increase in O_2^- production was completely inhibited ($p < 0.001$) by BH4, MTHF and FA (15.8 ± 1.6, 24.2 ± 3.3 and 17.5 ± 1.0 mV.s/million cells respectively)

In conclusion, these data demonstrate that (a) HC-induced increases in O_2^- production are not a non-specific effect of thiol-containing compounds and (b) addition of BH4, MTHF and FA inhibits the HC-induced effect. This inhibition may be a direct antioxidant effect or may involve augmented NO production due to the increased availability of NO synthase co-factors, eg. BH4 itself.

P409 Chronic renal failure impairs endothelial cell viability and enhances proliferation

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Patients with chronic renal failure are more likely to develop atherosclerosis when compared to age and sex matched controls. Endothelial injury is thought to represent one of the earliest stages in the development of atherosclerosis. These experiments were designed to determine whether uraemia may contribute directly to vascular damage.

Fresh serum was collected from 36 patients with pre-dialysis chronic renal failure and 36 healthy controls. Serum samples were heated to inactivate complement and added to sub-confluent human umbilical vein endothelial cells grown in multiwell plates. Cell viability was assessed by estimating the capacity of endothelial mitochondria to metabolise a tetrazolium salt to a blue formazan product, the development of which was measured by spectrophotometry. Incorporation of tritiated thymidine into nuclear DNA was used to estimate cell proliferation rate. The results shown below represent cells grown in 20% human serum and are expressed as a percentage of values obtained under standard growth conditions (20% foetal calf serum).

Results

	Controls	Renal failure	Significance
Patient age	60.0 (33.5–68.5)	56.0 (48.5–62.5)	NS*
Sex (M:F)	20:16	17:19	NS**
Viability (%)	79.9 (66.2–87.7)	66.2 (62.8–76.5)	0.006*
Proliferation (%)	197.0 (168.5–216.0)	222.2 (209.3–261.7)	0.001*

median (inter-quartile range) * Kruskal-Wallis ** Chi-squared

When compared to serum from normal controls, uraemic serum was more toxic to endothelial cells and stimulated a greater increase in the rate of cell division. These data suggest that in patients with chronic renal failure, the endothelium may be more vulnerable to injury and responds by cellular proliferation. This process may result from exposure to circulating uraemic toxins and could directly contribute to the development of premature vascular disease.

P410 Plasminogen activator and plasminogen activator inhibitor expression in vascular culture

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We have studied the expression of tissue-type plasminogen activator (t-PA) and its inhibitor (PAI-1), which regulate fibrinolysis and are relevant to the process of tissue remodelling, in organ cultures of human saphenous vein (HSV) and coronary endarterectomy tissue (CEA).

Methods: HSV and CEA samples were obtained from patients undergoing coronary artery surgery, and cultured for up to 14 days. The expression of t-PA and PAI-1 in tissue cultures was investigated using immunohistochemical, biochemical (Elisa; Western blotting) and molecular (RT-PCR) techniques.

Results: Immunostaining showed basal levels of t-PA in preculture controls. t-PA antigen expression increased in vascular cultures. PAI-1 immunostaining was intense in controls but declined in postculture tissue. Immunoblotting of vascular extracts revealed an up-regulation of t-PA and a down-regulation of PAI-1 antigen expression in HSV culture confirming the findings from the immunohistochemical study. RT-PCR demonstrated that the relative amounts of mRNA encoding t-PA increased ($P < 0.05$) while PAI-1 decreased ($P < 0.05$) in 10 days postculture tissue.

Conclusion: Local expression of t-PA is up-regulated while that of PAI-1 down-regulated during SMC proliferation in tissue culture. A down-regulation of PAI-1 mRNA is in contrast to the situation in complex human atheroma. We suggest that this crucial difference may be due to the inflammatory cells in the vessel wall.

P411 Isolation of Chlamydia pneumoniae-specific T lymphocytes from atheromatous plaque

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Chlamydia pneumoniae (Cpn) infection has been implicated in the pathogenesis of atheroma, but its role is unclear. Since atheroma plaques contain activated T cells, we have determined whether any of these cells have specificity for Cpn.

Methods: T cell lines were generated from plaque material from 14 carotid endarterectomy patients. T cell lines were readily established by culture with IL-2 and either recall antigens or PHA; IL-2 alone was not sufficient.

Results: Although PHA was more effective than recall antigens ($p < 0.05$) in establishing T cell lines from plaques, each of three recall antigens – tetanus toxin (TT), PPD and Chlamydia trachomatis (Ct, used as a source of chlamydial antigens) was equally effective. When the specificity of the T cell lines was examined in proliferation assays, PPD-specific lines predominated in cultures initially stimulated with PHA. In cultures initially stimulated with PPD or TT, the frequency of TT- or PPD-responsive lines was similar, whereas Ct-responsive lines were less common ($p < 0.05$). Conversely, initial stimulation with Ct resulted in predominantly Ct-specific lines ($p < 0.05$). Ct-responsive lines were expanded and further characterized by stimulation with recombinant Cpn or Ct antigens, including OMP-2 and hsp60. Several lines responded to one or more of these antigens.

Conclusions: The atheromatous plaque contains memory T lymphocytes with various specificities, including C. pneumoniae. Whether Cpn-specific T cells are present at higher frequency in plaques than in PB, and whether they show evidence of activation by Cpn in the plaque remains to be investigated.

P412 Dehydroepiandrosterone relaxes rabbit coronary arteries by a calcium antagonistic mechanism

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Epidemiological studies demonstrate an inverse association between levels of DHEA (3-b hydroxy-5-androsten-17-one) and cardiovascular mortality in men, but not in women. The effects of DHEA on the coronary vasculature is unknown, therefore we investigated the effect of DHEA on rabbit coronary arteries in vitro. Epicardial coronary arterial rings of male and female rabbits were suspended in organ baths for measurement of changes in isometric tension. DHEA (3, 10, 30 mM) induced significant relaxation of coronary arterial rings precontracted with K^+ (30 mM) in a dose-dependent manner (mean ± SEM; 24.6 ± 3.6, 47.0 ± 3.9, and 86.1 ± 4.2% respectively, $P < 0.001$) compared with control (3.2 ± 1.5, 4.2 ± 1.5, 5.1 ± 1.5; n = 11). Relaxation to DHEA at lower concentrations (0.3, 1 mM) was not significant. There were no differences between arteries from male or female rabbits (n = 10; $P > 0.05$), or between rings with or without endothelium (n = 8–12; $P > 0.05$). L-NAME (n = 10), ICI 182,780 (a specific estrogen receptor antagonist n = 6) and barium chloride (n = 7) did not affect DHEA-induced relaxation compared with control rings with an intact endothelium (n = 8; $P > 0.05$). Calcium concentration-dependent contraction curves (4, 3.5, 3, 2.5 and 2 – log M calcium) in K^+ depolarization medium were shifted to the right after incubation with DHEA (10 mM) (8.9 ± 5.2, 21.6 ± 6.7, 48.0 ± 5.1*, 79.5 ± 4.3** and 99.9 ± 2.6% contraction respectively; *$P < 0.05$; **$P < 0.01$) compared to control (10.7 ± 2.9, 35.0 ± 4.9, 66.2 ± 3.1, 86.2 ± 6.4 and 100 ± 0.0% contraction respectively). Maximal contraction was not reduced however. We have demonstrated that DHEA induces significant relaxation in isolated rabbit coronary arteries independent of the endothelium and nitric oxide. Potassium channels are unlikely to be involved.

ADULT CARDIOVASCULAR PATHOLOGY

P413 Effect of intracellular acidification on free intracellular Mg^{2+}: an ETH 7025-Mg^{2+}-ion-selective microelectrode study on guinea pig papillary muscle

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The assessment of free, ionised, intracellular Mg^{2+} ($(Mg^{2+})_i$) in myocardial tissue is problematic and its metabolism has not been well understood as yet. This, for example, makes the design of trials on therapeutic use of Mg (e.g. LIMIT II and ISIS 4) difficult and the interpretation of conflicting results almost impossible.

Here, we assess the effect of changing intracellular pH (pH_i; measured with pH-selective microelectrodes) on cytoplasmic $(Mg^{2+})_i$ using a newly designed Mg^{2+}-selective microelectrode with the neutral carrier ETH 7025) and measure $(Mg^{2+})_i$ in isolated resting guinea pig papillary muscle (Tyrode, pH 7.4, 36°C; for details of method see our earlier work – J Physiol 431, 713–41, 1990 and Pflügers Arch 423, 338–42, 1993).

We find that changing extracellular pH for 15 minutes from 7.4 to 6.4 leads to a change of intracellular pH from 7.19 ± 0.03 to 6.81 ± 0.06 (n = 7; ± SEM for all exp.). This change of pH_i leads to a small, but detectable rise in $(Mg^{2+})_i$ by a maximum amount of 0.19 ± 0.06 mM from an initial value of 0.73 ± 0.08 mM after approximately 7 minutes, followed by a slow decrease of $(Mg^{2+})_i$ to almost normal. This would amount to a liberation of 1.5% of the cells total Mg content, assuming that $(Mg^{2+})_i$ constitutes 1/17 of the cells total Mg (J Physiol 224, 121–39, 1972).

In summary, we find that intracellular acidification liberates $(Mg^{2+})_i$ from intracellular binding sites. The transient nature of the observed $(Mg^{2+})_i$ rise further suggests, that the levels of cytoplasmic $(Mg^{2+})_i$ are well regulated and even small changes in $(Mg^{2+})_i$ are adjusted within short time.

P414 Decreased expression of insulin-like growth factor-I is associated with apoptosis of vascular smooth muscle cells in the human atheromatous plaque

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Insulin-like growth factor-I (IGF-I) plays an important role in survival of vascular smooth muscle cells (VSMCs) as well as in cell cycle progression and in migration of VSMCs.

Methods: In order to determine whether the specific localization of IGF-I is related to the localization of apoptotic cells in human aortic atherosclerotic lesions, IGF-I was determined using both immunocytochemical techniques and in situ hybridization. Alpha-smooth muscle (SM) actin, vimentin (a marker of dedifferentiated cells), and apoptotic cells were detected immunocytochemically or by the TUNEL assay.

Results: Microscopic analysis revealed that the expression of IGF-I was significantly lower in the intima just adjacent to the lipid pool, including the shoulder part of the plaque, as compared to the fibrous cap of the atheromatous plaque or the medial layer, which is compatible with the findings of in situ hybridization.

Comparison of the IGF-I labeling pattern with immunostaining for alpha-SM actin and vimentin showed that the intima close to the lipid pool contains areas characterized by poor or absent expression of IGF-I regardless of positive staining for alpha-SM actin and vimentin. In parallel serial sections, the TUNEL assay detected the presence of apoptotic cells in the regions with poor expression of IGF-I.

In conclusion, since IGF-I is a potent survival factor for VSMCs, its absence in areas close to the lipid pool and particularly in the shoulder region might be associated with apoptotic changes and predispose these regions to fissuring and plaque rupture.

P415 Differential development of hypoxia-induced pulmonary hypertension and right ventricular hypertrophy in transgenic mice with various deficiencies in the plasminogen/plasmin system

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Background & Aim: Hypoxia results in the development of pulmonary hypertension and right heart failure. The precise molecular mechanisms involved in the pathogenesis of hypoxia-induced pulmonary vascular remodeling are unknown, but several observations point to a potentially important role of the plasminogen system. Aim of this study was to investigate the development of pulmonary hypertension and vascular remodeling in mice with targeted disruption of genes of the plasminogen system.

Methods: Mice with a deficiency of tissue-type plasminogen activator (t-PA$^{-/-}$), urokinase-type plasminogen activator (u-PA$^{-/-}$), u-PA receptor (u-PAR$^{-/-}$), or plasminogen (plg$^{-/-}$), and wild-type (WT) mice were subjected to hypoxia (FiO_2 10%), whereas for each group control mice were kept under similar but normoxic conditions. Adult and neonate mice were placed under hypoxia for 28 and 10 days, respectively.

Main results: Hypoxia caused a significant 2.5-fold rise in right ventricular (RV) pressure in WT mice, associated with a 1.8-fold increase in RV weight. Deficiency of u-PA completely prevented this increase in RV pressure and hypertrophy, whereas t-PA$^{-/-}$ mice showed changes that were comparable with WT mice. Plg-deficient mice did also not develop pulmonary hypertension and RV hypertrophy and u-PAR$^{-/-}$ mice showed an intermediate reponse, indicating that the u-PA effect is in part mediated by the u-PA receptor. Histological analysis revealed that hypoxia induced an increase in smooth muscle cells within distal arterial walls and loss of peripheral vascular density in the lungs of WT mice, as evidenced by a 2-fold increase in the ratio of media thickness over vascular diameter and a 54% reduction in arteries per 100 alveoli. In u-PA$^{-/-}$ and plg$^{-/-}$ mice this vascular remodeling was completely blunted.

Conclusion: In the development of pulmonary hypertension, RV hypertrophy and pulmonary vascular remodeling, u-PA appears to play a pivotal role. Plg$^{-/-}$ mice showed a similar lack of response to hypoxia, suggesting that in the development of these changes u-PA acts by conversion of plasminogen to plasmin. The essential role of the plasminogen/plasmin system as a mediator of the adaptive response to chronic hypoxia and in the occurrence of hypoxic pulmonary vascular disease might be a point of impact for eventual future, novel therapeutic strategies.

EXCITATION–CONTRACTION COUPLING

P416 Effects of isoproterenol in phospholamban-deficient mouse hearts with altered thyroid states

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The aim of the present study was to determine the effects of beta-adrenergic stimulation in phospholamban-deficient (PLB-KO) mouse hearts with altered thyroid conditons. Examination of the beta-myosin heavy chain protein expression revealed similar increases in hypothyroid wild-type (WT) and PLB-KO hearts, while the alpha-myosin heavy chain levels were downregulated in both WT and PLB-KO hypothyroid hearts, as compared to their respective euthyroid controls. Quantitative immunoblot analysis of the cardiac SR Ca-ATPase tissue levels revealed significant increases in hyperthyroidism and decreases in hypothyroidism compared with euthyroidism, and these changes were similar between PLB-KO and WT hearts. An opposite trend was observed for PLB expression levels in the WT group, which were depressed (69%) in hyperthyroid hearts but increased (133%) in hypothyroid hearts. To examine whether the observed changes in SR calcium handling proteins were reflected in altered cardiac function, contractile parameters were assessed in isolated work-performing hearts. Hypothyroidism was associated with significantly depressed basal contractile parameters in both WT and PLB-KO hearts, when compared to their respective euthyroid controls. Increased basal contractile function was observed in the hyperthyroid WT hearts, while no further enhancement in the contractile parameters of the hyperdynamic PLB-KO hearts was noted in the hyperthyroid condition. During isoproterenol stimulation of WT hearts, the responses in the rates of contraction and relaxation were highest in the hypothyroid group, followed by the euthyroid and lastly by the hyperthyroid groups. Furthermore, there was a close linear correlation between the magnitude of the contractile parameter responses and the PLB/SERCA ratios in these WT hearts. However, the PLB-KO hypothyroid, euthyroid and hyperthyroid hearts did not exhibit significant responses to isoproterenol. Since the changes in SERCA, alpha- and beta-myosin heavy chains were similar in PLB-KO and WT hearts, under various thyroid conditions, the lack of isoproterenol response appeared to be due to ablation of PLB in the PLB-KO hearts. These findings suggest that PLB is an important regulator in the heart's responses to beta-adrenergic stimulation not only in the euthyroid myocardium, but also under various thyroid states.

P417 Functional difference of K_{ATP}-channels in young and adult rabbit hearts

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Objective: Age dependent differences in conductance and density of K_{ATP} channels have been demonstrated. We previously found that the K_{ATP}-channel opener cromakalim, at concentrations not causing action potential shortening, caused significant SR calcium depletion in ventricular myocytes of adult rabbits, suggesting presence of K_{ATP}-channels in the SR membrane. The aim of the present study was to investigate whether there is also age dependency of K_{ATP}-channel opening on SR calcium content.

Methods: Calcium transients and SR calcium content were measured in indo-1 loaded electrically stimulated (2 Hz) ventricular myocytes from young (7 weeks old, mean body weight 1.8 kg, 11 cells from 3 rabbits) and adult (>14 weeks old, mean body weight 3.0 kg, 16 cells from 6 rabbits) rabbits (37°C). SR calcium content was estimated from the change of cytosolic calcium following rapid cooling (RC) to 1°C. Each myocyte was stimulated for 5 minutes, subjected to RC, allowed to recover from RC for 5 minutes, subsequently treated with cromakalim (10 μM) during 5 minutes and again subjected to RC.

Results: Control transient amplitudes were not significantly different between groups. 10 μM cromakalim did not shorten action potentials. Calcium transient amplitude as well as SR calcium content were significantly reduced by cromakalim in adult, but not in young rabbits as shown in the table (all data expressed as % of control transient amplitude, mean ± SEM).

	Control RC	Recovery amplitude	Cromakalim amplitude	Cromakalim RC
Young (n = 11)	292 ± 25	106 ± 6	85 ± 5	259 ± 29
Adult (n = 16)	245 ± 15	97 ± 6	59 ± 3#§	131 ± 11#§

#p < 0.0001 adult versus young; §p < 0.0001 cromakalim versus control

Conclusion: Cromakalim, at a concentration not causing action potential shortening, substantially reduces calcium transients and SR calcium content in adult, but not in young rabbits. This suggests late expression of SR-specific K_{ATP}-channels.

P418 S100A1 increases intracellular Ca^{2+} transients of cultured neonatal cardiomyocytes as a paracrine factor

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S100A1 is a new regulatory protein of myocardial contractility increasing contraction and relaxation velocity as well as cell shortening in adult rat cardiomyocytes. Since S100 proteins have also been described as paracrine factors being involved in cell differentiation, it was the aim of this study to determine the effects of S100A1 as a culture medium additive on intracellular Ca^{2+} transients in cultured rat neonatal cardiomyocytes.

Recombinant S100A1 protein (2 μM) was added to culture medium every other day. On Day 5 and day 7 cells were loaded with FURA2PE3AM and intracellular Ca^{2+} transients measured under electric field stimulation (0.5–1 Hz). With S100A1 we observed a significantly increased velocity of cytosolic Ca^{2+} elimination ($-\Delta c/\Delta t$ +20%; $p < 0.015$) on day 5 compared to controls. Additionally, on day 7 there was a significant increase of systolic SR Ca^{2+} release ($+\Delta c/\Delta t$; +30%; $p < 0.01$) as compared to control cells.

These data show for the first time that recombinant S100A1 protein acts as a paracrine factor evoking similar effects on intracellular Ca^{2+} transients as seen after adenoviral overexpression of this Ca^{2+} binding protein. Since S100A1 is being expressed in embryogenesis as early as on day 9 our findings imply that S100A1 might represent a differentiation factor in foetal cardiogenesis.

P419 Regional dependent differences in the activity of the Na^+/Ca^{2+}-exchanger in human non-failing myocardium

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To test the hypothesis that the contribution of the Na^+/Ca^{2+}-exchanger (NCX) to the intracellular Ca^{2+}-homeostasis in human cardiomyocytes is different in atrial versus ventricular myocardium, we investigated the regional pattern of protein expression by immunoblot and the time dependent (1–60 s) and Ca^{2+}-dependent (0.3–1000 μM) activity by Na^+-dependent vesicular Ca^{2+}-uptake of the NCX in 14 human nonfailing hearts. The protein expression of the NCX was significantly lower in left atrial (LA) compared to left ventricular myocardium (LV) (0.5 ± 0.1 vs. 1.0 ± 0.2). This was paralleled by a reduced NCX-activity in myocardial vesicles from LA ($t_{1/2}$ 7.9 ± 1.5 vs. 2.5 ± 0.3 s). When measuring the NCX activity at different Ca^{2+}-concentrations (t = 3 s), we found a reduced maximal activity of the NCX in LA (0.78 vs. 1.02 nmol/mg protein * 3 s) and a reduced affinity of the NCX towards Ca^{2+} (K1/2 67μmol/l vs. 45 μmol/l).

These data indicate that the protein abundance and maximal activity of the NCX in left atria is reduced as compared to left ventricle. Interestingly, also the affinity of the NCX towards C^{2+} is reduced in left atria, indicating that structural or functional differences of the NCX are present. It is concluded, that the contribution of the NCX to the intracellular Na^+ and Ca^{2+}-homeostasis is different in atrial and ventricular myocardium.

P420 Contractile remodelling in human atrial fibrillation: lack of response to Bay K 8644

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Background: After the cessation of atrial fibrillation (AF) the mechanical function of the atria is reduced (contractile remodeling). Altered intracellular Ca^{2+} handling and myolysis have been proposed to underlie this phenomenon.

Methods: We studied the positive inotropic effect of Ca^{2+}, the L-type Ca^{2+} channel agonist Bay K 8644 and isoprenaline (Iso) on thin isolated trabeculae of right atrial appendages of patients undergoing mitral valve repair. 11 patients were in sinus rhythm (SR), whereas 10 had developed chronic (≥6 month) AF. Force of contraction was measured under isometric conditions at a stimulation frequency of 1 Hz at 37°C (baseline conditions).

Results:

	Mean force of contraction (mN/mm²) ± SEM			
	baseline	Ca^{2+} 12 mM	Bay K 8644 10 μM	Iso 1 μM
SR n = 11	3.1 ± 0.3	7.4 ± 0.5#	7.3 ± 0.1#	7.5 ± 0.7#
AF n = 10	0.6 ± 0.1*	6.7 ± 0.7#	0.7 ± 0.1*	4.6 ± 0.6#*

*: $p < 0.05$ AF versus SR, #: $p < 0.05$ versus baseline.

Conclusions: 1) Since the maximal achievable force of contraction at a high extracellular Ca^{2+} concentration was only slightly smaller in AF patients myolysis is not the prevailing mechanism of contractile remodeling in AF patients. 2) The lack of response to Bay K 8644 in AF patients suggests either a downregulation or an altered function of the L-type Ca^{2+} channel. 3) The reduced β-adrenergic responsiveness in atrial myocardium of AF patients might be explained by altered expression or function of the L-type Ca^{2+}-channel.

P421 Synchronization of rigor contracture in end-to-end connected cardiomyocites

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During myocardial ischemia or anoxia, depletion of ATP to critical levels results in rigor contracture, followed by Ca^{2+} rise and progression of cell injury. In situ cardiomyocytes are efficiently connected to each other through specialized connections including gap junctions that communicate the cytoplasm of adjacent cells. Although cytosolic changes associated to energy depletion including acidosis and Ca^{2+} rise, have been described to produce uncoupling, some of these changes, specially Ca^{2+} rise occur only after rigor onset. The purpose of this study was to investigate whether cell-to-cell communication may allow synchronization of the onset of rigor contracture in cardiomyocytes. The time to onset of rigor shortening, its time course, and the changes in the cytosolic Ca^{2+} (fura2) and Na^+ (SBFI) concentrations were analyzed in isolated adult rat cardiomyocytes submitted to simulated anoxia (metabolic inhibition 2 mM NaCN at extracellular (pHo) of 7.4) or ischemia (pHo = 6.4). The changes observed in end-to-end connected cell pairs resulting from incomplete dissociation were compared with those observed in pairs of non-connected cells. The experiments were performed at 37°C on the stage of an inverted microscope connected to a ratiofluorescence image system. Rigor contracture appeared after 20.4 ± 1 min of energy depletion at pH 6.4, and after 15.3 ± 1.3 min at pH 7.4, without differences between connected and separated cells, and resulted in a homogeneous reduction of cell length of 28.6 ± 1%. The onset of rigor contracture in non-connected cell pairs was asynchronous, with a mean difference of 180 ± 174 sec at pH = 7.4, and 306 ± 66 sec at pH = 6.4. However, there was a marked synchronization in the onset of rigor in connected cell pairs, with a mean difference of 6.4 ± 1.4 sec and 9.8 ± 4.2 sec at pH 7.4 and 6.4 respectively ($p < 0.001$ respect the corresponding values in non-connected cell pairs), and an excellent correlation between the time of onset in the 2 cells ($r = 0.99$ and $r = 0.99$ respectively at pH 7.4 and 6.4). Ca^{2+} rise occurred after rigor onset in all cells, and was virtually identical in connected cells but largely variable in separated cells. Na^+ rise preceded rigor onset, and its time course was also superimposable in connected cells and largely variable in separated cells. It is concluded that intercellular communication synchronizes the progression of ischemic injury in adjacent cardiomyocytes, even in the presence of acidosis.

P422 Role of FKBP12.6 in excitation-contraction coupling in rabbit ventricular myocytes

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The cardiac ryanodine receptor (RyR2) is tightly associated with the FK-506 binding protein FKBP12.6. However, the function of FKBP12.6 in excitation-contraction coupling (E-C coupling) processes in cardiomyocytes is poorly understood.

We used adenovirus-mediated gene transfer to overexpress the human FKBP12.6 gene (Ad-FKBP12.6) together with green fluorescent protein (GFP) as a reporter gene in isolated rabbit ventricular myocytes.

Contractile function of Ad-FKBP12.6 infected myocytes was analysed by a video edge detection-system after 24 h (weak expression of the transgene) and 48 h (strong expression of the transgene) and compared with control (Ad-GFP) infected myocytes. The data are summarised in the following table.

	24 h		48 h	
	Ad-GFP	Ad-FKBP12.6	Ad-GFP	Ad-FKBP12.6
Fractional shortening (%)	4.2 ± 0.2 (*P = 0.07 *vs.* Ad-GFP)	4.8 ± 0.2* (*P = 0.07 *vs.* Ad-GFP)	3.6 ± 0.1 (*P < 0.01 *vs.* Ad-GFP)	4.3 ± 0.1* (*P < 0.01 *vs.* Ad-GFP)

Stimulation frequency 2 Hz; [Ca^{2+}] 1.8 mM; Ad-GFP, n = 48; Ad-FKBP12.6, n = 58.

At 48 h post transfection, myocyte shortening was significantly increased by 18% in FKBP12.6 overexpressing cells as compared with control transfected myocytes. This study demonstrates a direct role of FKBP12.6 in E-C coupling in cardiac myocytes.

P423 Interruption of the positive sarcoplasmic reticulum load-frequency relationship in guinea pig cardiac myocytes occurs prior to demonstrable spontaneous calcium release

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Myocardial tissue of most mammalian species, including human, demonstrates a positive force-frequency relationship, meaning that developed force (or cell shortening, or sarcoplasmic reticulum (SR) load in isolated cells) increases as stimulation frequency increases. However as one reaches high stimulation frequencies, or under other conditions which increase intracellular calcium levels, developed force may start to decrease. At about this point aftercontractions (ACs), caused by spontaneous release of calcium from the SR, are frequently noted, and it has been hypothesized that the decline in systolic mechanical function is the direct result of ACs. We investigated this relationship further by direct measurement of SR load in isolated guinea pig left ventricular myocytes following drive trains. Cells were impaled with microelectrodes and subjected to rapid application of caffeine under voltage clamp conditions, following conditioning drive trains but before the onset of ACs. The resulting inward charge movement was used to calculate SR load. Cell shortening during the final stimulus of the drive train and delay from caffeine application to the onset of an inward current were also recorded, as surrogate measures of SR load. Measurements were taken after drive trains of 0.2 Hz, 0.5 Hz, at threshold frequency for ACs, and at maximal frequency. Directly measured SR loads, normalized to load at 0.2 Hz, were as follows (mean ± SEM (n)): 0.5 Hz, 1.5 ± 0.3 (14)*; threshold frequency, 1.1 ± 0.2 (12); maximal frequency, 1.5 ± 0.1 (19)* (*$p < 0.05$). The other two surrogate measures of SR load yielded identical "N shaped" curves, with a decline in load at threshold frequency. Cell edge detection records indicated that there had been no ACs during the drive train or prior to the caffeine application, and further experiments using caffeine applications at different times following the final stimulus showed no decline in SR load between drive train and AC. We therefore conclude that the positive load-frequency relationship is interrupted at frequencies which lead to ACs before there has been any evidence of spontaneous SR release.

P424 Ca^{2+} handling and sarcoplasmic reticulum Ca^{2+} content in isolated human atrial myocardium

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Nonfailing human ventricular myocardium is characterized by a frequency-dependent increase in twitch force (positive force-frequency relation) and a rest-dependent increase in twitch force (post-rest potentiation). This physiological behavior is paralleled by increases in intracellular Ca^{2+}-transients due to increases in sarcoplasmic reticulum (SR) Ca^{2+}-content. Whether human atrial myocardium shows a similar behavior is unknown.

Methods: Isolated muscle strips from human atria (n = 10), electrical stimulation, isometric contractions, 37°C. Increase in stimulation rates (0.25–3 Hz), rest-intervals (1–240 s). SR Ca^{2+}-content was measured by rapid cooling contractures (RCCs) as index for SR Ca^{2+}-content. To test for the relative contribution of SR Ca^{2+}-ATPase vs. Na^+/Ca^{2+}-exchange to cytosolic Ca^{2+} elimination we used paired RCCs: After brief rewarming after RCC1 a second RCC (RCC2) tests for the amount of Ca^{2+} taken up by the SR at the end of RCC1. In another set of experiments, intracellular Ca^{2+}-transients were measured with the Aequorin-method.

Results: In atrial human myocardium, twitch force frequency-dependently increased by 157 ± 38% (3 vs. 0.25 Hz; $p < 0.05$) which is paralleled by an increase in SR Ca^{2+}-content by 44 ± 14% ($p < 0.05$). Intracellular Ca^{2+}-transients increased by 80 ± 17% ($p < 0.05$). With increasing stimulation frequency RCC2/RCC1 increased from 41 ± 7 at 0.25 Hz to 57 ± 7% at 3 Hz ($p < 0.05$). When increasing rest intervals, post-rest twitch force decreased by 68 ± 5% and SR Ca^{2+}-content by 49 ± 10% ($p < 0.05$).

Conclusions: In atrial human myocardium, the positive force-frequency relation is due to increased intracellular Ca^{2+}-transients and SR Ca^{2+}-content. The SR Ca^{2+}-ATPase competes more effectively with Na^+/Ca^{2+}-exchange at increasing stimulation frequencies. In contrast, at long rest intervals SR Ca^{2+}-content decreases resulting in the post-rest decay of twitch force.

P425 Total calcium handling assessed from mechanoenergetics in a beating left ventricle: integrative analysis

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Purpose: We aimed to assess total Ca handling in excitation-contraction coupling (ECC) in a beating left ventricle (LV). To this end, we have developed a new integrative analysis method. The method utilizes the internal Ca recirculation fraction (RF) and O_2 cost of contractility (Emax).

Methods: We obtained RF from the time constant (t_c) of the exponential decay component of the postextrasystolic potentiation. We obtained the O_2 cost of Emax from LV O_2 consumption (Vo_2) at different Emax levels. Our equation calculated the unknown total Ca handling, futile Ca cycling and Ca reactivity of Emax from the measured RF and Vo_2 for ECC.

Results: The representative results in canine cross-circulated LVs are listed below. The calculated total Ca handling fell between 31 and 111 μmol/kg. This range is comparable to the literature data obtained by in vitro biochemical methods using excised myocardium. These total Ca values are two order of magnitude higher than the well-known Ca transient (free Ca concentration) values obtained by Ca indicators.

Measured cardiac mechanoenergetics and the calculated Ca handling parameters

Treatment	Measured				Calculated			
	Emax (mmHg/ml/100 g)	Vo_2 for ECC (ml O_2/beat/100 g)	O_2 cost of Emax: Ca Vo_2/Emax	t_c (beats)	RF	Futile Ca cycling	Ca reactivity: Emax/Total Ca	Total Ca (μmol/kg)
Control	4.7	0.011	0.00234	1.9	0.55	0#	0.12	40
Ca	11.3	0.029	0.00257	2.3	0.62	0*	0.10	111
Eplnephrine	10.8	0.028	0.00259	1.8	0.54	0*	0.11	102
Control	7.8	0.013	0.00167	2.7	0.67	0#	0.15	53
Ca overload	5.0	0.009	0.00180	3.5	0.71	0*	0.13	37
Control	4.2	0.015	0.00357	1.9	0.55	0#	0.075	56
Ryanodine	2.3	0.013	0.00565	1.4	0.45	1.4	0.075*	31
Control	7.4	0.015	0.00203	2.4	0.63	0#	0.13	54
Stunnlng	4.2	0.013	0.00310	1.3	0.43	0*	0.10	44
Stunning	4.2	0.013	0.00310	1.3	0.43	1.2	0.13*	33

(#: assumed to be zero in control. *: assumed to be unchanged from control)

Conclusion: The present method for the first time has enabled assessment of major parameters of ECC Ca handling in a beating LV. These data had not been available by any conventional methods. Our integrative analysis method may be useful to better understanding of the pathophysiology of total Ca handling in a beating heart.

P426 The effects of changes in pHi on cell contraction, Ca transients and the Ca sensitivity of myofilaments in rat ventricular myocytes: study with dual-loading method of indo-1 and SNARF-1

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The objectives of this study were to develop the method to measure Ca transients (CaT), pHi and cell length simultaneously, and to examine the effects of pHi on CaT, cell contraction and the Ca sensitivity of myofilaments.

Method: In order to measure $[Ca]_i$ and pHi, microscopic fluorescent measurements were carried out in isolated rat ventricular myocytes dual-loaded with indo-1/AM (10 μM) and SNARF-1/AM (5 μM). Cell length was measured from the bright-field image. Intracellular acidosis or alkalosis were induced by propionate (20 mM) or NH_4 < Cl (15 mM), respectively.

Result: The method was validated since there was no interaction between each indicator and in vivo calibration curves of Ca and pH from dual- and single-loaded myocytes were not different. The amplitude of twitch cell shortening and CaT, and pHi in control myocytes were 5.0 ± 0.7 μm, 468.8 ± 42.6 nM, and 7.27 ± 0.07, respectively. NH_4Cl induced an intracellular alkalosis (pHi 7.66 ± 0.08) and significantly increased the twitch cell shortening (10.5 ± 1.3 μm) without a change in the amplitude of CaT (377.0 ± 70.2 μM). Propionate induced an intracellular acidosis (pHi 6.89 ± 0.08) and significantly decreased the twitch cell shortening (2.1 ± 0.6 μm) without a change in the amplitude of CaT (471.9 ± 90.4 μm). The effects of pHi on the Ca sensitivity of myofilaments were assessed with phase-plane analysis of cell length and $[Ca]_i$. Propionate or NH_4Cl shifted the trajectories to the rightward or to the leftward, respectively. The shift of the trajectories by intracellular alkalosis was larger than that by acidosis. The ratios of% changes in twitch cell shortening to% changes in CaT (CS/CaT:1.0 in control) were calculated to estimate the Ca sensitivity of myofilaments. Propionate decreased the CS/CaT (0.48 ± 0.06) whereas NH_4Cl increased the CS/CaT (2.97 ± 0.56). In order to compare the relative influence of intracellular acidosis and alkalosis to the Ca sensitivity of myofilaments, CS/CaT was divided by the change of pHi in each individual myocyte (CS/CaT/delta-pHi:an index reflecting the change in the Ca sensitivity by unit change in pHi). CS/CaT/delta-pHi in myocytes exposed to NH_4Cl was significantly larger than the index in myocytes exposed to propionate (8.1 ± 1.5 vs 1.8 ± 0.4).

Conclusion: CaT, pHi and cell length could be simultaneously measured with dual-loading method of indo-1 and SNARF-1. Intracellular acidosis decreased the Ca sensitivity of myofilaments while alkalosis increased the Ca sensitivity of myofilaments. The relative influence of changes in pHi to the Ca sensitivity of myofilaments was larger in intracellular alkalosis.

P427 Soluble mediator released from postischaemic reperfused rat hearts reduce Ca^{2+} transient and contractility by blocking the L-type Ca^{2+} channel

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We have recently reported that after myocardial ischemia (IS) during reperfusion (R) a cardiodepressant mediator is released from isolated hearts. The mediator is very small (<1 kD), soluble, stable up to 24 hours and not a protein. Aim of the present study was to elucidate mechanisms of the cardiodepressant effect.

Methods: After 10 min global ischemia of isolated rat hearts the coronary effluent was collected during the first 30 sec of reperfusion and was diluted with experimental buffer 1:2, 1:4, 1:8, and 1:16. This effluent induced a concentration-dependent reduction in cytosolic Ca^{2+} transients and cell shortening in field stimulated isolated rat ventricular myocytes loaded with Fluo-3-AM. At a dilution of 1: 4, the effluent caused a 46% reduction of cell shortening and a 26% reduction of cytosolic Ca^{2+} transients. To elucidate the underlying mechamism, we investigated the effect of the postischemic effluent on L-type Ca^{2+} channel current. In voltage-clamped myocytes, the effluent (dilution 1:4) reduced the peak L-type Ca^{2+} current by 54%: an effect resulting from reduced maximal conductance, and not from changes in voltage- and time-dependent gating. When undiluted, the effluent completely blocked contractions, Ca^{2+} transients and Ca^{2+} currents.

Conclusion: Cardiodepressant mediators released from isolated hearts after ischemia during reperfusion reduce Ca^{2+} transients and cell contractions via a block of L-type Ca^{2+} channels.

P428 Blunted positive inotropic response to endothelin-1 in rabbit ventricular myocytes overexpressing protein kinase Cε

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Protein kinase C (PKC) is discussed to be involved in e-c coupling processes in cardiomyocytes. By means of adenovirus-mediated gene transfer we overexpressed PKCε in rabbit ventricular myocytes. Infection of isolated myocytes with increasing virus titers resulted in a dose-dependent increase in PKCε protein expression accompanied by a >20-fold increase in basal PKCε kinase activity at a multiplicity of infection of 100.

Contractile behaviour of PKCε overexpressing myocytes was analysed by a video edge detection-system 48 h post transfection. As compared with control (Ad-LacZ) infected myocytes, basal fractional shortening increased significantly by 21% in Ad-PKCε transfected myocytes. Interestingly, the positive inotropic effect of endothelin-1 (ET-1) was completely abolished in Ad-PKCε transfected myocytes. The data are shown in the following table.

	Ad-LacZ	ET-1	Ad-PKCε	ET-1
Fractional shortening (%)	1.9 ± 0.8 ($^*P < 0.05$)	$2.9 \pm 0.4^*$	$2.3 \pm 0.8^*$ ($^*P < 0.05$ *vs.* Ad-LacZ)	2.3 ± 1.0 ($^*P < 0.05$ *vs.* Ad-LacZ)

1 Hz; $[Ca^{2+}]$ 2 mM; Ad-LacZ, n = 29; Ad-PKCε, n = 36; [ET-1] 10^{-9} M.

Myocyte shortening in response to Angiotensin II was unchanged in Ad-PKCε *vs.* Ad-LacZ infected myocytes.

These data demonstrate a direct involvement of PKCε in ET-1 signal transduction pathway.

P429 Contracting human myocardium in multi-day cell culture

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Functional studies of many different human cell types have been successfully conducted under in vitro conditions. Despite many efforts, it has not been possible to develop either a stable human or animal cardiac myocyte cell line or a human primary culture in which contractile functionality can unambiguously be studied over several days. We hypothesize that by mimicking the in vivo situation in an in vitro environment we can preserve viability and function of human myocardial preparations over several days. From explanted hearts of patients undergoing cardiac transplantation, small (average diameter < 0.5 mm) multicellular myocardial preparations (n = 11) were dissected. Preparations were mounted in a custom build, sterile muscle chamber, in a modified culture medium containing 1.75 mM Ca^{2+}, pH of 7.4 and 37° C. Muscles were stimulated at 0.5 or 1 Hz and were kept contracting isometrically for at least 48 hours and up to 6 days. Our data show that contractile function of human myocardial tissue can be preserved over several days, allowing for continuous measurements of myocardial function ex vivo; active force development after 48 hours was 11.4 ± 2.8 mN/mm^2 and had not changed significantly from the initial value of 10.6 ± 1.2 mN/mm^2 at t = 0. Diastolic tension also remained unchanged, from 0.9 ± 0.1 mN/mm^2 at the start of the experiment to 1.0 ± 0.1 mN/mm^2 after 48 hours. After at least 48 hours, the contractile response to stimulation with 1 μM Isoproterenol was clearly present: developed force increased to 631 ± 146% of control values, while half-relaxation time declined to 57 ± 6% of control (n = 7). This implies that not only the entire signal transduction cascade including beta-receptors, protein kinases and cAMP are functionally preserved, but also demonstrates the presence of cardiac reserve in these preparations. After 2–6 days of continuous contractions the cultured preparations still behave similar to the in vivo situation, while also regulatory physiological (like post-rest potentiation and force-frequency relationship) and pharmacological responses are well preserved. This technique now allows studying regulation of contractile function of human myocardium in vitro and can be used in a variety of research areas because correlation between changes in protein expression (including application of gene-transfer) and consequent changes in function can now be directly examined.

P430 Inositol 1,4,5-trisphosphate receptors in cardiac myocytes: isoform expression, subcellular localisation and physiological function

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Increased intracellular Ca^{2+} levels have been suggested to mediate cardiac hypertrophy, but the mechanism of this Ca^{2+} increase is not established. Many cardiovascular hormones inducing hypertrophy, such as angiotensin-II (AT-II) and endothelin (ET), are coupled to the inositol 1,4,5-trisphosphate Ca^{2+} release channels (InsP3R). We therefore investigated the isoform specific expression and subcellular localisation of InsP3Rs in rat heart. The hormonal modification of Ca^{2+} release from sarcoplasmic reticulum was examined by real-time confocal imaging with the Ca^{2+} indicator fluo-3.

Ratiometric PCR analysis indicated that isolated ventricular and atrial myocytes almost exclusively expressed InsP3R type II mRNA, while aortic endothelial cells and Purkinje fibres mainly contained type I mRNA. [^{3}H]InsP3 binding and Western blot analysis showed that atrial myocytes expressed 5-fold higher levels of InsP3R protein than ventricular myocytes. These findings were substantiated by a higher InsP3-induced Ca^{2+} release in permeabilised atrial as compared to ventricular myocytes. Probing of Purkinje fibres with isoform specific antibodies against InsP3Rs showed a strong positive staining for InsP3R type I. Ventricular and atrial myocytes stained mostly with InsP3R type II antibodies in the perinuclear region. In the atrial cells additional InsP3R type II was found as a punctated staining pattern in the sub-sarcolemmal region. Double labelling of atrial myocytes for InsP3Rs and RyRs revealed a co-localisation of these two Ca^{2+} release channels. Stimulation of atrial myocytes, but not ventiricular myocytes, with InsP3-mobilising agonists (ET, AT-II and phenylephrine), increased the frequency of Ca^{2+} sparks in the sub-sarcolemmal and perinuclear region. Sparks frequently triggered waves generating action potentials. After inhibiting RyRs with a high concentration of ryanodine (100 mM), we observed very small (~30 nM) and brief (lifetime ~66 ms) Ca^{2+} release signals most likely originating from single or a few InsP3Rs. Inhibition of InsP3Rs with xestospongin C (10 mM) suppressed any effect of hormonal stimulation.

This study revealed the potent role of InsP3-generating hormones in regulating Ca^{2+} signalling in cardiac myocytes. InsP3Rs were able to trigger Ca^{2+} sparks by activating co-localised RyRs. The sparks induced Ca^{2+} waves generating spontaneous electrical activity. The localisation of InsP3Rs in the perinuclear area suggests an involvement of these channels in the regulation of gene expression.

P431 Acute ischaemic asynchronic segmental motion: is this passive motion or active contraction? A segmental velocity versus strain and strain rate imaging study

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Implanted microcrystals have shown segmental diastolic thickening to occur in acute ischemia in open chest animals. This phenomenon has been linked to viability. Diastolic thickening can now be produced in an animal model using PTCA circumflex occlusion.

Aim of the study: To determine whether this thickening represents a passive event or active contraction, segment motion was analysed pre during and post PTCA occlusion by a combination of M mode, Doppler Myocardial Imaging (DMI) and Strain (S) and Strain Rate (SR) parameters

Methods: Radial S and SR' values were calculated for ischemic segments (LV short axis view) for a 20 sec PTCA circumflex occlusion in 7 consecutive closed chest pigs. S, SR and DMI velocity data were collected (178 fps) and compared to wall thickening M-mode and segmental DMI velocity data for the ischemic segment (posterior basal). Peak values, integrals and time duration of both velocity (Vel) and strain rate (SR) curves were computed for both systolic (I) (pre, during, and post occlusion) and diastolic (II) wall thickening phases (during occlusion). Mitral valve opening (MVO) was used as a reference to monitor changes in global diastolic function.

Results: Ischemic segment diastolic thickening consistently occurred after a 20 sec occlusion. Peak systolic thickening (motion I) was 0.55 ± 0.09 cm and preceded mitral valve opening by 140 ± 36 ms (240 ± 34 ms after onset of QRS) while the peak thickening (0.66 ± 0.1 cm) of motion II occurred 26 ± 22 ms after MVO (407 ± 40 ms after onset of QRS). For velocity and atrain parameters see table.

	Baseline Motion I	Occlusion Motion I	Occlusion Motion II	Occlusion p I vs II	Recovery Motion I
Peak Vel (cm/s)	5.24 ± 1.33	4.22 ± 0.91	2.31 ± 1.11	p = 0.007	5.12 ± 0.92
Vel Integr	0.64 ± 0.25	0.43 ± 0.16	0.13 ± 0.01	ns	0.58 ± 0.19
Peak SR (Hz)	2.96 ± 0.36	1.88 ± 0.55	2.78 ± 1.03	p = 0.04	2.61 ± 0.48
Strain	0.37 ± 0.08	0.21 ± 0.09	0.15 ± 0.04	p = ns	0.35 ± 0.14
Duration (ms)	246 ± 35	193 ± 39	84 ± 16	p < 0.001	248 ± 45

Conclusions: Diastolic thickening had peak SR's similar to systolic SR's pre ischemia but low strain values. As segmental SR's better reflect contractile function than S values this gives added evidence that diastolic thickening is active contraction and not a passive event.

INFLAMMATION AND CYTOKINES

P432 Increase in the interstitial nitric oxide concentration during myocardial ischaemia

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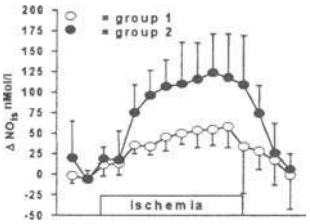
In dogs, the coronary venous concentration of nitric oxide (NO) metabolites is increased during acute myocardial ischemia. However, it is the interstitial, not the intravascular NO concentration that impacts on cardiomyocyte function. We therefore tested whether or not the interstitial NO concentration (NO_{is}) increases during myocardial ischemia in 14 enflurane-anaesthetized swine. The LAD coronary artery was cannulated and perfused from an extracorporeal circuit. Microdialysis probes were implanted into the anterior wall and perfused with oxyhemoglobin. After control measurements, 90 minutes ischemia were followed by 120 min reperfusion. At the beginning of ischemia, coronary arterial flow was reduced to decrease a work index of the anterior wall (sonomicrometry and micromanometry) by 50% in group 1 (n = 4) and 90% in group 2 (n = 10). Microdialysis samples were obtained in 10 min intervals, and NO_{is} was derived from the conversion of oxy- to methemoglobin, as assessed by spectrophotometry. Transmural blood flow (microspheres) was reduced from 1.06 ± 0.25 (SD) to 0.45 ± 0.11 ml/min/g in group 1 and from 0.91 ± 0.26 to 0.13 ± 0.07 ml/min/g in group 2. After 120 min reperfusion, the myocardium was completely viable in group 1, whereas in group 2 infarct size was 15.7 ± 10.8% of the area at risk (TTC). During 90 min ischemia, NO_{is} was increased by 42 ± 14 nMol/l in group 1 and by 96 ± 33 nMol/l in group 2.



Since superoxide radicals can also induce conversion of oxy- to methemoglobin, in a subset of experiments (n = 4) an additional microdialysis probe was perfused with oxyhemoglobin plus superoxide dismutase solution. Addition of superoxide dismutase to oxyhemoglobin did not decrease the measured concentrations of NO_{is}.

P433 Increased tumour necrosis factor in canine model of reversible myocardial ischaemia: relation to the extend of ischaemia

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Tumor necrosis factor (TNF) is increased in acute myocardial infarction. The purpose of this study was to estimate whether TNF is elevated during shorter periods of ischaemia followed by reperfusion and to investigate its relation to the extend of ischaemia.

Methods: Eleven dogs underwent 15 min of left anterior descending coronary occlusion followed by reperfusion. Cardiac TNF was determinated at baseline, at 15 min of ischaemia and after 10 min of reperfusion. TNF was detected on L 929 TNF sensitive cell line (bioassay). Two dimensional echocardiography (short axis view) was used to analyzed left ventricular function. Risk area (RA) (ischaemic) was expressed in % of total short axis area.

Results: TNF was 944 ± 290 pg/ml at baseline, increased during ischaemia to 1376 ± 470 pg/ml and further more during reperfusion 1548 ± 635 pg/ml (p < 0.05). TNF during ischemia-reperfusion was slightly lower in cases (n = 6) with RA less than 25% in comparison to those with RA greather than 25% (n = 5). It was 1275 ± 462 v 1492 ± 574 pg/ml (NS) in ischaemia and 1482 ± 578 v 1635 ± 623 pg/ml (NS) during reperfusion.

In conclusion, this study shows that the release of TNF during ischaemia-reperfusion is present even in short and reversible ischaemia and tend to be related to the ischaemic deterioration in myocardial mechanical performance.

P434 Interleukin-1 in cardiodepressant concentration suppresses arrhythmias provoked by α-adrenoceptor stimulation

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In severe heart failure and systemic inflammatory response syndromes elevated blood levels of interleukin-1β (IL-1β) have been reported. Several mechanisms of an IL-1-mediated cardiodepression have been proposed, including the induction of an inducible nitric oxide (NO) synthase. Conflicting results have been reported regarding the potential of IL-1 to induce or suppress arrhythmias. Thus we investigated the antiarrhythmic and cardiodepressant potential of IL-1β in neonatal rat cardiomyocytes (CM).

Methods: CM were incubated for up to 24 h in the absence or presence of IL-1β (100 U/ml) in serum-free medium. Production of NO was assessed by a NO-sensitive microelectrode and the Griess reaction. CM were electrically triggered at constant pace, contractions were monitored continously.

Results: Il-1β (24 h) did not alter morphological appearance of the cells, but resulted in a significant increase in the contents of NO, nitrite and lactate (indicative of altered energy metabolism) in the culture supernatants, which was suppressed by simultaneous administration of dexamethasone (Dex.) (0.1 μM). A lacking response in pulsation amplitude of the IL-1β treated CM to isoproterenol (control: n = 20, 148% ± 20 *versus* IL-1β: n = 27, 103% ± 3*, p < 0.05) was preserved, if Dex. was added (control: n = 21, 131% ± 10 *versus* IL-1β: n = 27, 130% ± 8). Arrhythmias were regularly elicited in controls upon α-adrenoceptor-stimulation (16/17), even if the duration of the electrical pulse was increased to keep the cells in pace. In contrast, recordings of IL-1β-treated CM (n = 11) did not display beating irregularity. If, however, Dex. was added to the incubation medium, arrhythmias occurred both in the groups without IL-1β (9/11) and with IL-1β (9/10).

Conclusion: A potentially beneficial antiarrhythmic effect of IL-1β may accompany its cardiodepressant action *in vivo*.

P435 Time course of nitric oxide release during myocardial ischaemia and reperfusion

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Background: Nitric oxide (NO) is widely considered to be protective against myocardial ischaemia/reperfusion (I/R) injury, leading to suggestions that NO supplementation is a desirable therapeutic goal.

Methods: Isolated rabbit hearts (n = 6) were perfused at 37°C with Krebs-Henseleit solution. A quartz electrode (30 μm), coated with porphyrin and nafion was advanced into the coronary sinus. The electrode system (Bio-logic) was specific for NO and was calibrated using saturated NO solution (1 pA current change equated to 1 nM [NO] change). Reference and counter electrodes were inserted into the right atrium and organ bath, respectively, and continuous [NO] measurements were made each 500 ms by differential amperometry. After 10 minutes control perfusion, normothermic low-flow global ischaemia (1–3 ml/min) was imposed for 60 mins, followed by 60 mins reperfusion at mean perfusion pressure 80 mmHg.

Results: Left ventricular developed pressure was 82 ± 14 mmHg before ischaemia and 55 ± 16 mmHg after 60 minutes reflow ($p < 0.01$). There was an early increase in NO release from the myocardium (peak at 13 ± 4 minutes after onset of ischaemia, peak current = 3.06 ± 0.47 nA vs basal current = 2.54 ± 0.36 nA, $p < 0.01$) which declined during later ischaemia and decreased further during reperfusion (table).

Change in NO concentration with time

	Ischaemia			Reperfusion	
Time	Peak	30 mins	60 mins	5 mins	30 mins
d[NO] (nM)	513 ± 159	282 ± 82*	146 ± 86**	159 ± 112**	−56 ± 69**

Mean ± sem, d[NO] = Change in [NO] relative to baseline. **p < 0.01, *p < 0.05 vs peak [NO]

Conclusion: The net increase in NO release for ischaemic myocardium does not support the hypothesis of NO deficiency during ischaemia. Reduced NO release during reperfusion is more likely due to oxygen free radical scavenging than impaired synthesis of NO.

P436 cDNA arrays provide new insights into the cytokine pattern of chemokine-stimulated monocytes

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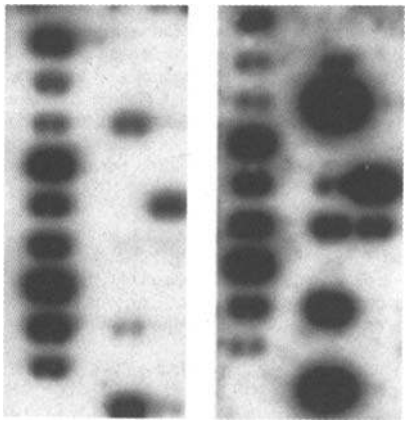
Introduction: The invasion of monocytes into proliferating collateral arteries is a key-event during early arteriogenesis. After maturation these macrophages create an inflammatory environement by producing several growth factors, chemokines etc.. To elucidate this complex biological cascade Human cDNA-Arrays were used to analyze the simultaneous expression-pattern of monocytes after treatment with CC-chemokines.

Methods: Monocytes were isolated from buffy-coats by density-gradient centrifugation. Cells were further isolated by elutriation. The final cell-supension contained >90% of monocytes. Monocyte-stimulation was done for 6 and 12 hours with MCP-1 (200 ng/ml). Total-RNA was isolated, revers transcribed and radioactive labelled. The probes were hybridized to Cytokine/Receptor cDNA-Arrays. Signal evaluation was done by phosphorimaging. Verification was done via RT-PCR and Northern-Blot-Analysis. To our knowledge this is the first monocyte gene-expression study analyzing the simultaneous expression-pattern of 266 genes at m-RNA level after chemokine-stimulation.



Results: MCP-1 stimulation of isolated human monocytes leads to a specific pro-inflammatory and angiogenic expression-pattern of several proteins and their receptors. TNF-alpha, VEGF and MIP-alpha are significantly upregulated as compared to control while the housekeeping genes show an unchanged pattern (left row of cDNAs) (figure)

These factors are a prerequisit for tissue remodelling and vessel growth, confirming our data with CC-chemokines in vivo.

P437 Peripheral benzodiazepine receptors expression on leukocytes in patients with ischaemic heart disease

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Background: The opioids are involved in the endogenous pain-modulating system and differences in endogenous opiate levels between symptomatic and asymptomatic patients during episodes of myocardial ischemia have been reported.

Objectives: The purpose of this study was to assess the benzodiazepine receptors expression in leukocytes of patients (pts) with ischemic heart disease.

Methods: The study population consisted of 57 male patients with reproducible exercise-induced myocardial ischemia. The presence of a unique behaviour in the anginal pain perception both during exercise-induced ischemia and during daily life was the most important inclusion criterion. In all the enrolled patients venous blood samples were taken to evaluate the expression of peripheral benzodiazepine receptors by means of flow cytometry. The study cohort was classified into two groups: Group 1 (G1) 24 pts referring anginal pain both at home and during exercise stress test; Group 2 (G2) included 33 pts asymptomatic both during daily life and during exercise-induced ischemia. Results were expressed as mean ± SD. The tMann-Whitney analysis was used to investigate differences among the two different groups.

Results: In patients with silent ischemia (G2) the pBZRs expression resulted significantly higher than in the symptomatic patients (G1) in all types of leukocytes. The pBZr expression on lymphocytes of asymptomatic patients was 2.0 ± 0.4 × 10^{-5} sites per cell and on the same type of cells of the symptomatic group it was 1.2 ± 0.4 × 10^{-5} sites per cell, $p < 0.005$. The pBZRs expression on granulocytes was 7.22 ± 0.8 × 10^{-5} sites per cell in G2 pts and it was 4.25 ± 0.9 × 10^{-5} sites in G1 pts ($p < 0.001$). A similar increase of pBZRs expression on monocytes of asymptomatic patients compared to that of symptomatic patients was demonstrated (G2 = 13.4 ± 0.9 × 10^{-5} sites per cell, G1 = 8.0 ± 0.5 × 10^{-5} sites per cell, $p < 0.001$)

Conclusions: An increase in peripheral benzodiazepine receptors on leukocites was documented in pts with silent ischemia in comparison to the symptomatic ones. These results suggest an involvement of the pBZRs in anginal pain perception.

FAILING MYOCARDIUM

P438 Adrenoreceptor sensitivity and contractile function in failing human myocardium

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Adrenoreceptor down-regulation and altered calcium regulation are important cellular abnormalities observed in failing myocardium. We have explored the relation between these two abnormalities in electrically stimulated isolated cardiac muscle strips from the right ventricles of patients with heart failure (n = 8) prior to cardiac transplantation. Right atrial strips from patients with ischaemic heart disease (n = 7) but no evidence of heart failure were used as controls. Small muscle strips (0.3–0.5 mm diameter) were mounted for measurement of isometric tension, stretched to Lmax and stabilised for 60 minutes. Force frequency response was diminished or negative in all failing strips but had a positive relationship in all non-failing atrial strips (23 ± 3.8% vs −10.8 ± 4.6% at 100 min^{-1}, P = 0.02). Post-rest responses (30–180 seconds) were reduced in failing muscle strips compared with non-failing strips (13.7 ± 6.2% vs 37.2 ± 12.9% increase after 180 s rest, P = 0.03). Responsiveness to isoprenaline was assessed and dose-response curves constructed for individual muscle strips. EC50 (isoprenaline) correlated with the force frequency response as assessed by the change in force between maximum and minimum stimulation frequencies (r = 0.61, P = 0.04) and demonstrated a weak relation with post rest responses (r = 0.32, P = 0.29). Isoprenaline re-established a positive force frequency response in 3 of 9 (n = 7 hearts) failing preparations, all of which had EC50s close to those of normal atrial strips. Isoprenaline had no significant effect on post-rest responses in failing myocardium but significantly increased post-rest contractures in non-failing strips. These results suggest a close relation between adrenoreceptor down-regulation and abnormal mechanical properties of failing myocardium. Contractile dysfunction in heart failure may therefore be secondary to changes in adrenoreceptor responses and not due to intrinsic alterations in calcium cycling.

P439 Effects of adrenomedullin on contractile function in isolated rat, rabbit and human cardiomyocytes

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Adrenomedullin (ADM) is an endogenous vasoactive peptide. Positive inotropic effects of ADM have been shown in rat hearts. In patients with heart failure, ADM plasma levels are elevated. Therefore, we investigated the influence of ADM on isolated human, rat and rabbit myocytes.

Methods: A: Isolation of ventricular myocytes from endstage failing human hearts (n = 6) by enzymatic digestion (Protease 0.5 mg/ml; Collagenase 1 mg/ml). B: Isolation of rat and rabbit ventricular myocytes (n = 8, n = 7 hearts) by enzymatic digestion (Collagenase 1 mg/ml, Langendorff-perfusion). Electrical stimulation (0.5 Hz), registration of fractional shortening (FS) and relaxation characteristics by video-edge-detection. ADM-concentration-response- curves (10^{-10}–10^{-7} M).

Results: In end-stage failing human myocytes, ADM did not increase FS, (108 ± 27% at 10^{-8} M and 96 ± 29% at 10^{-7} M, compared to control). Time to peak shortening (TPS) increased slightly from 365 ± 34 to 397 ± 47 ms, n.s.. Relaxation time (RT50%) did not change (174 ± 73 ms at 10^{-7} M vs. 187 ± 35 ms). In contrast, ADM increased FS in rat myocytes to maximal 172 ± 31% (at 10^{-8} M) compared to control ($p < 0.05$). TPS increased from 76 ± 3 ms to 94 ± 15 ms and RT50% increased from 22 ± 2 ms to 44 ± 7 ms ($p < 0.05$). Increasing ADM to 10^{-7} M led to development of arrhythmias. In rabbit myocytes, ADM decreased FS to 72 ± 13%, compared to control, $p < 0.05$. TPS increased from 175 ± 23 to 225 ± 38 ms and RT50% from 61 ± 11 to 79 ± 21 ms ($p < 0.05$).

Conclusions: In human failing myocytes, ADM did not affect contractile function. In contrast, an increase in contractility, associated with increased contraction and relaxation times, could be observed in rat myocytes. In rabbit myocytes, ADM decreased contractility. At higher concentrations, ADM induced arrhythmias in all species. The functional effects of ADM are species-dependent and deserve further investigation.

P440 Tachycardia-induced electrical and structural remodelling. Differences between atria and ventricles

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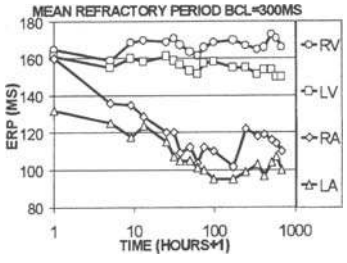
Background It is well known that chronic atrial tachycardia causes atrial and ventricular dilatation and atrial electrical remodelling, characterised by shortening of atrial refractory periods (AERP) and loss of physiological adaptation of AERP to rate. However, to date the nature and time course of changes in ventricular refractory periods (VERP) caused by chronic rapid rates and their relation to mechanical changes are to be established.

Methods After being instrumented with epicardial electrodes on both atria and both ventricles and piezoelectric transducers on the right atrium (RA) and left ventricle (LV), five goats were subjected to four weeks of rapid atrioventricular (AV) sequential pacing with a rate of 240 bpm. AV pacing was only interrupted for measurement of left and right AERP and VERP at three basic cycle lengths (BCL) of 400 ms, 300 ms and 200 ms and measurement of RA and LV endsystolic (ES) and enddiastolic (ED) diameters during sinus rhythm.

Results Left and right AERP decreased at all BCL, reaching minimum values after 168 hours. In contrast, left and right VERP did not change at any BCL during four weeks of rapid AV pacing. RA and LV diameters increased progressively to 139%/144% and 120%/116% of baseline, respectively (ED/ES).



Conclusions This study demonstrates a difference between the atria and ventricles with respect to tachycardia induced electrical remodelling and a discrepancy between tachycardia induced ventricular electrophysiological and mechanical changes.

P441 Regulation and localisation of endothelin receptors, ET-1 peptide, and ECE in non-failing and end-stage failing human hearts

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The purpose of this study was to characterise endothelin (ET) receptors, ET-1 peptide and Endothelin-converting-enzyme (ECE) in human ventricular myocardium from non-failing (NF; n = 5) and endstage failing hearts with ischemic (ICM, n = 5) or dilative (DCM; n = 7) cardiomyopathy.

Methods: Radioligand competition binding in microsomal membranes from human myocardium using [125 I] ET-1 as labelled ligand and ET-1, ET-3 and the selective ETA subtype antagonist BQ123 as unlabelled ligands. ET-1 peptide content was assessed by radioimmunoassay. Localisation of ET-1 peptide and ECE by immunohistochemistry

Results: In nonfailing myocardium, endothelin receptor density was 67 ± 14 fmoles/mg protein. Subtype receptor analysis showed 59 ± 4% ETA and 41 ± 4% ETB receptors and no significant difference between left and right ventricles was observed. In ICM, the overall receptor density was decreased to 45 ± 6 fmoles/mg protein, but the relative proportions of receptor subtypes remained similar (64 ± 3% ETA and 36 ± 3% ETB). In DCM, ET-receptor density was significantly increased to 105 ± 18 fmoles/mg protein. This resulted from a selective increase in ETA receptor density to 73 ± 10 fmoles/mg protein with no change in ETB receptor density. ET-1 content was 4530 ± 800 pg/mg protein in NF, and increased significantly to 11800 ± 2600 in ICM and to 13800 ± 1880 pg/mg protein in DCM. Semiquantitative optical analysis revealed enhanced ET-1 and ECE staining in ICM and DCM as compared to nonfailing myocardium. ET-1 and ECE were expressed in endothelial cells, smooth muscle cells and cardiac myocytes, but little in connective tissue. Increased ET-1 staining in ICM and DCM resulted from overexpression in myocytes.

Conclusion: Activation of the ET-system in human heart failure is associated with altered endothelin receptor, ET-1 peptide and ECE-expression on the level of the myocardium. While differences in ETA-receptor regulation may exist between ICM and DCM, ET-1 is increased similarily in both types of disease.

P442 Cardioprotective effects of carvedilol in a rat model for adriamycin-induced cardiomyopathy

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Objective: To investigate macrobiotic and cardioprotective effects of carvedilol in a rat model for adriamycin-induced cardiomyopathy.

Methods: Male Wistar rats aged 8 weeks were used for this study. A rat model for adriamycin-induced cardiomyopathy was developed by intraperitoneal administration of adriamycin at a dose of 1 mg/kg (as a 10 mg/ml solution) repeated 15 times (to a total dose of 15 mg/kg) within a period of 3 weeks. From 2 weeks after the start of administration period, 49 animals assigned to the carvedilol administration group (Group C) were given diet containing 3.44 mg/kg carvedilol while 53 animals of the no-treatment group (Group N) were given control diet containing no drug. After the end of the administration period, follow-up observation was conducted for 12 weeks. Echocardiogram was obtained 4, 8 and 12 weeks after the end of adriamycin administration, as well as before starting the inducer administration, to investigate changes in heart volume and cardiac function. At the end of the follow-up period, all surviving animals were sacrificed for histo-pathological examination.

Results: 1) Mortality in Group C, 14.3% (7/49), was significantly lower than that in Group N, 35.8% (19/53) (Log-Rank test ($p = 0.04$)). 2) Starting from a baseline value of 85 ± 5.3%, difference in ejection fraction (EF) observed between Groups C and N became evident with time after the end of adriamycin administration: Week 4, 79.6 ± 5.5% for Group C vs. 74.3 ± 7.9% for Group N ($P = 0.03$); Week 8, 75.2 ± 8.4% for Group C vs. 67.9 ± 9.1% for Group N ($P = 0.03$); and Week 12, 73.4 ± 8.6% for Group C vs. 62.3 ± 8.5% for Group N ($P = 0.0003$). This indicates that carvedilol significantly improved cardiac functional impairment, especially 12 weeks after the end of adriamycin administration. 3) Fibrogenesis around microarteries within cardiac muscle tissue, interstitial fibrinogenesis and adria cells were observed in both groups, but these myopathic changes were apparently milder in Group C than in Group N.

Conclusion: Carvedilol significantly diminished mortality of heart failure and significantly improved cardiac functional impairment in a rat model for adriamycin-induced cardiomyopathy.

P443 Adrenomedullin does not improve contractility and decreases intracellular Ca^{2+} transients in human non-failing and failing myocardium

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In patients with heart failure, plasma levels of the endogenous vasoactive peptide Adrenomedullin (ADM) are elevated. Positive inotropic effects of ADM have been shown in rat myocardium. However, functional effects of ADM in human myocardium remain to be established. We investigated the effects of ADM on contractile function and intracellular Ca^{2+} transients (aequorin method) in human nonfailing and end-stage failing myocardium.

Methods: A: Isolation of ventricular myocytes from failing human hearts (n = 7); enzymatic digestion, Collagenase 1 mg/ml via perfusion of a left ventricular arterial branch. Electrical stimulation (0.5 Hz) and registration of fractional shortening (FS) and relaxation characteristics by video-edge-detection. B: Preparation of left ventricular muscle strips from the same hearts, and from 3 nonfailing hearts, isometric contractions at Lmax, electrical stimulation. Macroinjection of the photoprotein aequorin. Registration of isometric force (IF) and intracellular Ca^{2+} transients with ADM (10^{-9}–10^{-7} M) or increasing $[Ca^{2+}]_o$ (1.5–7.2 mM).

Results: ADM did not affect FS in isolated myocytes (91 ± 10% at 10^{-9} M and 102 ± 14% at 10^{-7} M, vs. control = 100%). Time to peak shortening (TPS) and relaxation time (RT50%) increased slightly (297 ± 33 to 354 ± 45 ms; 147 ± 28 to 178 ± 38 ms at 10^{-7} M, respectively, n.s.). However, arrhythmias were induced by ADM at 10^{-7} M. Increasing $[Ca^{2+}]_o$ to 5.6 mM in the same myocytes led to an increase in FS to 228 ± 45% ($p < 0.05$ vs. control). In muscle strip preparation from the same hearts, ADM decreased IF to 88 ± 4 at 10^{-9} M and 89 ± 5% at 10^{-7} M (n.s. vs. control). Aequorin light emission decreased to 73 ± 7% at 10^{-7} M ($p < 0.05$ vs. control). In nonfailing myocardium, ADM did not increase IF and slightly decreased Ca^{2+} transients to 89 ± 12%, (n.s. vs. control). Increasing $[Ca^{2+}]_o$ to 5.6 mM increased IF to 266 ± 55%, and aequorin light emission to 258 ± 42% ($p < 0.05$ vs. control) in the muscle strips.

Conclusions: In contrast to rat hearts, ADM does not increase contractility in human venticular failing and nonfailing myocardium. The small negative inotropic effect of ADM was related to a parallel decline in intracellular Ca^{2+} transients. Functional effects of ADM in heart failure patients may primarily result from vasodilatory activities of this peptide.

P444 Genetic analysis of a new form of autosomal dominant dilated cardiomyopathy

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Emery-Dreifuss muscular dystrophy (EDMD) is characterized by early contractures of elbows and Achilles tendons, slowly progressive muscle wasting and weakness and an adult onset of cardiac conduction defect, ventricular dysrhythmias with an evolution to severe cardiomyopathy that is life threatening. Two modes of inheritance exist, X-linked and autosomal dominant. Mutations in the *EMD* gene encoding emerin are responsible for the X-linked form.

We have studied a large French family with the autosomal form of EDMD (EDMD-AD). In this family, 17 members were affected, 5 presented both cardiac and skeletal muscle involvement and interestingly 12 members presented exclusively cardiac manifestations.

We have mapped EDMD-AD locus in this pedigree to a 8-cM interval on chromosome 1q11–q23, and found that four other small families were potentially linked to this locus. This region contains the lamin A/C gene (*LMNA*), a candidate gene encoding two proteins of the nuclear lamina, lamins A and C originated through alternative splicing. We identified four mutations in *LMNA* that co-segregate with the disease phenotype in the five families: a non-sense mutation and three missense mutations.

These results are the first to identify mutations in a component of the nuclear lamina as a cause of inherited cardiac and skeletal muscle disorder. Further analysis of phenotype/genotype relationship will help to clarify the variability of the phenotype observed in the large pedigree.

P445 Left ventricular remodelling in chronic heart failure: relevance to changes in exercise performance

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Objective: In recent years, emphasis has begun to shift from functional to structural changes (referred to as remodelling) that occur in the failing heart. The impact of ventricular structural changes on clinical course and exercise performance remains to be elucidated. This study sought to determine whether changes in left ventricular structure with emphasis on left ventricular size, mass and geometry over time were related to changes in exercise capacity in patients with chronic heart failure (CHF).

Methods: Sixty-two patients with CHF (58 men; mean [± SD] age 60 ± 10 years) underwent echocardiographic examination and treadmill cardiopulmonary exercise testing at baseline and after median of 14 months (at baseline: mean left ventricular fractional shortening (LVFS) 16 ± 8%, mean peak oxygen consumption (VO_2) 18 ± 6 ml/kg/min).

Results: Changes in peak VO_2 per year were significantly related to changes per year in measurements of left ventricular size ($r = -0.48$, $p < 0.001$ for end-diastolic diameter and $r = -0.55$, $p < 0.001$ for end-systolic diameter), mass ($r = -0.44$, $p < 0.001$) and relative wall thickness ($r = 0.40$, $p < 0.01$) but did not correlate with changes over time in LVFS ($r = 0.28$, $p = 0.032$). Stronger relationships were found between changes in the ventilatory responce to exercise (VE/VCO_2) and those of left ventricular cavity dimensions ($r = 0.62$, $p < 0.001$ for end-diastolic diameter and $r = 0.57$, $p < 0.001$ for end-systolic diameter) and mass ($r = 0.71$, $p < 0.001$).

Conclusions: Changes over time in objective measures of left ventricular dimensions, mass and relative wall thickness in patients with CHF are significantly related to changes in exercise capacity and respiratory efficiency.

P446 Effective atrial contribution in sequentially paced patients with impaired ventricular function

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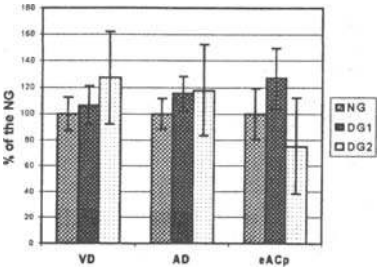
Objective: To assess the effective atrial contribution (eACp) to the ventricular contraction in sequentially paced patients (pts) with various degrees of left ventricular dysfunction.

Methods: Thirty pts with implanted Physios DDD pacemaker were examined. Pressure in the ascending aorta was measured by the Millar catheter. The pressure signal was digitized and the data were accepted only if the defined criteria of the signal stability were met. Switching-off the atrial stimulus at AV intervals of 50, 100, 150, 200 and 250 ms from the DDI into the VVI mode during quiet expiration induced a drop in the pressure-pulse amplitude, which was expressed in per cent of the amplitude of the preceding beat. By definition, the maximal drop indicated the optimal AV interval and quantified the eACp. Ejection fraction (EF) was measured by radionuclids, left atrial (AD) and ventricular (VD) dimensions by ultrasound. Pts were divided into 3 groups according to their EF. NG included 10 pts with a normal values (>55%), DG1 9 pts with $50 < EF \leq 55\%$ and DG2 11 pts with $EF \leq 50\%$.

Results: There was a trend for the eACp and the atrial dimension to be higher in DG1 than in NG (mean 51.1 ± 13.8 v. 40.4 ± 14.0 and 22.5 ± 2.5 v. 19.5 ± 2.9 respectively). In DG2, the atrial dimension was similar as in DG1 (mean 22.9 ± 4.4 v. 22.5 ± 2.5) while the eACp was significantly ($p = 0.012$) lower (mean 51.1 ± 13.9 v. 30.4 ± 14.9). There was a significant association of the eACp and EF ($r = 0.554$, $p = 0.011$) in pts with the $EF \leq 55\%$. In the same pts, no significant correlation was found for the eACp and the left atrial dimension ($r = 0.28$, $p = 0.23$).



Conclusions: In sequentially paced pts with slightly decreased left ventricular EF the augmented atrial pump function compensates for ventricular dysfunction. In severe ventricular dysfunction the atrial pump function is significantly depressed.

MYOCARDIAL PROTECTION

P447 Sodium/hydrogen exchange inhibitor HOE 642 attenuates myocardial reperfusion injury in rabbits by inhibition of polymorphonuclear leukocyte–endothelium interaction

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Myocardial reperfusion injury has been to neutrophil released mediators like oxygen derived radicals loss of endogenous nitric oxide and increased neutrophil adherence.

We studied the effect of the sodium/hydrogen exchange inhibitor HOE 642 in vivo in a rabbit myocardial reperfusion injury model (60 minutes ischemia followed by 3 hours reperfusion). HOE 642 (1 mg/kg) or its vehicle were injected 5 minutes prior to reperfusion. Myocardial injury following HOE 642 treatment was significantly reduced compared to vehicle treated animals (13% ± 3.1% vs 22.6% ± 2.5% necrosis related to ischemic myocardium, $p < 0.05$). Plasma creatine kinase (CK) activity, another marker for myocardial injury increased from 1.5 ± 0.2 IU/g protein at baseline to 21.3 ± 3.3 IU/g protein following 3 hours of reperfusion in the vehicle group. Administration of HOE642 significantly decreased plasma CK release throughout the reperfusion period (13.8 ± 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 HOE 642 treated animals compared to the vehicle group ($p < 0.01$). Histologic analysis of ischemic reperfused myocardium of vehicle treated animals showed 85 ± 12 PMN/mm^2. HOE 642 treatment resulted in a significant reduction of neutrophil accumulation in the reperfused myocardium (24 ± 9 PMN/mm^2, $p < 0.001$). *In vitro* adhesion assays demonstrated reduced PMN adherence to ischemic-reperfused coronary arteries in HOE 642 treated animals. Further, HOE642 significantly reduced PMN adherence to thrombin activated vascular endothelium.

Thus, blocking of sodium hydrogen exchange pump with HOE 642 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.

P448 Anaplerotic carboxylation of pyruvate in the in vivo swine heart

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It has been suggested that optimal mitochondrial function requires a constant rate of pyruvate carboxylation to provide anaplerotic substrate for the citric acid cycle (CAC). The use of [U-^{13}C]pyruvate tracer was recently introduced in the isolated heart to measure the contribution of pyruvate carboxylation and decarboxylation to the synthesis of citrate in the CAC (Comte et al. J Biol Chem 272:26125, 1997). Comparison of triply labeled and doubly labeled isotopomers of citrate by gas liquid chromatography-mass spectrometry (GCMS) analysis enables one to calculate the relative rate of entry of pyruvate into the CAC through pyruvate carboxylation (via malic enzyme and/or pyruvate carboxylase) and decarboxylation (via pyruvate dehydrogenase(PDH)) pathways. In this study we measured these rates in the anterior free wall of intact anesthetized open chest domestic swine (n = 6). [U-^{13}C] pyruvate was infused into the left anterior descending coronary artery for one hour via an extracorporeal perfusion circuit. Constant values in LAD arterial blood were reached after 5 min of pyruvate infusion for both [U-^{13}C]pyruvate enrichment (80%) and concentration (0.8 mM). At the end of the protocol a myocardial biopsy was taken from the LAD bed and freeze clamped. GCMS analysis was performed on the tissue for the enrichment of [U-^{13}C]pyruvate and isotopomers of citrate. After correction for recycling of carbon in the CAC, the relative rates of citrate formation from pyruvate decarboxylation and carboxylation were calculation from the doubly and triply labeled isotopomers of citrate, and the tissue enrichment of triply labeled pyruvate. Pyruvate decarboxylation accounted for 55 ± 13% of citrate formation and carboxylation for 2.3 ± 1.1%, with the balance (42 ± 12%) presumably coming from lipid oxidation. We investigated this further by performing the same studies in the presence of an intracoronary infusion of octanoate (1 mM in LAD blood) to inhibit the flux of pyruvate through PDH. This resulted in profound inhibition of pyruvate decarboxylation (3.9 ± 2.8% of citrate formation) without any effected on pyruvate carboxylation (1.8 ± 0.7% of citrate formation). In conclusion, this is the first study to measure the contribution of pyruvate carboxylation to the Krebs cycle in vivo, and demonstrate that it accounts of approximately 2% of the Krebs cycle flux in the intact working swine heart. Furthermore, we have shown that this rate is constant when flux through PDH is inhibited by >90%. The physiological importance of this anaplerosis could be related to the cardioprotective effects of pyruvate.

P449 Acute and chronic treatment with the NHE-1 inhibitor cariporide – influence on infarct size in rabbits with hypercholesterolaemia

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Hypercholesterolemia is a major risk factor associated with increased atherosclerotic diseases. In rabbits fed with an atherogenic diet we looked on infarct size and the cardioprotective effect of the NHE-1 inhibitor cariporide under these conditions.

Methods: White New Zealand rabbits were fed with atherogenic diet over 4 weeks (0.25% cholesterol and 3% coconut-oil) or with normal diet and randomized in 3 groups (n = 7/group): placebo, cariporide acute (0.3 mg/kg 10 min before occlusion of LAD) and cariporide chronic (4 weeks 0.1% in chow = 100% blockade of the NHE-1). Thereafter, the animals were subjected to a 30 min occlusion of the LAD, followed by 2-h reperfusion. The left ventricle was stained with triphenyl-tetrazolium chloride and the infarct size expressed as a percentage of area at risk.

Results: In cholesterol fed rabbits infarct size was significantly increased when compared with normal diet animals (63 ± 3% vs 41 ± 3%). Acute cariporide treament halved infarct size in normal diet rabbits to 16% ± 3% (−61%) as well as in atherogenic diet rabbits to 22 ± 3% (−65%). Chronic treatment with cariporide also reduced infarct size significantly: normal diet 19 ± 2% (−53%), atherogenic diet 32 ± 3% (−49%).

Conclusion: Acute and chronic treatment with the NHE-1 inhibitor cariporide significantly reduced infarct size in normal rabbits but also in rabbits with hypercholesterolemia.

P450 Ischaemic tolerance is attenuated in the spontaneously diabetic Otsuka Long-Evans Tokushima Fatty rats

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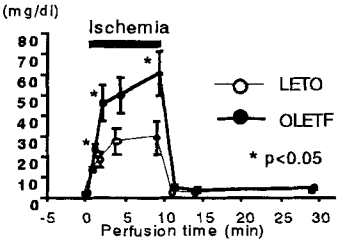
Previous studies have demonstrated that heart from streptozotocin-induced diabetes mellitus are less susceptible to ischemia and reperfusion injury. However, ischemic tolerance of spontaneously diabetic heart is largely unknown. The aim of this study is to put these past findings in context with spontaneously diabetic, insulin resistant rat heart.

Methods: Male Otsuka Long-Evans Tokushima Fatty (OLETF) strain of 4 and 8 months old and respective age matched non-diabetic Long-Evans Tokushima Otsuka (LETO) rats were used. The hearts from these 4 groups were perfused by the working heart mode with Krebs-Henseleit bicarbonate buffer. Whole heart ischemia was induced by use of one-way ball valve with 300 bpm pacing. Following 10 min of ischemia, the hearts were reperfused for 20 min without pacing. Cardiac output (CO) and left ventricular pressure (LVP) were monitored. Coronary effluent was collected and lactate, pyruvate and H^+ were measured.

Results: At age of 4 months, OLETF showed a slight increase in body weight, while there were no differences in blood glucose level and postischemic recovery of cardiac function between these strains. At 8 months old, however, body weight (518.8 ± 16.1 vs 433.8 ± 16.0 g, $p < 0.05$), HbA1c (3.62 ± 0.14 vs 2.72 ± 0.28%, $p < 0.05$), and blood glucose level during OGTT (60 min; 315.8 ± 22.3 vs 153.6 ± 7.8 mg/dl, $p < 0.01$) were significantly higher in OLETF compared with those in LETO. Recovery of cardiac work (CO × LVP) on reperfusion was significantly lower in OLETF than that in LETO (10 min; 1561.2 ± 453.7 vs 3645.6 ± 834.9 ml · mmHg/min, $p < 0.05$). Lactate level in coronary effluent during ischemia was significantly higher in OLETF compared with that in LETO (Figure).



Conclusion: Hearts from spontaneously diabetic OLETF rat (of 8 months old) are shown to be more susceptible to ischemic insult which is different from that seen in streptozotocin-induced diabetic heart. Mechanism is unknown, but significantly lower level of lactate may be involved.

P451 Enhanced endogenous adenosine production protects the heart after transplantation

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Increase in endogenous adenosine (Ado) production could protect the heart after transplantation due to potent antiplatelet, antiinflammatory and immunosuppressive effects of Ado. We aimed to optimise the procedure to increase endogenous Ado production by combined application of Ado metabolism inhibitors and nucleotide precursors using isolated cardiac cells and to evaluate this intervention in a protocol mimicking conditions of cardiac preservation for transplantation.

Methods: Isolated rat heart capillary endothelial cells and cardiomyocytes were incubated with various combinations and different concentrations of: Ado deaminase inhibitor – erythro-9(2-hydroxy-3-nonyl)adenine (EHNA), Ado kinase inhibitors – 5′-iodotubercidin (ITu) or 5′-aminoadenosine (AA) and nucleotide precursors – adenine (A) or ribose (R). The optimal combination and concentrations were established to maximise Ado production and cellular ATP content. Cardioprotective effects were then evaluated using heterotopic rat heart transplanation model. Donor hearts were collected, infused with St.Thomas' No. 1 cardioplegic solution and subjected to 4 h of storage at 4°C followed by heterotopic abdominal transplantation. The solution containing EHNA/AA/A/R was infused 10 min before reperfusion of transplanted heart into one group of recipient rats (T, n = 8) while vehicle was infused in control group (C, n = 8). Hearts were than collected after 24 h and mechanical function was evaluated in Langendorff perfusion system using balloon inserted into the left ventricle.

Results: Ado content increased in the incubation medium of both the endothelial cells and cardiomyocytes incubated with Ado kinase and Ado deaminase inhibitors, but addition of A (endothelial cells) or A with R (cardiomyocytes) was necessary to protect cellular ATP pool. Cardiac function was markedly improved in group T: +dP/dt was 2658 ± 195 and 3801 ± 216 mmHg/s, −dP/dt was −2465 ± 189 and −3415 ± 290 mmHg/s and maximum developed pressure was 87.0 ± 6.8 and 118.1 ± 8.2 mmHg in C and T respectively. Left ventricular static compliance was also improved in T as indicated by balloon volume – end diastolic pressure relation.

In conclusion: Inhibition of Ado kinase and Ado deaminase together with supply of adenine and ribose is effective procedure to increase endogenous Ado production in heart cells and to protect hearts from injury following prolonged cold storage during transplantation.

P452 Time-dependent changes of cardiac gene transcription levels of angiotensin II receptors after myocardial infarction: effects of ramipril treatment

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Aim: To study the early changes of cardiac angiotensin (Ang) II receptor gene transcription after myocardial infarction (MI) in rats chronically treated with the angiotensin converting enzyme (ACE) inhibitor ramipril.

Methods: MI was induced by left anterior descending coronary artery ligation in rats and sham-operated rats were used as control. Rats were treated daily with ramipril (1 mg kg^{-1}) or water, initiated 1 week before surgery. Quantitative RT-PCR was applied to determine the Ang II receptor AT1, AT2 receptor gene mRNA levels in the non-infarcted myocardium. Hymodynamic parameters such as mean blood pressure (MBP), left ventricular end-diastolic pressure (LVEDP), left ventricular systolic pressure (LVSP), left ventricular contractility (LV dp/dtmax) were measured by arterial and intraventricular catheterization at 3 h, 1 d, 3 d, and 7 d after operation.

Results: AT1 and AT2 mRNA levels increased time point dependently in the cardiac septum after MI reaching a peak on day 1. There was no significant difference of the myocardial AT1 and AT2 receptor mRNA levels between the ramipril-treated- and water-treated rats after MI. LVEDP increased 1 d after MI and myocardial contractile function decreased at 3 h, 1 d, 3 d, and 7 d after MI. Ramipril significantly lowered LVEDP at 1 d and 3 d after MI, and improved myocardial contractility at the 7 d after MI.

Conclusion: The AT1 and AT2 receptor gene transcription in the non-infarcted myocardium was associated with the process of cardiac remodeling after MI but not affected by ACE inhibition.

P453 Urocortin protection of cardiac myocytes from lethal ischaemia is mediated by MAP-kinase

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Urocortin (UCN), a peptide related to CRH, protects neonatal cardiac myocytes from lethal ischaemic injury UCN is expressed predominantly in tissues of the CNS, however is found in cardiac muscle. UCN binds with high affinity to the CRH-R2b receptor which has specific expression in the heart. In this study we show that UCN blocks ischaemic induced cardiacmyocyte death in vitro and ex vivo when administered prior to the lethal stress and during reoxygenation and investigate the role of the MAP-kinase (p42/44 ERK-1/2) pathway in this mechanism.

Methods: Immunoblot analysis using anti UCN anti-body was used to detect the expression of UCN peptide in primary cardiomyocytes isolated from 2-day old neonatal rats. These cells were subjected to simulated ischaemia in ischaemic buffer (IB) and placed in an atmospheric chamber of 5% CO_2 and 95% argon at 37°C for 6 hrs. UCN (10-8 M) was added to the cells prior to this stress and in 2 hrs of reoxygenation. Cell death was assessed by TUNEL, Trypan blue, FACS and annexin-V labelling. To explore the potential down stream pathways responsible for this effect, immunoblot analysis using anti-active p42/44 anti-body was used to investigate ER-2 phosphorylation by UCN. A MAP kinase 1 (MEK) dominant negative mutant cDNA (MEK-1 DN) transfected by calcium phosphate co-precipitation into cardiomyocytes, was used to investigate the cell survival effect of UCN. PD098059 is capable of blocking the activation of the MEK-1, ERK1/2 (p42/44) cascade and was added to the cells 10 min prior to the incubations with UCN, similarly with the PKC inhibitor H7. Ex-vivo ischaemia/reperfusion studies were performed on isolated rat hearts using the Langerdoff perfusion apparatus. Following 20 min stabilisation, all hearts underwent 35 min regional ischaemia followed by 120 min reperfusion. UCN (10-8 M) was perfused on the heart 30 min before or for 30 min during reperfusion. Infarct size (I) was determined using TTC staining, the risk zone (R) with fluorescent microspheres and the % I/R was calculated.

Results: UCN peptide expression levels decrease following ischaemia and further during reoxygenation suggesting release of the peptide. UCN causes rapid phosphorylation of LRK1/2 (p42/44) and protects cardiac myocytes from ischaemic injury when added prior to this stress and in reoxygenation. MEK-1 DN, PD098059 and H7 block the survival effect of UCN, indicating the requirement of a MAP kinase, PKC pathway. UCN protects the intact rat heart from simulated ischaemia/reperfusion

Conclusion: UCN peptide is expressed by cardiac cells and administration of exogenous UCN inhibits ischaemia/reperfusion induced cell death via a ERK1/2 (p42/44) pathway. Hence UCN is a potential novel therapeutic peptide against ischaemia/reperfusion injury.

P454 Pretreatment with inhibitors of KATP channels or PKC abolished the cardioprotective effects of the EP3-receptor agonist TEI-3356 in a model of myocardial injury in the rat

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Introduction: The cardioprotective effects of E-type prostaglandins have been attributed to vasodilatation, inhibition of platelet and neutrophil function (all due to activation of EP2-receptors) and a 'cytoprotective effect', the mechanism of which is still unknown. We have recently reported that the prostanoid-derivatives, ONO-AE-248, GR 63799X and M&B 28767 reduce myocardial injury in the rat.

Objective: This study investigated the effects of the prostanoid EP3-receptor agonist TEI-3356 on the infarct size caused by regional myocardial ischaemia and reperfusion in the rat. In addition, we have also elucidated the role of protein kinase C (PKC) and ATP-sensitive potassium (KATP) channels in the cardioprotective effects of TEI-3356.

Methods: Male Wistar rats (240–350 g) were anaesthetised, tracheotomised and ventilated. The jugular vein and carotid artery were cannulated to administer drugs and to measure mean arterial blood pressure, respectively. The chest was opened by a left-side thoracotomy and an atraumatic needle was placed around the left anterior descending coronary artery (LAD). After 30 min of recovery, the rats were subjected to 25 min occlusion of the LAD followed by 2 h of reperfusion. At the end of the experiments, the LAD was re-occluded and 1 ml of Evans Blue dye (2% w/v) was i.v. injected to determine the perfused and the non-perfused (area at risk, AR) myocardium. Infarct size (IS) was determined by using p-nitro-blue tetrazolium. All drugs used in this study were i.v. administrated 10 min prior LAD-occlusion.

Results: The mean values for the AR ranged from 46 ± 2% to 54 ± 3% ($p > 0.05$). Treatment of rats with TEI-3356 (1 μg/kg/min) resulted in a significant reduction in IS from 60 ± 3% (control, n = 12) to 36 ± 3% (n = 8; $p < 0.05$) of the AR. The reductions in IS caused by TEI-3356 was not due to a reduction in blood pressure. Pretreatment of rats with either 5-hydroxydecanoate (5-HD, 5 mg/kg, inhibitor of KATP-channels), staurosporine or chelerythrine (Stau, 1 μg/kg, or Chel, 0.7 mg/kg, inhibitors of PKC) attenuated the cardioprotective effects of TEI-3356. However, 5-HD, Stau or Chel did not affect IS ($p > 0.05$). In sham-operated animals, none of the drugs used had any affect on any of the parameters measured.

Conclusions: Thus, activation of the EP3 receptor leads to protection of the heart against ischaemia-reperfusion injury. The cardioprotective effect of TEI-3356 may involve the activation of PKC and the opening of KATP-channels.

P455 Initial report of AMP579 delivery for myocardial infarction reduction (ADMIRE)

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Introduction: AMP579 is a mixed adenosine agonist with both A1 and A2a effects which has been found to have myocardial protectant properties in animal models of acute MI.

Methods: The ADMIRE Study evaluated AMP579 in a double-blind multicenter placebo controlled trial of 321 patients with acute ST elevation anterior or non-anterior MI undergoing primary PTCA within 6 hours of the onset of symptoms. Patients were randomized to either placebo (P) vs 15 mcg/kg, 30 mcg/kg or 60 mcg/kg continuous infusion over six hours. The primary endpoint was final myocardial infarct size measured by sestamibi scanning at 120 to 216 hours post-PTCA. Secondary endpoints were: 1)myocardial salvage (%LV) and salvage index at 120 to 216 hours in a subset of patients with a baseline sestamibi scan; 2)ejection fraction and heart failure at 4–6 weeks; 3)duration of hospitalization; and 4) cardiac events at 4 weeks and 6 months.

Results: In all treatment groups combined the median final MI size was 10.0% without a significant difference between the P and AMP groups. There was however a trend in final MI size in the anterior MI subgroup receiving P vs. AMP 30 vs. 60 mcg/kg (18.3% vs. 14.0% vs. 13.5%, respectively). In addition, there was a trend towards increased myocardial salvage in the anterior MI group with scans both at baseline and at day 5–9 (Table).

There were no significant differences between treatment groups in the incidence of hypotension, hemorrhage, non-cardiac adverse events or mortality related to treatment.

Treatment Trends

Treatment	P	AMP 15 mcg/kg	AMP 30 mcg/kg	AMP 60 mcg/kg
No. Patients	9	11	14	11
Myocardial Salvage (%LV)				
Median	17.0	27.0	30.0	42.0
(25, 75 percentile)	(12.36)	(1.36)	(5, 45)	(18.54)

Conclusion: 1) AMP579 is safe in acute MI at the doses tested; 2) Although there was no significant difference in the primary endpoint, there was a trend towards smaller infarct size and greater myocardial salvage in patients with anterior MIs treated with the two higher dose groups of AMP579 compared to placebo.

P456 Factors improving survival of Sarcoglycan deficient myotubes subjected to cyclic stretch

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Sarcoglycans (SGs), which are the muscle specific components of the dystrophin-associated protein, are essential for the normal function of myocytes. Mutations or deficiencies of sarcoglycan proteins cause severe cardiac and skeletal myopathies in humans and animal models such as cardiomyopathic hamster.

To investigate how the lack of SGs can produce dystrophic phenotype in myocytes, we used both L6 cell line and skeletal muscle primary cultures, from which SGs were depleted by specific SGs antisense oligonucleotide (ASODN) treatment. In SGs-deficient myotubes subjected to cyclic tension at 6 cycle/min of up to 20% elongation for 1 hour using Flexercell Strain Unit, a marked increase in creatine phosphokinase (CPK) release was observed compared to the control. The confocal microscopic images showed a normal distribution of actin in SGs deficient myotubes and comparable gross morphology to the control before and after stretching. However, dystrophin immunostaining was markedly reduced in SG-deficient myotubes subjected to stretching compared to the control. Nifedipine or Tranilast medium supplementation or intracellular loading of BAPTA were able to reduce the stretch-induced CPK release. In contrast, an increase of extracellular Ca++ concentration enhanced the stretch-induced CPK release in ASODN-treated L6 myotubes. We also evaluated the effects of immunosuppressive drugs and Na/H exchanger inhibitors on CPK release from SG-deficient myotubes. We found that FK506, HOE-694 effectively reduced CPK release from SG-deficient myotubes subjected to stretching. These results suggest that the lack of SGs causes cell damage by making the cell membrane weaker to applied mechanical strain; a change in Ca++ or pH homeostasis appear to be involved in the stretch-induced damage of SG-deficient myotubes.

P457 Ischaemic preconditioning attenuates nf-kb activation and gene expression of inflammatory cytokines in ischaemia-reperfused rat heart

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Background: Repetitive brief episode of ischemia and reperfusion make the myocardium more tolerant to the subsequent prolonged ischemia. The cardioprotective effect of this phenomenon is known as ischemic preconditioning. However, the exact molecular mechanisms for ischemic preconditioning remain unknown. NF-κB plays a pivotal role in the regulation of immune and inflammatory responses via the gene expressions of such inflammatory cytokines and adhesive molecules as IL-1, IL-6, TNF-α, and ICAM-1. The aim of this study is to investigate the effects of ischemic preconditioning on the expression of cardiac NF-κB and inflammatory cytokines in ischemia-reperfused (I/R) rat model.

Methods: Rats undergoing ischemic preconditioning (IP group n = 6) and controls (C group n = 6) were subjected to 30 min of left coronary artery occlusion followed by 3 hours of reperfusion. Ischemic preconditioning was achieved four 5-min cycles of ischemia, each followed by 10 min of reperfusion. Risk area was determined by injection of Evan's blue and infarct size was measured by triphenyl tetrazolium chloride method. The nuclear DNA binding activity of NF-κB was evaluated by electrophoretic mobility shift assays (EMSA). The mRNA levels of TNF-α, IL-1 β, and IL-6 were measured by semi-quantitative RT-PCR. The localization of activated NF-κB was evaluated by immunohistochemical method using anti-p65 NF-κB polyclonal antibody.

Results: Infarct size was significantly reduced in IP group as compared with C group. The DNA binding activity of NF-κB was also significantly reduced in IP group. The immunohistochemical method revealed that NF-κB immunopositivities were mainly localized in the infiltrated imflammatory cells and cardiomyocytes in infarct zone. In contrast, the percentage of immunopositive cells was decreased in IP group. The semi-quantitative RT-PCR revealed that the mRNA levels of IL-6 and TNF-α were also significantly downregulated in IP group as compared with C group.

Conclusion: These data suggest that (1) the induction of inflammatory cytokines and NF-κB plays an important role in I/R injury and that (2) the attenuated gene expressions of these inflammatory cytokines may contribute to the infarct size reduction via NF-κB downregulation by ischemic preconditioning in this model.

P458 Stimulation of glucose oxidation during reperfusion is mediated by calcium-dependent activation of pyruvate dehydrogenase

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We have previously observed that oxidation of glucose is enhanced early during reperfusion following prolonged ischemia. To determine the role of activation of pyruvate dehydrogenase (PDH), a mitochondrial key enzyme of glucose oxidation, isovolumically beating isolated rat hearts, perfused with erythrocyte-enriched Krebs-Henseleit buffer (8 mM glucose, 0.4 mM palmitate, 70 mU/l insulin), were subjected to 20 or 35 min of no flow ischemia followed by 60 min of reperfusion. Myocardial activity of PDH was mesured by the method of J.G. MacCormack and R.M. Denton (Meth. Enzymol. 174, 95. 1989). Ruthenium red (RR) was added to the perfusate (6 μM) to inhib mitochondrial calcium uptake.

Results: Hearts subjected to 20 minutes of ischemia exhibited complete recovery of left ventricular pressure development (LVDP: 81 mmHg). In contrast, after 35 minutes of ischemia, recovery of LVDP was poor (30 mmHg; $p < 0.001$) compared to control.

	Glucose oxidation (nmole min^{-1} g w w^{-1})				% of PDH activation			
Ischemia:	control	20 min	35 min	35 min + RR	control	20 min	35 min	35 min + RR
Reperfusion + 5 min	18 ± 3	24 ± 5	$112 \pm 19^{**}$	$42 \pm 3^{+}$	13.3 ± 3	$38 \pm 4^{*}$	$73 \pm 2^{**}$	$15 \pm 3^{+}$
Reperfusion + 60 min	20 ± 8	10 ± 1	52 ± 16	45 ± 12	15 ± 2	12 ± 3	$50.2 \pm 2^{**}$	13 ± 4

$^{*}p < 0.05$; $^{**}p < 0.001$ versus control; $^{+}p < 0.05$ versus 35 min

Conclusion: The results indicate that glucose oxidation and activity of PDH increase during reperfusion depending on the severity of ischemia injury. Activation of PDH seems to be mediated by myocyte calcium overload.

CARDIAC HYPERTROPHY

P459 Activation of the transcription factor NF-κB and expression of cyclooxygenase-2 in angiotensin II-stimulated cardiac fibroblasts

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Increasing evidence suggests that angiotensin II, one of the most important mediators of cardiac hypertrophy and fibrosis, may act as a direct growth factor for the heart. However, direct effects of angiotensin II on cardiac cells have not been well characterized. Angiotensin II may exert its effects by inducing inflammatory mediators. Because transcription factor NF-κB is crucial in activating the transcription of genes coding for inflammatory mediators, we examined the activation of transcription factor NF-κB and expression of NF-κB-dependent COX-2 after angiotensin II stimulation in adult rat cardiac fibroblasts.

Methods: The effects of angiotensin II and AT_1- and AT_2-receptor antagonists on modulation of transcription factor NF-κB were examined with electrophoretic mobility-shift assays and confocal immunofluorescence experiments. COX-2 expression was analyzed by RT-PCR and Western blotting.

Results: Angiotensin II (10^{-6} M) increased NF-κB (p50/p65) DNA binding activities in rat cardiac fibroblasts and induced COX-2 expression. AT_1- but not AT_2-receptor-antagonists (10^{-6} M) inhibited NF-κB activation and nuclear translocation of NF-κB as well as COX-2 expression (n = 6).

In conclusion our data raise the possibility that the NF-κB signal-transduction pathway may contribute significantly to myocardial inflammation, injury, and fibrosis.

P460 Coordinated upregulation of left ventricular TGFβ, collagen and fibronectin mRNA in aortic stenosis

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The activation of the renin angiotensin system (RAS) has been associated with increased myocardial fibrosis in heart failure and in pressure overloaded hearts. Growth factors like TGFβ are probably also involved in this process. Our aim was to investigate whether the ACE mRNA together with TGFβ, collagen (col) I, col III, and fibronectin (fn) mRNA is increased in pressure-overloaded human hearts.

We investigated human left ventricular myocardium which was harvested from patients undergoing aortic valve replacement due to aortic stenosis (AS, n = 16). Probes from non-transplanted donor-hearts and pts with mitral valve disease were used as controls (n = 7). For mRNA quantitation, we used an externally standardized RT-PCR-HPLC system. GAPDH and PDH mRNAs were used as external reference genes.

We measured a significant increase of ACE (157%), col I (230%), col III (192%), fn (254%) and TGFβ (167% of control) mRNA content in AS.

Group	ACE	Col I	Col III	fn	TGFβ
Control	1.08 ± 0.5**	0.1 ± 0.07*	0.12 ± 0.06*	0.13 ± 0.9*	3.0 ± 0.7*
AS	1.7 ± 0.3	0.23 ± 0.11	0.23 ± 0.11	0.33 ± 0.19	5.0 ± 1.9

*p < 0.007 or **p < 0.03 compared with AS

A highly significant correlation existed between the expression of coll, III and fn (col I vs. col III: r = 0.91, p < 0.001, col III vs. fn: r = 0.91, p < 0.001, col I vs. fn: r = 0.91, p < 0.001) although these genes are located on different chromosomes. A significant correlation was also observed between TGFβ and coll (r = 0.37, p < 0.05) and fn (r = 0.41, p < 0.02) but not with ACE.

Pressure overload induces the coordinated upregulation of collagen I, III and fibronectin in the human myocardium. ACE and TGFβ are probably involved in this process.

P461 Alterations in right ventricular remodelling and regional function in primary versus thromboembolic pulmonary hypertension using magnetic resonance imaging

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Pulmonary hypertension (PH) causes adaptive remodeling of the right ventricle (RV), often leading to RV failure. Magnetic resonance imaging (MRI) with tissue tagging (MRTT) enables an integrated evaluation of RV structure and regional intramural function. To characterize the ventricular response and the remodeling process in primary PH (PPH) vs. thromboembolic PH (TPH) under similar loading conditions, MRI studies were performed on a 1.5 T MR scanner (Signa, GEMS) using a fast breath-hold sequence and 2D MRTT.

Methods: Six patients with PPH (mean age 47, 4 female) were compared to seven patients with TPH (mean age 43, 4 female). Pulmonary artery (PA) systolic pressure was similar in PPH and TPH (80 ± 11 vs. 75 ± 10 mmHg, p = NS). Short axis images were acquired from the PA to the RV apex using 6 mm slices. Global RV parameters of end diastolic volume (EDV, in ml), mass (M, in g), mass-to-volume ratio (M:V), and ejection fraction (EF, in%) were measured by modified Simpson's method. RV free wall thickness (RVWT, in mm) was measured at the mid-ventricular level. Regional RV systolic function was measured at 3 short axis locations (Basal Inflow, Mid-Ventricle, Apex). Regional 2D strain parameters E1 (comparable to wall thickening) and E2 (comparable to circumferential shortening) were measured and pooled by location.

Results: RV EDV was greater in TPH (110 ± 21 vs. 82 ± 17, p < 0.05), while RV M was similar (p = NS). RV M:V was greater in PPH (1.7 vs. 1.3, p < 0.05), and RVWT was greater in PPH (10 ± 2 vs. 7 ± 2, p < 0.05). RV EF was depressed in both groups, but was greater in PPH (28 ± 3% vs. 20 ± 4%, p < 0.05). E1 was similar in the two groups at all locations (p = NS). E2 was greater in the Basal Inflow and Mid-Ventricular regions in PPH vs. TPH (−0.125 vs. −0.101, p < 0.05).

Conclusion: MRI and MRTT permit characterization of 2 distinct global and regional remodeling patterns in PH, with differing impacts on RV contractile function despite similar loading conditions. These data may provide new insights into the mechanisms and prognosis of RV failure in PH.

P462 Chronic effects of p70S6-kinase-inhibitor rapamycin on left ventricular function, heart morphology and vascular reactivity in rats

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Rapamycin (R) inhibits angiotensin II induced cardiomyocyte hypertrophy by p70S6 kinase inactivation in vitro. The effects of R in vivo are unclear. We treated rats with R (0.5 mg/kg/day, R0.5 or 2.0 mg/kg/day, R2.0) or placebo (P) per gavage for 8 weeks. Mean arterial pressure (MAP), cardiac index (CI) were measured by Millar-tip catheter and electromagnetic flowmeter, respectively and total peripheral resistance index (TPRI, mmHg/ml/min/kg) calculated. After hemodynamic measurements, hearts were excised, weighed and analyzed morphometrically. The phenylephrine (PE) induced vasoconstriction as well as acetylcholine (Ach) and nitroprussid (SNP) induced relaxation were studied in aortic ring in vitro. Results are shown below:

	P (n = 10)	R0.5 (n = 10)	R2.0 (n = 10)
MAP (mmHg)	109 ± 4	120 ± 3	135 ± 6*
TPRI	0.28 ± 0.02	0.37 ± 0.02*	0.39 ± 0.02*
CI (ml/min/kg)	308 ± 9*	268 ± 17	258 ± 17*
LV weight (mg/g)	2.26 ± 0.07	2.39 ± 0.05	2.55 ± 0.06*
RV weight (mg/g)	0.58 ± 0.03	0.66 ± 0.03	0.70 ± 0.04*
LV cavity area (mm^2)	41 ± 2	37 ± 2	32 ± 2*
LV wall thickness (mm)	1.47 ± 0.08	1.68 ± 0.09	1.91 ± 0.10*
LV myocyte CSA (μm^2)	181 ± 17	188 ± 22	230 ± 25
PE, Kmax (% KCl)	155 ± 8	174 ± 16	212 ± 10*
Ach, EC50 (−logM)	6.71 ± 0.05	6.70 ± 0.08	6.39 ± 0.06*
SNP, EC50 (−logM)	8.6 ± 0.10	8.5 ± 0.12	7.9 ± 0.09*

(mean ± sem; *p < 0.05 vs. P; CSA, cross section area; Kmax, maximal contraction)

Thus, Rapamycin induced dose-dependent hypertension, LV hypertrophy in vivo and vascular dysfunction with increased constriction and reduced response to vasodilator stimuli.

P463 Physiological left ventricular hypertrophy induced by voluntary exercise in rat hearts

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Introduction: Exercise training has been demonstrated to induce physiological cardiac hypertrophy with normal or enhanced cardiac performance. Pathological cardiac hypertrophy caused by clinical disorders such as valvular heart disease and hypertension eventually results in congestive heart failure. Difference between exercise-induced hypertrophy and pathological hypertrophy is not clear. Recently, calcineurin was shown to be involved in pathological hypertrophy. Whether calcineurin participates in exercise-induced cardiac hypertrophy is unknown. The purposes of this study were 1) to assess mechanical performance of rat hearts with the exercise-induced hypertrophy; 2) to determine whether calcineurin plays a role in the exercise-induced hypertrophy. Previous animal studies of exercise training used short and intense exercise such as forced treadmill running and swimming. These types of exercise may not be physiological with excessive stress inducing unfavorable neurohumoral responses. Therefore, we rather elevated a baseline physical activity level of rats in the environment allowing them to exercise voluntarily.

Methods: 7 week-old male Wistar rats were assigned to either 10 weeks of voluntary exercise training program (Ex) or sedentary condition (Sed). Ex rats ran at their favorite time, with speed and duration of their choice in our specially manufactured cages with a controlled running wheel and distance counter. We did echocardiography, histologic examination, and evaluation of myocardial calcineurin level by Western blotting.

Results: Ex rats ran 2.0 ± 0.7 km a day. Exercise increased left ventricular (LV) weights per body weights by 12% ($p < 0.05$). There was a positive correlation between LV weights and running distance ($r = 0.73$, $p < 0.05$). No obvious fibrotic change was induced by the exercise. LV myocyte width was 22.7 ± 1.2 mm in Ex rats and 19.3 ± 1.4 mm in Sed rats (statistically not significant). Exercise increased LV diastolic dimension (7.8 ± 0.3 in Ex rats vs. 6.9 ± 0.3 mm in Sed rats, $p < 0.05$) and stroke volume (0.20 ± 0.02 vs. 0.18 ± 0.02 ml, $p < 0.05$). Protein level of calcineurin did not significantly differ between the two groups.

Conclusion: Voluntary exercise induced LV hypertrophy without impairment in mechanical performance. Increased LV diastolic dimension without significant change in myocyte width may correspond to eccentric hypertrophy observed in athlete hearts. Protein level of calcineurin was not affected by the voluntary exercise. These findings may distinguish physiological hypertrophy in the voluntary-trained rats from pathological hypertrophy.

P464 Transgenic mice with cardiac specific overexpression of the β1-adrenergic receptor

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The heart expresses both β1- and β2-adrenergic receptors which mediate the stimulation of heart rate and contractility by catecholamines. To study the function of the predominant β1-subtype we have overexpressed it in transgenic mice under the control of the heart-specific α-myosin heavy chain promoter. Two independent lines were identified by Southern blotting and receptor density was determined by radioligand binding. Transgene expression was age-dependent with 5-fold and 15-fold overexpression at six weeks of age. *In vitro* experiments determining the spontaneous frequency of isolated atria in response to agonist stimulation revealed a shift of the concentration-response curve to the left. This effect was more pronounced in the line with 15-fold overexpression. *In vivo* basal heart rate and contractility were higher in both transgenic lines at young age (12 weeks) but a pronounced decrease of contractility was observed in the line with high overexpression with increasing age. Pathological examination revealed age-dependent progressive myocyte hypertrophy. At 35 weeks of age there was an increase in myocyte cross-sectional areas of 252 ± 20% in transgenic mice as compared to wild-type littermates. We conclude that modest overexpression of β1-adrenergic receptors in the heart results in increased responsiveness to catecholamines, but that higher levels of these receptors are ultimately detrimental.

P465 Endothelin-1-induced increases in coronary microvascular endothelial superoxide anion production: a possible role in left ventricular hypertrophy?

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Elevated plasma angiotensin II (ang II) levels in guinea pigs with left ventricular hypertrophy (LVH) are associated with activation of NAD(P)H oxidase-induced superoxide (O_2^-) generation from coronary microvascular endothelial cells (CMVE), and subsequent endothelial dysfunction. Ang II has also been shown to modulate the release of endothelin-1 (ET-1) from endothelial cells. We have therefore studied the possible role of ET-1 in LVH and endothelial dysfunction.

Methods: In the present study we measured plasma levels of ET-1 by radioimmunoassay in a guinea pig supra-renal aortic-banded, pressure overload model of LVH. Subsequently, CMVE (isolated from normal guinea pigs) were cultured for 14 days (including one passage) and lucigenin-chemiluminescence used to measure ET-1-induced changes in CMVE NADH/NADPH-dependent O_2^- production following cell lysis. The integral for the first 10 minutes of the reaction represents the total O_2^- produced over this time, and was normalised to CMVE lysate protein content.

Results: Plasma ET-1 levels were unaltered in sham-operated animals compared to normals (21.9 ± 2.5 cf. 25.4 ± 1.4 pg/ml respectively), but were significantly ($p < 0.05$) elevated in aortic-banded animals (31.7 ± 1.9 pg/ml). In control CMVE, NADH and NADPH oxidase activity was 1097.9 ± 105.5 & 273.1 ± 24.7 V.s/mg protein respectively. NADH oxidase activity was significantly ($p < 0.01$) increased (1540.2 ± 121.2 V.s/mg protein) by incubation with ET-1 (1 nM for 9 hours), but NADPH oxidase activity (280.8 ± 30.8 V.s/mg protein) was unaltered. This ET-1 induced increase in NADH oxidase activity was significantly ($p < 0.05$) inhibited (1050.8 ± 104.2 V.s/mg protein) by the ETA receptor antagonist BQ123 (1 μM for 9 hours).

In conclusion, these data demonstrate that (a) plasma levels of ET-1 are elevated in our model of LVH and (b) ET-1 stimulates increased O_2^- production by CMVE. ET-1 may therefore play a role in the endothelial dysfunction associated with LVH.

P466 Induction of BNP expression in human atrial myocardium by diastolic stretch

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Recently, BNP has been described as an "emergency hormone" which is quickly and markedly expressed in isolated neonatal rat myocytes under a variety of conditions. Using the published sequence of human BNP, we synthetized a cDNA-probe and studied gene-expression of BNP (total RNA, northern-blots) in right atrial muscle preparations obtained from patients undergoing aorto-coronary bypass surgery without any clinical signs of congestive heart failure. N = 20 muscle preparations were mounted in an isometric myograph, stimulated at 60 beats per minute at an experimental temperature of 37°C, and stretched to l_{max}, the muscle length at which maximum systolic force is developed. Half of the preparations were overstretched to 120% of l_{max}, increasing diastolic tension exponentially and decreasing systolic tension significantly. Gene expression of BNP was determined at 1, 2, 4 and 8 hours after start of overstretch. Gene expression of BNP was found to be linearly related to the time of diastolic overstretch: $y = 1.21 + 0.62t$, when y represents the relative increase in mRNA of BNP and t the time of diastolic overstretch. In control experiments without diastolic overstretch, no increase in BNP-mRNA was found. The stretch-induced increase in BNP-expression was suppressed by preincubation with losartan (10^{-6} M). In conclusion, BNP, an "emergency hormone" for hemodynamic overload, is increasingly expressed by diastolic overstretch in human cardiac muscle obtained from right atria of patients without heart failure, an effect which is mainly mediated by angiotensin II.

P467 Midwall myocardial shortening in athletic left ventricular hypertrophy

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Patients with pathological LVH have depressed midwall systolic shortening (MS)in spite of normal indices of left ventricular chamber function. Whether MS is depressed in physiological hypertrophy is unknown. In order to assess the effects of LVH induced by physical exercise on midwall left ventricular function 12 professional football players and 15 athletes recruited from the British Olympic Medical Centre were divided into those with concentric hypertrophy (group 1) and those with eccentric hypertrophy (group 2). Systolic left ventricular function was assessed at the midwall and endocardium using echocardiography and compared with 15 age and sex matched normal control subjects (group 3). Left ventricular mass index was significantly greater than controls in both athletic groups (Group 1 155 ± 5.8*, group 2 141 ± 11.1*, group 3 101 ± 5.8 g/m^2; *$p < 0.01$ compared with group 3). Left ventricular systolic function assessed at the endocardium was similar among all three groups (Ejection fraction; group 1, 63.7 ± 1.66; group 2, 66.8 ± 1.44; group 3, 66.2 ± 2.38%. Endocardial fractional shortening; group 1, 35.1 ± 1.25; group 2, 37.6 ± 1.13; group 3, 37.1 ± 1.71%). Additionally, MS was also similar among the three groups (MS; group 1, 21.2 ± 0.96; group 2, 21.9 ± 0.86; group 3, 21.9 ± 1.31%).

In contrast to patients with pathological LVH, subjects with physiological left ventricular hypertrophy due to exercise have a normal MS. There was no discrepancy between midwall and endocardial shortening in athletes with either eccentric or concentric hypertrophy compared with normal controls. This finding is reassuring but does imply that cardiac geometric changes alone cannot explain the discrepancy between midwall and endocardial systolic function in pathological LVH.

P468 Enhanced expression of cardiac adenosine A1-receptor in rats with pressure-overload left ventricular hypertrophy

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Myocardial adenosine (Ado) is increased in the compensated stages of pressure-overload hypertrophy (POH). In this setting, which is characterized by increased cardiac adrenergic stimulation, this may represent an important cardioprotective mechanism due to the known antiadrenergic properties of Ado. However, the ultimate effect of Ado will depend on the behaviour of the myocardial receptor that mediates the response, i.e. the Ado A1-receptor. We therefore examined whether left ventricular (LV) Ado A1-R gene expression is modified in the early stages of POH.

Methods: Sprague-Dawley rats aged 6 weeks were subjected to abdominal aortic banding (B) or sham operation (S). One and two weeks (wk) later, left ventricular systolic pressure (LVP, mmHg, transcarotid catheter) was measured under ketamine anesthesia. LV weight (LVw, mg/100 g body weight) was obtained post-mortem. A1-R mRNA expression (densitometric units) was measured in tissue fragments from the LV, the right ventricle (RV) and the aortic arch (AoA) by reverse transcription polimerase chain reaction, the data being normalized for the reference gene GAPDH. LV atrial natriuretic peptide (ANP) mRNA expression was also measured.

Results:

	n	LVP	LVw	LV ANP	LV A1-R	RV A1-R
S-wk1	10	108 ± 10	2.05 ± 0.03	0.13 ± 0.06	1.42 ± 0.14	0.99 ± 0.13
B-wk1	11	142 ± 13*	2.93 ± 0.17*	0.89 ± 0.14*	1.73 ± 0.18*	1.26 ± 0.14
S-wk2	10	110 ± 11	2.09 ± 0.05	0.11 ± 0.03	1.75 ± 0.09	n.a.
B-wk2	12	153 ± 14*	3.12 ± 0.19*	0.47 ± 0.11*§	3.01 ± 0.47*§	n.a.

Means ± SEM; *$p < 0.05$ vs respective sham; §$p < 0.05$ vs wk 1. No significant intergroup differences in AoA A1-R were observed.

In conclusion, gene expression of LV, but not aortic, Ado A1-receptor is markedly enhanced since the early stages of POH, further supporting the notion that activation of this "antiadrenergic" receptor may represent a cardioprotective mechanism in the adaptation to pressure overload.

P469 The effect of growth hormone and insulin-like growth factor-I on isolated rat cardiomyocytes

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Cardiac hypertrophy is a mechanism of adaptation to increased workload of the heart. Initially, it reduces wall stress and increases cardiac output. However, hypertrophy is a predictor of heart failure and associated with a bad prognosis. However, recent studies suggested a clinical benefit of the hypertrophy-inducing hormones growth hormone (GH) and/or its effector molecule insulin-like growth factor-I (IGF-I) in heart failure.

In order to characterize the signal transduction of GH and IGF-I, rat cardiomyocytes (CM) were incubated with GH (100 nM) and IGF-I (100 nM), respectively. The expression of immediate early genes such as c-myc, c-fos and c-jun as well as of phospholipase C (PLC)-isozymes and of GAPDH were determined by RT-PCR.

Both GH and IGF-I resulted in an increase of expression of c-myc, c-fos and c-jun. Expression of PLCβ3 was also increased by GH and IGF-I. The induction of immediate early genes by GH was not abolished by preincubation od CM with the IGF-I receptor antagonist IGF-I anolog. The early growth response of CM to IGF-I was abolished by preincubation with wortmannin (25 nM), an inhibitor of phosphoinositide-3-kinase (PI3K), and rapamycin, an inhibitor of the p70 S6-kinase (p70^{S6K}) pathway. Moreover, preincubation of CM with antisense oligonucleotides (AO; 5 μM) directed against PLCβ3 abolished the induction of immediate early genes, while the corresponding sense oligonucleotides (SO) had no effect.

In conclusion, the data suggest that the induction of immediate early genes by IGF-I requires PI3K and p70 S6K activity and the expression of PLCβ3. The induction of immediate early genes by GH involves a signalling mechanism beyond IGF-I.

P470 Left ventricular hypertrophy and myocardial damage in response to aortic banding differ between male and female rats

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Several lines of evidences demonstrate that incidence and behavior of cardiovascular diseases are gender related and females (F) have distinct advantages over males (M). To test whether myocardial response to an increased afterload may differ in time and magnitude between sexes supraventricular aortic banding was obtained with a calibrated ring to reduce the aortic diameter by 30%. M(n = 72) and F(n = 72) rats were sacrificed 2, 4, 6, 10, 15 and 90 days after surgery. Control animals matched for age and body weight (bw) were submitted to a sham operation (SO)(M = 41,F = 53) in which the aorta was not constricted. Following measurement of intraventricular pressure by puncturing the left ventricular (LV) chamber with a needle connected to a fluid filllled transducer, hearts were arrested with cadmium chloride, the weight of the ventricles determined and replacement myocardial fibrosis morphometrically measured on paraffin embedded tissue. LV pressure increased to 273 ± 17 mmHg in M and 257 ± 35 mmHg in F 2 days after surgery and remained elevated until 90 days without evidences of LV dysfunction and differences between sexes. In comparison with SO, LV weight in F rats increased 18% ($p < 0.05$) at 2 days and progressively with time reaching a 56% ($p < 0.005$) increase at 90 days. In contrast, in M the hypertrophic response of LV was 18% ($p < 0.01$) at 6 days and only 46% ($p < 0.005$) at 90 days. During the entire experiment bw was not affected by the surgical procedure so that the changes in LV weight to bw were similar to those found at ventricular level. Aortic banding did not affect RV weights although at 90 days a 20% (ns) increase was seen in both M and F rats. Myocardial damage characterized by reparative tissue at the early stages and fibrotic tissue in the later intervals was limited to LV and was already present at 2 days after surgery. Quantitatively, in F rats the amount of tissue damage increased more than 2-fold from 69 ± 38 mm^3 at 2 days to 144 ± 58 mm^3 at 90 days whereas in the same interval in M LV a 4.5-fold increase was seen from 51 ± 23 mm^3 to 230 ± 82 mm^3. In conclusion, acute aortic banding in rats induces LV hypertrophy and myocardial damage progressively increasing with time in both sexes. However, in F rats LV hypertrophy takes place earlier, is greater than in M rats and is accompanied by less amount of damage. The attenuated myocardial growth of LV in M rats may be the consequence of the larger amount of scarred tissue. Thus, the growth reserve capacity of the LV in response to stressful conditions in M is significantly lower than in F rats.

P471 Identification of a silencer element in the 5.1 kb rat atrial natriuretic peptide promoter in acute and chronic pressure overload

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Upregulation of left ventricular atrial natriuretic peptide (ANP) is a conserved marker of cardiac hypertrophy. In the present study we investigated the activity of the 3.6 kb promoter region of the rat ANP gene and characterized an additional 1.5 kb fragment upstream of the 3.6 kb fragment in chronic and acute pressure overload.

Design and Methods: The upstream 5′ flanking site of the previously cloned 3.6 kb ANP promoter was extended by 1.5 kb using the promoter walker method. The newly cloned 1.5 kb fragment shows no homologies with any known sequence (EMBL). Promoter-reporter gene (luciferase) constructs carrying the 3.6 kb fragment or different sections of the newly cloned 1.5 kb upstream sequence together with the 3.6 kb fragment, were transfected (lipofection) into rat left ventricles (LV) after 8 weeks of supraaortal banding. Luciferase activity was measured in LV tissue 3 days after transfection. Similarly, promoter constructs were transfected into normal rat hearts 3 days prios to acute wall stress (isovolumetric balloon in the Langendorff apparatus for 2 hours) before assessment of luciferase activity (n = 5).

Results: In vivo transfection of the construct carrying the previously cloned 3.6 kb promoter revealed a significant 2.2-fold ($p < 0.05$) and 40-fold ($p < 0.01$) upregulation of luciferase activity after chronic and acute stimulation, respectively. Upstream extension of the 3.6 kb promoter by the newly cloned DNA stretch (0.6 or 1.5 kb) resulted in a substantial 50% or 90% loss of luciferase activity in chronic hypertrophy or after acute wall stress, respectively ($p < 0.05$ vs. 3.6 kb fragment).

In conclusion, acute and chronic wall stress activate the 3.6 kb ANP promoter. However, the physiological relevance of this promoter section may be overestimated since a dominant silencer in the newly cloned upstream promoter inhibits the response of the promoter to both acute and chronic wall stress. Specifically, an inhibitory element was located 3388 to 4225 bp upstream of the ANP transcription start site that that may have important functional implications for the in vivo regulation of ANP.

P472 In compensated human cardiac hypertrophy relaxation velocity correlates with myocardial SERCA 2a levels

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Background: Reduced activity of the sarcoplasmic reticulum (SR) Ca^{2+}-ATPase (SERCA) contributes to alterations of intracellular Ca^{2+} handling and contractile behavior in human failing myocardium. In compensated cardiac hypertrophy relaxation impairment precedes the development of reduced systolic pump function but alterations of the SR Ca^{2+} transport proteins are not yet established.

Methods: We studied the diastolic contractile properties and the myocardial SR Ca^{2+} ATPase (SERCA) protein expression in septal myocardium from patients with hypertrophic obstructive cardiomyopathy (HOCM, n = 7) or aortic valve stenosis (AoSt, n = 8) and in nonfailing myocardium (NF) of 4 organ donors. Force of contraction of thin isolated muscle preparations was measured under isometric conditions at a stimulation frequency of 0.5 Hz and 37°C. SERCA protein expression was determined by Western blot analysis.

Results: Mean relaxation velocity (−dT/dt) and mean SERCA protein expression (1000 cpm/mg protein) ± SEM.

	NF	HOCM	AoSt
−dT/dt (mN/mm²/s)	12.4 ± 1.1	6.6 ± 1.2*	6.7 ± 0.9*
SERCA (10^3 cpm/mg protein)	72.5 ± 5.8	45.1 ± 2.2*	46.1 ± 2.1*

*: $p < 0.05$ versus NF.

Within all patients with cardiac hypertrophy there was a significant correlation between −dT/dt and SERCA expression ($r = 0.69$, $p = 0.004$).

Conclusion: The results support the hypothesis that reduced SERCA protein expression contributes to the relaxation impairment in compensated cardiac hypertrophy before pump failure due to progressive dilation of the left ventricle develops.

P473 Translocation of annexin V in cardiac cells during calcium overload

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Annexin V (An V) has the ability to bind to membranes in a Ca^{2+} dependent manner. However, the function of An V requires further clarification. We had reported that An V moves from cytosol to the cell membrane during ischemia and reperfusion and that An V may play a role of cardiac cell injury. However several papers reported recently that An V had already bound to cell membranes in the physiological state.

It is our aim to show that An V is in cytosol in the physiological state and that An V translocates to the cell membrane during calcium overload.

The trabecule of the rat right ventricle was permeabilized by alpha-toxin. They were then incubated in a Ca^{2+} buffered solution (pCa 6.3, 6.0, 5.6, or 4.5) containing 30 mM Pipes, 5 mM Mg-ATP, 10 mM creatine phosphate, $MgCl_2$ calculated to 2 mM Mg^{2+}, 10 mM total EGTA and Ca-EGTA/EGTA calculated for the desired pCa. Another group was incubated in pCa 6.3 for 30 min after it was exposed to pCa 4.5 for 30 min.

At the end of incubation, muscles were homogenized and centrifuged at 48,000 × g at 4°C for 30 min. The pellets were suspended in the same buffer but containing 1% Triton-X-100 and centrifuged at 48,000 × g. Annexin V was stained with polyclonal antibody in the western blot method.

The staining of annexin V was strongly pronounced in a cytosolic fraction in pCa 6.3, which means the physiologic state. An V was both in the membrane fraction and in the cytosolic fraction in pCa 6.0, and An V was also strongly stained in the membrane fraction in pCa 5.6 and 4.5, which indicates Ca overload. In the muscles exposed in pCa 6.3 after pCa4.5, An V was found in both the cytosol and membrane.

This result shows that annexin V is present in cytosol under the physiological Ca^{2+} concentration and translocates to the cell membrane in response to the rise in intracellular Ca^{2+} and that this binding is reversible. It should be suspected that An V may play a role of cardiac cell injury.

PULMONARY CIRCULATION

P474 Modulation by nitric oxide of the endothelin B receptor mediating pulmonary hypertension in the guinea pig

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The endothelins (ETs) play a significant role in pathophysiology of pulmonary disorders, notably of pulmonary hypertension. Since the diverse effects of ETs are mediated via distinct receptor subtypes, aims of the present study were a) to characterize which receptors are involved in the potent pulmonary hypertensive effect of ETs and b) to verify whether endogenous production of nitric oxide (NO) may modulate such hypertension.

Methods: The work was performed on the heart-lung preparation of guinea pig (HLP) perfused with homologous blood, according to the previous described method (Argiolas et al., Br. J. Pharmacol. 114: 203–9, 1995).

Results: Bolus injections (12.5–400 ng) of ET-1 and of the ET B selective agonist, ET-3,into the venous cannula of the HLPs produced a dose-dependent increase of pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR, calculated as PAP-LAP/CO). Adding to the perfusing blood the selective ET B receptor antagonist BQ 788 (0.0001 mM) the pulmonary hypertensive effects elicited by both ET-1 and ET-3 were almost completely abolished. In addition, the dose-response curves elicited by ET-3 for PAP and PVR were significantly shifted to the left by the presence of the NO synthase inhibitor, L-Nw-Nitro-L-Arginine (L-NNA, 0.2 mM).

In conclusion, our data on HLPs of guinea pigs indicate that the pulmonary hypertensive effects of endothelins are mainly mediated via stimulation of ET B receptor subtype. Moreover, it is suggested that generation of NO attenuates these hypertensive effects, thus contributing to the overall pulmonary hypertension induced by ETs.

P475 Intensive short-term observation for clinically stable patients with acute pulmonary embolism and right ventricular dysfunction

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Background: Optimal treatment for patients with pulmonary embolism (PE) presenting with acute right ventricular dysfunction (RVD) but no evidence of shock is still under debate. While some advocate extensive use of thrombolysis, conservative treatment strategies based on the initial clinical course may represent a viable alternative to identify patients at higher risk and reduce treatment-related complications. We report our experience with intensive short-term observation of clinically stable patients with acute PE and RVD.

Methods: Among 223 consecutive patients with PE (diagnosed by by lung scintigraphy, spiral CT scan, and/or pulmonary angiogram), 89 (40%; age 69 ± 15 years; female 64%), were normotensive or moderately hypotensive on presentation (but not in shock), and had echocardiographic evidence of RVD, defined as RV dilatation (end-diastolic dimension > 30 mm or right/left ventricular ratio > 1 in 4-chamber view), and/or paradox septal systolic motion, in the absence of RV hypertrophy. These patients were observed for >24 hours in our Chest Pain Unit, with continuous monitoring of blood pressure, pulse oxymetry and ECG, and serial heart and venous ultrasound scans. The decision of instituting "rescue" thrombolysis was based on the clinical course and associated conditions of each patient.

Results: Of the 89 study patients, the majority (n = 75; 84%) had an uneventful clinical course and were discharged: all were treated with i.v. heparin except 5 who received temporary vena cava filter and urokinase infusion for proximal floating venous thrombosis. Two additional patients remained stable but later died of cancer. The remaining 12 (13%, age 70 ± 15 years) experienced clinical deterioration due to PE (worsening dyspnea and/or hypotension leading to shock) <48 hours after admission. Of these, 7 patients (age 66 ± 17 years, range 34–85) were immediately treated with "rescue" thrombolysis with urokinase (n = 5) or rtPA (n = 2): all recovered and were successfully discharged. In the remaining 5 patients (age 76 ± 11 years, range 62–87), thrombolysis was withheld because of very recent surgery (1 patient, who died of PE), or advanced cancer (4 patients, 3 of whom died of PE). Therefore, total acute mortality for PE in the study group was 4.5%, with all deaths but 1 occurring in terminally ill patients.

Conclusions: Intensive short-term observation represents a valid management strategy for patients with PE and RVD who are clinically stable on presentation, allowing timely and selective use of "rescue" thrombolysis to suitable candidates and minimising treatment-related complications.

P476 Prognostic indicators in scleroderma-associated pulmonary hypertension

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Scleroderma associated pulmonary hypertension (SSc-PHT) and primary pulmonary hypertension (PPH) are distinct conditions. Continuous prostacycline therapy may induce dramatic reductions of pulmonary artery pressure (PAP) in PPH and is prognostically beneficial. PAP rarely falls significantly in SSc-PHT during chronic prostacycline therapy and prognostic benefit has not been shown to date. Right atrial pressure (RAp), cardiac index (CI), mixed venous oxygen (SVO_2), and response during vasodilator challenge are prognostic markers in PPH. Appropriate prognostic indicators for SSc-PHT are not known.

We have performed vasodilator challenges in and followed 35 patients with SSc-PHT over the past 26 months, 29 are female, mean age is 64. 13 patients have died after a mean follow up of 39 weeks, survivors have been followed for an average of 36 weeks. Survivors had a lower right atrial pressure, higher cardiac index and lower baseline pulmonary vascular resistance (PVR), than non-survivors. 10/14 non-survivors had a baseline PVR > 850 dynes cm^{-5}, versus 5/21 survivors. But preserved vasodilator reserve has no influence on survival (see table).

Baseline Haemodynamic Data

	PVR (dynes cm^{-5})	RA (mmHg)	CI (l/min/m^2)	SVO_2 (%)	Fall PVR (%)
Non-survivors	1247 ± 676	11 ± 6.4	1.94 ± 0.6	60 ± 12	38 ± 13
Survivors	661 ± 390	6.8 ± 4.4	2.4 ± 0.6	65 ± 9	35 ± 15
p Value	<0.003	<0.03	<0.03	=0.16	=0.5

Data as Mean+SD, statistics: unpaired T test

Catheterisation was repeated between 4 & 6 months in 14 patients of whom 7 subsequently died. A fall in mixed venous oxygen despite treatment was the most powerful predictor of subsequent death (−19 + 18% v +1 + 6% p < 0.02).

Right ventricular failure develops at relatively low pulmonary pressures in SSc-PHT. PVR in excess of 850 dynes cm^{-5} and progressive fall in mixed venous oxygen appear suitable markers for poor prognosis in this population.

P477 Effects of pulmonary hypertension on right ventricular function in the newborn lamb

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Severe respiratory diseases of the newborn are often accompanied by pulmonary hypertension causing an increased afterload of the right ventricle (RV). To determine the effects of this increased afterload on RV function, we examined RV function before, during and after partial balloon occlusion of the pulmonary artery, in nine newborn lambs. RV function was quantified by indices derived from RV pressure-volume relations, obtained by a combined pressure-conductance catheter during inferior vena cava occlusion.

Results: An almost 2-fold increase of end-systolic RV pressure (Pes) was applied during 4 hours. Cardiac output (CO) and stroke volume (SV) were maintained while end-diastolic volume (Ved) did not change significantly during this period. RV systolic function improved significantly; the end-systolic pressure-volume relation (ESPVR) shifted leftward, indicated by a significantly decreased volume intercept at a pressure of 25 mmHg (V-25), and an increased slope (Ees).

	Pes (mmHg)	V-25 (ml)	Ees (mmHg/ml)	CO (ml/min)	SV (ml)	Ved (ml)
Before	21.9 ± 1.6	4.96 ± 0.71	3.84 ± 0.64	0.74 ± 0.08	4.30 ± 0.40	7.95 ± 1.32
15 min	38.4 ± 3.9*	1.42 ± 1.30*	4.28 ± 1.14	0.73 ± 0.14	4.38 ± 0.40	8.01 ± 3.24
30 min	37.3 ± 4.0*	1.66 ± 1.30*	4.49 ± 1.17	0.79 ± 0.15	4.15 ± 0.40	9.16 ± 3.32
1 hr	37.1 ± 3.8*	2.81 ± 1.30*	5.32 ± 1.12	0.77 ± 0.14	3.71 ± 0.40	11.30 ± 3.18
2 hr	36.7 ± 3.8*	3.51 ± 1.23	5.81 ± 1.12*	0.72 ± 0.14	4.17 ± 0.42	9.34 ± 3.18
3 hr	38.4 ± 3.8*	2.40 ± 1.23*	5.50 ± 1.12	0.87 ± 0.14	4.82 ± 0.40	9.16 ± 3.18
4 hr	35.7 ± 3.8*	2.50 ± 1.23*	5.50 ± 1.12	1.02 ± 0.14*	4.77 ± 0.42	8.73 ± 3.18
After	24.2 ± 3.8	5.53 ± 1.23	3.73 ± 1.12	1.20 ± 0.14*	5.44 ± 0.40*	8.97 ± 3.18

* = $p < 0.05$, compared to 'Before'

Conclusion: In this newborn model, maintenance of CO during increased RV afterload is *not* obtained by an increased end-diastolic volume (Frank Starling mechanism). Instead, the RV maintains its output by improving systolic function, known as homeometric autoregulation.

P478 Right and left diastolic ventricular dysfunction in primary pulmonary hypertension: an echocardiographic and radionuclide study

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Primary pulmonary hypertension (PPH) induces RV systolic dysfunction but few data exist regarding RV and LV diastolic function. To assess both RV and LV diastolic functions in PPH, we compared 12 normal pts (gr 1: 6 M/6 F, 40 ± 15 yrs) to 22 pts (gr 2: 5 M/17 F, 51 ± 14 yrs, ns for sex and age) with PPH. Radionuclide determination of RV and LV peak filling rate (PFR) and EF, and echocardiographic measurements of pulsed wave Doppler indexes of RV and LV diastolic function (E max and A max) were performed. We also recorded RV and LV inflow by colour M-mode to assess RV and LV flow propagation velocity (FPV).

Results:

		Group 1	Group 2	p value
LV function:	LV EF (%)	68 ± 9	61 ± 12	ns
	Mitral E (m/s)	0.78 ± 0.21	0.57 ± 0.25	0.02
	Mitral A (m/s)	0.63 ± 0.21	0.67 ± 0.10	ns
	Mitral E/A	1.32 ± 0.48	0.74 ± 0.22	0.001
	LV FPV (cm/s)	72.7 ± 20.2	45.4 ± 18.8	0.003
	LV PFR	4.1 ± 0.9	2.3 ± 0.7	0.003
RV function:	RV EF (%)	58 ± 6	33 ± 10	0.0001
	Tricuspid E (m/s)	0.57 ± 0.21	0.58 ± 0.29	ns
	Tricuspid A (m/s)	0.44 ± 0.24	0.61 ± 0.13	0.03
	Tricuspid E/A	1.41 ± 0.44	0.80 ± 0.38	0.002
	RV FPV (cm/s)	42.0 ± 11.5	31.9 ± 8.0	0.02
	RV PFR	2.5 ± 0.5	1.7 ± 1.0	0.05

Both systolic and diastolic RV functions are severely depressed in primary pulmonary hypertension. Additional LV diastolic dysfunction exists and might be attributable to RV pressure overload causing leftward ventricular septal shift, thereby impairing LV filling.

P479 Prevalence of heart valve abnormalities in patients with pulmonary hypertension associated with intake of the appetite-suppressant drug menocil (aminorex)

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Recent reports have revealed an increased prevalence of mitral and aortic valve fibrosis and valvular incompetence in patients on the appetite suppressant drugs fenfluramine and phentermine (*fen-phen*). To test the hypothesis that pulmonary hypertension may be driven by a serotonin-dependent mechanism leading to carcinoid-like changes of the valve apparatus, we reviewed the autopsy reports, charts and echocardiograms of 137 patients newly diagnosed with primary pulmonary hypertension (PPH) in Austria between 1967 and 1985. Three patients had been on phentermine and three on preludin and were excluded from the analysis. Time to death was 132 months (13–348) for Menocil-PPH patients. In 58 patients a sufficient description of valvular morphology was available through autopsy reports. Six patients are alive and were examined by echocardiography.

Diagnosis	n	BMI (body mass index)	Mean PAP at diagnosis (mmHg)	PVR (dynes sec cm^{-5})
CTEPH	10	21.9 ± 3.5	52.6 ± 19.2	854 ± 523.6
Menocil PPH	60	30.3 ± 6.5	53.7 ± 18.5	528 ± 103.6
PPH	55	23.7 ± 4.2	64.1 ± 24	865.9 ± 176.8

Anoretic drug intake (months)	Valve condition (aortic [AV] and mitral valve [MV])
0	3 normal, 1 thickened MV
6–91	18 normal, 1 thickened MV, 4 thickened AV + MV
0	29 normal, 1 thickened MV + AV, 1 calcified MV

In two Menocil patients descriptions of extensive whitish thickenings of MV and AV and the right ventricular myocardium were found (time to death 48 months). Although the number of patients is small, and the analysis focused on patients with pulmonary hypertension, there is evidence of the kind of valvular pathology recently observed in patients on *fen-phen*.

P480 Determinants of pulmonary arterial wall morphology in patients undergoing the Ross operation (pulmonary autograft)

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Background: Following pulmonary autograft replacement of the aortic valve and root the pulmonary arterial wall is subjected to substantially higher pressures. There is concern about the progress of dilatation of the pulmonary arterial wall in patients due to the different morphology of that vessel compared to the aorta. In an attempt to clarify this issue we have examined the structure of the pulmonary artery (PA) wall and aorta in 18 patients undergoing the Ross operation at our institution and compared it to the structure of 8 organ donors.

Methods: *Autograft series:* Ages varied from 6–60 yrs, mean 36.1 yrs. Fourteen were male, 4 were female. The disease was endocarditis (4), aortic stenosis (7), aortic regurgitation (4), mixed aortic valve disease (2), previous VSD and aortic valve repair (1). The preoperative PA pressure was estimated to be normal in 14, slightly elevated in 2, moderately elevated in 1 and severely elevated in 1. The degree of pre operative aortic regurgitation was none in 3, mild in 4, moderate in 3 and severe in 8. *Donor series:* Ages varied from 29–65 yrs, mean 52 yrs. Three were male, 5 were female. Samples were taken from the anterior wall of the PA and aorta at operation. Media thickness was measured in each aorta and PA. Immunocytochemistry was performed using the primary antibodies Collagen I and III and sections were stained with Elastic von Gieson to measure the elastic fibre distribution. Distribution of staining was measured using image analysis. The fragmentation of the elastic fibres in the PA media was graded from 1 (no/little fragmentation) to 4 (severe).

Results: The aortic media was thicker than the PA media in both patient and donor populations. In the autograft series Collagens I and III showed more order in the aorta than in the PA, but were distributed similarly in both. The elastic fibre in all aortas showed little or no variation, whereas in PAs there was considerable variation in fragmentation. Fragmentation did not correlate with patient age, sex, primary diagnosis, symptom duration or pre operative degree of aortic regurgitation, but patients with higher pre operative PA pressures had lower fragmentation scores. To date there has been no correlation between PA structural parameters and subsequent regurgitation of the autograft.

Conclusions: In conclusion detailed PA wall composition is different from that of the aortic wall in our patients undergoing the autograft operation. There is wide variation in PA structure within our patients receiving autografts and these changes appear to be influenced by PA pressure. The implications of these findings on the long-term function of the autograft requires further evaluation.

P481 Prevalence of pulmonary hypertension in liver transplant recipients

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Pulmonary hypertension (PH) defined as mean pulmonary artery pressure (PAP) > 25 mmHg at rest is a well recognised complication in patients with portal hypertension. In this setting, PH is considered to be due to the increase of cardiac output (hyperdynamic state) and/or to the increase of pulmonary vascular resistance.

Methods: to characterize pulmonary hemodynamics, a group of 352 liver transplant recipients underwent right heart catheterization with Swan-Ganz catheter after the induction of anesthesia and before skin incision for liver transplantation. 233 were males and 119 females, mean age was 46 ± 12 years. 202 (57%) patients had post-hepatitic cirrhosis, 30 (8.5%) had alchoolic cirrhosis, 27 (7.6%) had primary biliary cirrhosis and 93 (26%) had other conditions leading to liver transplantation.

Results: right atrial pressure (RAP), PAP, cardiac index (CI), pulmonary wedge pressure (PWP), pulmonary (PVR) and systemic vascular resistance (SVR) were as follows:

RAP mmHg	PAP mmHg	PWP mmHg	CI l/min/m2	PVR UR	SVR UR
8 ± 4	17 ± 6	9 ± 4	4.6 ± 1.6	1.1 ± 0.7	9.2 ± 3.8

PH was detected in 21 (6%) patients. In 9 (2.5%) of them an increase of PVR (PVR > 2 RU) was also present. An hyperdynamic state (CI > 3.5 l/min) was detected in 276 (78%) patients. RAP was increased (>7 mmHg) in 191 (54%) patients. In patients without PH, PAP correlated with RAP ($r = 0.65$, $p < 0.0001$) and PWP ($r = 0.62$, $p < 0.0001$) but not with CI. In patients with PH no correlations between PAP, filling pressures and CI were found.

Conclusions: 1) PH is present in a small percentage of candidates to liver transplantation; 2) hyperdynamic circulation is the most frequent hemodynamic condition; 3) in patients without PH, PAP is correlated with the filling pressures of the ventricles; 4) in patients with PH the increase of PAP is not related to hyperdynamic state and/or to filling pressures.

P482 Pulmonary arterial elasticity in the clinical practice

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Since the introduction of sonographic techniques, the distensibility of the large elastic vessels can be studied under clinical conditions. The elastic behavior of the systemic large arteries has been well documented but less information is available about the pulmonary vessels. The aim of the present study was to determine the elasticity of the pulmonary artery, namely its pressure-diameter relationship and to investigate the effect of age on elastic parameters in humans.

Healthy volunteers (n = 7, 23 ± 3 years) and patients (n = 8, 55 ± 14 years) of our department of cardiology were studied. The pressure in the main left branch of the pulmonary artery was measured at right heart catheterization, while the diameter and its change with the pulse were measured simultaneously by ultrasound (3.5 MHz) from suprasternal position at rest and during light exercise. Dynamic distensibility (D_{dyn}) was determined using the pulse pressure, while the static distensibility (D_{stat}) was determined during exercise. Data are given as mean ± 1 SD.

We found that the end-diastolic diameter of the pulmonary artery was greater in older (>35 years) than in younger (<35 years) subjects (1.30 ± 0.18 vs 0.91 ± 0.09 cm; $p < 0.05$). In younger subjects D_{dyn} of the pulmonary artery was higher than of the systematic elastic arteries (normal range: 5–15 × 10^{-3} $mmHg^{-1}$). During exercise the pressure-diameter relationship shifted upwards, resulting in a further increased value of D_{stat} (39 ± 27 × 10^{-3} $mmHg^{-1}$). In older subjects D_{dyn} was considerably less (14 ± 11 × $10^{minus;3}$ $mmHg^{-1}$), and the pressure-diameter relationship shifted to the right, often indicating complete lack of D_{stat}.

It is concluded that pulmonary elasticity can be determined by ultrasound and that the age-related decrease of pulmonary distensibility is greater than that of systematic elastic arteries.

P483 Use of an echo-enhancer agent for the estimation of pulmonary artey pressure by Doppler echocardiography in patients with chronic obstructive pulmonary disease

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Objective: to assess the added value of using an echo-enhancer agent (EEA) in the estimation of systolic pulmonary artery pressure (PAPs) by Doppler, provided the increase in the intensity of the Doppler signal of tricuspid regurgitation (TR) produced by the agent, in patients with chronic obstructive pulmonary disease (COPD).

Patients: 27 consecutive patients from the Pneumology Department were studied, all of them with COPD without clinical signs of congestive heart failure.

Methods: tricuspid valve flow was obtained by continuous wave Doppler (CWD) from a 4-chamber echocardiographic apical view. When an adequate spectral velocity curve allowing the determination of peak velocity (Vmax) was recorded, PAPs was calculated by application of the equation: PAPs = $4(Vmáx)^2 + 5$. The same procedure was repeated after the administration through a peripheral vein of a bolus of Levovist® (microparticles of galactose and palmitic acid) (2.5 g at a concentration of 200 mg/ml).

Results: In all cases but one a reliable signal of tricuspid valve flow was obtained. Basally, a Doppler signal of TR was detected in 21 patients (78%), in all cases of trivial or mild degree. The determination of Vmax and, thus, the calculation of PAPs was judged as appropriate in 14 patients (52%). After the administration of the EEA the TR Doppler signal intensity was greatly increased, allowing the calculation of PAPs in 24 cases (89%) ($p < 0.001$). Compared with the basal study, the recording of the velocity profile curve improved in 21/24 cases (88%), this allowing the measurement of Vmax with a higher degree of confidence and showing also a systematic underestimation of PAPs measurements in those 14 patients in whom PAPs could be measured both basally and after the use of the EEA (37 ± 10 vs. 51 ± 17 mm Hg, $p < 0.001$).

Conclusions: The use of an EEA in patients with COPD increases the sensitivity of CWD to detect Vmax form a Doppler signal of TR, this allowing the estimation of PAPs in 89% of cases. In those 14 patients in whom a comparison betweeen basal an enhanced determinations could be performed, a systematic underestimation of PAPs in the basal condition was observed, probably due to an unadvertedly insufficient signal intensity of the TR Doppler signal.

P484 Troponin I can predict the decision for thrombolysis in acute pulmonary embolism

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Decision for thrombolysis (Lys) in acute pulmonary embolism is based on the presence of right ventricular overload (RO) and severity in clinical presentation. Troponin I (TnI) is a marker for myocardial injury which might be elevated in PE due to RO. In order to find out whether there is a correllation between the severity of PE and TnI we conducted a retrospective study on TnI in pulmonary embolism.

Method: We measured TnI levels in 46 patients with APE. The use of lys was left to the discretion of the physician in charge. For analysis patients were divided into 5 groups: (A) minor PE (PE, no RO, no systemic hypotension), (B) submassive PE (PE, RO and no systemic hypotension) and (C) massive APE (PE, RO and systemic hypotension) as well as TnI elevation (TnI+) and no TnI elevation (TnI−). The rate of lys (LR) between groups was compared.

Results: Table 1 shows results for class A-C, table 2 for TnI+ and TnI−.

Table 1

	A (n = 10)	B (n = 25)	C (n = 11)
TnI+	1	11	9
Lys	1	10	8
LR	10%	40%	72.7%

Table 2

	TnI+ (n = 21)	TnI− (n = 25)
Lys	15	4
LR	71.4%	16.0%

Of the TnI+ patients 3 did not receive lys due to contraindications. If these patients were excluded from analysis LR was be 83.3% for TnI+.

Conclusion: For the decision on use of lys in PE physicians often rely on clinical presentation and presence of RO. TnI is a good marker to select pat. that should receive lys on this basis ($p < 0.001$). It might be a useful marker for decision making of therapy in PE.

P485 Reversal by indapamide of monocrotaline-induced changes in the pulmonary circulation and in the right ventricle in the rat

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This study investigated the sequence of structural and biochemical changes in the pulmonary circulation and in the right ventricle (RV) in Monocrotaline (MCT)-treated rats. The reversibility of these changes was tested using Indapamide (IND), a Ca^{2+} channel blocker with cardioprotective properties.

Methods: Pulmonary vascular lesions were initiated and sustained by one single s.c. injection of MCT 80 mg/kg. IND 0.1 m g/kg was given daily by gavage to MCT treated animals. (RV) ww, (LV) ww, lung ww/dw, total protein (TP) in mg/g RVdw and% medial thickness (MT) of pulmonary vessels were measured in controls, MCT- and (MCT + IND)-treated animals at one, two and three weeks respectively. The results are shown below.

	Control	MCT			MCT + IND		
		Week 1	Week 2	Week 3	Week 1	Week 2	Week 3
RV/LV × 10^3	282 ±7.54	289.1 ±8.5	331** ±19.6	325.8** ±10	276.32 ±11.8	291.8** ±3.83	284.4** ±3.9
LV/BW × 10^3	1.9 ±6 × 10^2	1.9 ±2 × 10^2	1.9 ±7 × 10^2	1.9 ±10^{-1}	1.9 ±8.5 × 10^2	1.9 ±8 × 10^2	1.92 ±4 × 10^2
Lung ww/dw	4.85 ±0.11	5.4** ±0.08	5.46 ±0.12	5.31** ±0.08	5.16** ±0.06	4.87++ ±0.08	4.87++ ±0.05
TP	738.7 ±26.4	685.5 ±20	520.1** ±18	619.8** ±24	639.6 ±23.24	580.5*+ ±25.2	820.7++ ±51.5
TC	47.8 ±1.67	55.6** ±0.9	58.06** ±1.2	56.32** ±1	50.92 ±1.57	53.6*+ ±0.97	51.58+ ±1.3
% MT	10.2 ±0.81	15.2** ±0.3	20.22** ±1	20.56** ±0.7	16.38** ±0.47	15.94**+ ±0.7	17.1**++ ±0.4

*$p < 0.05$, **$p < 0.01$ MCT- and (MCT + IND)-experiments compared to controls, +$p < 0.05$, ++$p < 0.01$ (MCT + IND)-compared to MCT experiments.

The results above show that MCT induced in parallel, an increase in RV/LV, lung wet/dry weight, TC and%MT. In contrast TP was reduced. IND reversed all above changes to control level except for%MT which IND only partially reversed but to a significant degree.

Conclusion: While it significantly reversed the vascular changes, (IND) completely abolished RV changes that resulted from MCT administration.

ACTIVATION OF VASCULAR SMOOTH MUSCLE: GROWTH FACTORS AND OTHER MEDIATORS

P486 Troglitazone inhibits mitogenic signaling by insulin in vascular smooth muscle cells

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Troglitazone (TRO) is an oral insulin-sensitizer which improves glucose utilization by skeletal muscle and adipose tissue. In vascular smooth muscle cells (VSMC), insulin transduces a mitogenic signal that is dependent on the extracellular signal regulated kinases 1 and 2 (ERK 1/2). We examined the effects of TRO on this pathway and found that it inhibits mitogenic signaling by insulin in VSMC. Insulin (1 μmol/L) stimulated DNA synthesis, measured by BrdU-incorporation, in quiescent VSMC by 3.2-fold. Treatment with TRO (1–20 μmol/L) inhibited insulin-induced DNA synthesis in a dose-dependent manner, leading to a 72.8% inhibition at the maximal concentration. TRO at 1 and 10 μmol/L had no significant effect on insulin-stimulated ERK 1/2 activity. At 20 μmol/L, however, TRO surprisingly enhanced insulin-stimulated ERK 1/2 activity by 1.5-fold. Mitogenic signaling through the ERK 1/2 pathway involves translocation of ERKs to the nucleus, where they phosphorylate transcription factors such as Elk-1 which regulate critical growth response genes. In transfection experiments using GAL-Elk-1 chimera expression plasmids, TRO at 1–20 μmol/L inhibited insulin-stimulated, ERK 1/2-dependent Elk-1 transcription factor activity. In contrast, TRO had no effect on events in the insulin-stimulated association of PI3 kinase and IRS-1. TRO is a known ligand for the nuclear transcription factor peroxisome proliferator-activated receptor gamma (PPARγ), and may exert its antiproliferative effects through the activation of this nuclear receptor. Two other PPARγ ligands rosiglitazone (RSG) and 15-deoxy-$\Delta^{12,14}$-prostaglandin J2 also inhibited insulin-induced DNA synthesis. In summary, these data show that TRO inhibits mitogenic signaling by insulin at a point distal. of ERK 1/2 activation, potentially by a PPARγ-mediated inhibition of ERK-dependent phosphorylation and activation of nuclear transcription factors.

P487 Latent transforming growth factor-beta (TGF-β) binding proteins: a role in targeting TGF-β following arterial injury

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Background: TGF-beta1 has a key role in wound healing and in the arterial response to injury. However, the processes governing the distribution and activity of this multifunctional cytokine in vivo remain poorly understood. LTBPs, members of the fibrillin superfamily of matrix proteins, are thought to regulate TGF-beta1 release, targeting and activation in vitro. Thus, after vascular injury, LTBPs may play an important role in controlling TGF-beta1 availability and function while also forming essential components of the extracellular matrix.

Methods and Results: We investigated the upregulation, distribution and processing of LTBP isoforms 1 and 2 and their association with TGF-beta in vivo in a porcine model of coronary artery balloon injury and ex vivo using organ cultures of injured coronary arteries (1 week post angioplasty). Using immunohistochemistry, we detected LTBP1 in the thrombus acutely after injury and upregulation of both LTBP1 and LTBP2 in the neointima and neoadventitia at 1 and 2 weeks post-angioplasty. These isoforms co-localised with TGF-beta. Immunoprecipitation from 35S-radiolabelled organ cultures confirmed an increase in the synthesis of LTBP1 and 2 in injured vessels compared to uninjured controls. Unlike LTBP2, multiple proteolytically processed forms of LTBP1 were found. Plasmin digests of matrix released newly incorporated LTBP1. On Western blotting latent TGF-beta1 was found to be associated with LTBP1 through a disulfide bond.

Conclusions: LTBPs are significantly upregulated following arterial injury. Differential processing of the isoforms implies different roles for LTBP1 and LTBP2. Association of latent TGF-beta1 and LTBP1 plus the ability to release LTBP1 from the matrix by proteolysis suggests that this isoform may control TGF-beta1 targeting and provide an extracellular reservoir of latent growth factor after coronary angioplasty.

P488 Human vascular smooth muscle cells take up aggregated LDL through the low-density lipoprotein receptor-related protein

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One of the main events in the atherogenic cascade is the lipid deposition. The internalization of modified LDL by macrophages and vascular smooth muscle cells (VSMC) produces cholesteryl ester (CE) accumulation, the hallmark of foam cell formation. Macrophages become foam cells through the uptake of diverse modified LDLs, whereas aggregated LDL (agLDL) seems to be a key condition for lipid accumulation in VSMC. While in atherosclerotic plaque scavenger receptors are mainly expressed in macrophages, low density lipoprotein receptor-related protein (LRP) is highly associated to VSMC. The aim of this study was to analyze whether LRP mediates the uptake of agLDL by VSMC.

Methods: Cultured human VSMC were obtained from human aortas of explanted hearts at transplant operations performed at the Hospital de la Santa Creu i Sant Pau. Human LDL was aggregated by vortexing and labeled with 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine (DiI). Binding experiments were performed by incubating VSMC with DiI-LDL (native or ag-) at 4°C for 30 min followed by the internalization during 4 h at 37°C. Following DiI-LDL incubation, several samples were stained with anti-LRP antibodies to analyze the colocalization of DiI-LDL and LRP. The free and esterified cholesterol content of VSMC was analyzed by thin layer chromatography after 18 hours incubation with lipoproteins.

Results: The CE content of VSMC treated with 100 μg/ml of agLDL increased 70-fold over that in VSMC incubated with the same concentration of native LDL. Co-incubation of agLDL with anti-LRP antibodies decreased in a dose-dependent manner agLDL derived CE accumulation (from 20% at 12.5 μg/ml to 80% at 50 μg/ml) in VSMC. By the contrary, anti-LDL receptor antibodies did not show any effect. Lactoferrin (25 μg/ml), an agonist of low density lipoprotein receptor-related protein (LRP), strongly inhibited CE accumulation from agLDL (>85 ± 5.69%). Fluorescence microscopy analysis using agLDL labeled with DiI indicates that lactoferrin impairs agLDL binding. Confocal microscopic analysis using DiI-agLDL and antibodies against LRP indicates a colocalization of agLDL and LRP.

In conclusion: These results indicate that LRP is the receptor involved in the uptake of agLDL by human VSMC. Since LRP is highly expressed in atherosclerotic plaques and subendothelial LDL retention and aggregation are key events in atherogenesis, uptake of agLDL through LRP could have a crucial role in VSMC-lipid deposition in atherosclerotic lesions.

P489 Urokinase plasminogen activator/receptor expression precedes arterial contracture in a porcine model of coronary artery injury

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Current theories of arterial response to coronary injury highlight the role of the adventitia in arterial remodeling and the development of lumenal narrowing. Urokinase plasminogen activator and its receptor (uPA/R) are important molecular mediators of tissue remodeling through proteolytic and non-proteolytic functions. The purpose of our study was to examine the expression of uPA/R and its correlation with changes of arterial wall structure and lumenal narrowing after coronary angioplasty. Porcine coronary arteries were examined on days 3, 7, 14 and 28 after arterial injury using in situ hybridization and image analysis. Within 3–7 days after balloon injury, uPA/R mRNA was overexpressed particularly in adventitial myofibroblasts. At later time points uPA/R expression was absent. Adventitial dense connective tissue (ADCT) increased dramatically 3 days after injury, associated with an increase in external elastic lamina area (EELA) and lumenal area (LA). Later on (day 14) adventitial fibrosis occurred and EELA and LA decreased.

(mm^2)	Control	Day 3	Day 14
ADCT	0.7 ± 0.11	2.2 ± 1.65*	3.1 ± 0.89*
EELA	2.8 ± 0.70	6.6 ± 2.2*	3.3 ± 0.3
LA	1.9 ± 0.6	5.1 ± 2.1*	1.4 ± 0.3

[*$p < 0.05$ injury vs. control]

Early adventitial uPA/R expression correlates with an increase in ADCT, EELA and LA. Downregulation of uPA/R later after injury coincides with an decrease in EELA and lumenal narrowing. Adventitial contracture after coronary injury may be controlled in part by modulation of arterial wall structure through uPA/R system.

P490 Temporal modulation of negative growth regulators during development of vascular smooth muscle

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Temporal control of cell cycle exit in concert with differentiation is of key importance. We have previously demonstrated that conditionally-transformed smooth muscle cells (TsT-SMC) from adult transgenic mice expressing a temperature-sensitive mutant of the SV40 T antigen (tsA58) under control of the mouse vascular SMC alpha-actin promoter exhibit increased expression of the smooth muscle marker myosin heavy chain upon TAg inactivation, in conjunction with an increase in hypo-phosphorylated RB protein. To gain further insight into the role of negative growth regulatory proteins in smooth muscle differentiation and cell cycle exit, expression of smooth muscle markers as well as growth regulators was explored in tissue and cell populations derived from these mice as a function of development. Immunostaining and co-immunoprecipitation were performed for protein presence and Tag interaction. Immunoprecipitation demonstrated interaction of TAg in aortic cells with each of the negative growth regulators pRB, p107, p130 and p53. Progressive loss of PCNA occurred from tissue obtained at embryonic day 18, to neonatal day 1, into adulthood, correlating with reduction in proliferation. This was paralleled by a small increase in p130 level, a progressive increase in apparent molecular weight of the p107 immunoreactive band, and a remarkable increase (10-fold) in the expression of pRB. Smooth muscle markers increased their expression in parallel, including myosin heavy chain 204. These data further support that the expression and function of pRB, in particular among its homologs, may play an important role in the cell cycle exit and differentiation of vascular smooth muscle during normal development of thoracic aorta.

P491 Dynamic gene expression of proprotein convertases and their putative substrate precursor proteins in rat aorta organ culture

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The involvement of growth factors (GFs) in arterial pathology (e.g. atherosclerosis) is well established. Most of these proteins require posttranslational processing by proprotein convertases (PCs), which can potentially control their activation. These enzymes include members of the family of subtilisin/kexin-like mammalian PCs with specificity to Arg↓, as well as the novel enzyme SKI-1 with specificity to Ala↓ and Thr↓ at the cleavage site. We investigated the gene expression of PCs in rat aorta, using an organ culture system (serum-free DEMEM; 0, 4 and 24 h), which maintains cell-cell/cell-matrix interactions. Induction of cell proliferation and organ viability was assessed by PCNA immunoblotting, demonstrating the increase over time. Furthermore, PCNA immunostaining was localized to vascular smooth muscle cells (VSMCs) of aorta cultured for 24 h. As demonstrated by western blot analysis, PC5 isoform A and PC7 were present in tissue extracts, whereas shed PC5 isoform B was detected at 4 h (peak) and 24 h in culture medium (CM). PC7 was not found in CM. SKI-1 was found only after 24 h in tissue extracts and CM. Furin was detected at all time points and could not be found in CM. Other convertases, such as PC1 and PC2 were undetectable. Injury related GFs, like NGF, PDGF-A and TGF-beta 1 were released into CM and found in tissue extracts. Immunohistochemical detection of PCs was generally weak in normal arteries, mainly localizing to VSMCs at the adventitial border. In the rat aorta organ culture, PCs immunoreactivity increased and was found thoughout the medial layer in VSMCs, colocalized with proliferating VSMCs. In conclusion, this is the first report, demonstrating that several PCs are present in arteries and that their gene expression displays a dynamic course with the induction of VSMCs and their potential substrates (injury related GFs).

P492 Troglitazone inhibits all-induced ERK 1/2 nuclear translocation and activation in vascular smooth muscle cells

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Angiotensin II (AII) stimulates vascular smooth muscle cell (VSMC) proliferation and migration. These effects of AII are mediated via activation of the extracellular signal-regulated kinases 1/2 (ERK 1/2) and can be blocked by troglitazone (TRO), a novel antidiabetic agent. AII-induces ERK 1/2 activation in VSMC through the cytosolic PKCzeta → MEK → ERK pathway and the subsequent translocation of ERK into the nucleus, where ERK activates multiple transcription factors which modulate gene expression. To understand how TRO interferes with AII-induced mitogenic and chemotactic signal transduction, we examined the participating signaling events in rat aortic VSMC. We observed a significant increase in PKCzeta activity after stimulation with AII at 10 minutes and 2 hours, and a rapid and transient activation of cytosolic ERK 1/2 by AII at 10 minutes with a return to baseline levels at 2 hours. Nuclear translocation of ERK 1/2 was observed 10 minutes after stimulation with AII, with a further accumulation of total nuclear ERK 1/2 protein after 2 hours. This was accompanied by a marked increase in activated nuclear ERK 1/2. Although PKCzeta was constitutively present in the nuclear compartment and did not translocate upon stimulation with AII, we observed a significant increase in nuclear PKCzeta activity after AII treatment. TRO did not affect AII-induced activation of PKCzeta or its downstream signaling kinases ERK 1/2 in the cytosol. In contrast, AII-induced activation of PKCzeta and ERK 1/2 in the nucleus were both inhibited by TRO. Nuclear translocation of ERK 1/2 induced by AII was completely blocked by TRO. TRO, therefore, inhibits both AII-induced nuclear translocation and activity of ERK 1/2 and the nuclear activity of its upstream signaling kinase PKCzeta. Since ERK 1/2 nuclear translocation may be a critical signaling step for multiple growth factors that stimulate VSMC proliferation and migration, TRO may provide a new therapeutical approach for the prevention and treatment of atherosclerosis and restenosis.

P493 Expression of tumour necrosis factor-α and interleukine-6 in stenotic lesions of cholesterol fed rabbits after angioplasty

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Cytokines mediate modulation of cellular functions, activation of macrophages and proliferation of smooth muscle cells (SMC) after balloon injury. They play a major role in inflammatory processes which are involved in development of restenosis and plaque rupture. Aim of our study was to investigate the expression pattern of preinflammatory cytokines-tumor necrosis factor-α (TNF-α) and interleukine-6 (IL-6) – in stenotic lesions of rabbits aortas after angioplasty.

Newzealand white rabbits (3.0–4.5 kg) received either normal chow (A; n = 4) or 1% cholesterol rich diet for 6 weeks (B; n = 3), or were treated as B and underwent balloon injury of the abdominal aorta (C; n = 5), or received the treatment as C and angiographically controlled angioplasty of stenotic lesions (PTA) was performed 6 weeks after balloon injury. 1, 10 days and 5, 12 weeks after PTA (n = 5 each point of time) specimens were gained in regions of maximum plaque formation. Morphometry, immunhistochemistry and in-situ hybridisation were performed for evaluation.

In non-treated aortas (A) TNF-α and IL-6 mRNA were only erpressed in scattered cells in the subendothelium and adventitia. Cholesterol-diet (B) led to enhanced expression of TNF-α and Il-6 subendothelially and in inner medial layers. Stenotic lesions of balloon injured aortas (C) showed high transcription activity in areas of plaque cap and basis, mainly localized next to lipidloaden foam cells, less to SMC. 1 day after PTA (D) pronounced expression of IL-6 was observed in regions of plaque rupture, shoulder and cap, inner medial layers and medial/advential transition zone. TNF-α-mRNA expression was upregulated in all vascular layers, more pronounced in the neointima and media than in the adventitia. After 5 weeks the expression pattern of TNF-α-mRNA changes leading to upregulation in regions of cap and shoulder of plaques and areas of rupture of the internal elastic lamina. IL-6-mRNA revealed similar expression pattern, but more pronounced in plaque cap and shoulder. After 12 weeks expression pattern of TNF-α and IL-6 were mainly unchanged but less intense.

Distinct expression pattern of TNF-α and IL-6 were observed in the development of stenotic lesions, and especially macrophages, endothelial cells and SMC appear to influence the signal transduction. These results demonstrate the role of ongoing inflammatory processes in modulation of cellular functions and proliferation after vascular injury and in the development of restenosis.

P494 Locally-delivered oligodeoxynucleotides to mitogen activated protein kinase downregulate target protein and inhibit neointima formation following balloon angioplasty

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Vascular smooth muscle cell (VSMC) proliferation has a central role in the formation of the arterial neointima, the characteristic pathological lesion of atherosclerosis, angioplasty restenosis and saphenous vein graft failure. Mitogen activated protein kinase (MAPK) is centrally involved in the downstream transduction of growth signals from a variety of receptors and thus represents a potential target for modifying this proliferative response. We have previously shown that antisense oligodeoxynucleotides (ODN) directed against MAPK (AMK) down-regulate the target protein and inhibit proliferation of VSMC in vitro. In this study we investigated the effects of AMK on in vivo MAPK expression and neointima formation in a porcine model of angioplasty.

Methods: 11 Large White pigs (25–30 kg, female) were randomly divided into sense (n = 5) and antisense (n = 6) groups. Arterial injury was induced by high-pressure oversized balloon angioplasty in both carotids. AMK or matching sense ODN (SMK) was then introduced by liposomal transfection using a microporous delivery catheter. ODN concentration was 0.2 μM in all cases. In some animals fluorescein-labeled ODN was used to assess uptake. After 7 days, animals were sacrificed and the carotid arteries harvested. Some sections of artery were fixed for histological analysis and others frozen in liquid nitrogen for subsequent protein extraction. MAPK expression was assessed by Western blotting and neointima formation measured by computerized planimetry.

Results: Both cytoplasmic and nuclear uptake of fluorescein-labeled ODNs were noted in histological sections. Transfection of AMK resulted in a 43% decrease in MAPK expression compared with the sense ODN ($p < 0.01$; Fig. 1). This was matched by a significant reduction in both neointimal area and intimal/medial area ratio in the antisense group (Table).

	Sense (n = 5)	Antisense (n = 6)
Intimal area (mm^2)	0.043 ± 0.002	0.038 ± 0.005**
Intimal/Media ratio	0.022 ± 0.007	0.017 ± 0.008*

Data represent mean ± s.e.m. Compared with sense group, $^{**}p < 0.01$, $^{*}p < 0.05$

Figure 1. Representative Western blot showing downregulation of MAPK by antisense ODNs.

Conclusion: Antisense ODNs to MAPK down-regulated the expression of MAPK and inhibited neointima formation following porcine carotid angioplasty. The data indicate that MAPK is important in regulation of VSMC proliferation following arterial injury and suggest that its downregulation may have therapeutic potential in limiting the response to injury.

P495 Differential activation of mitogen-activated protein kinases in smooth muscle cells by angiotensin II: involvement of free radical generation via NAD(P)H-oxidase

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Background: The atherogenic effect of the renin-angiotensin system can be explained in part by the influence of its effector, angiotensin II (Ang II) on vascular smooth muscle cell (VSMC) growth. Previous reports have shown that Ang II can stimulate O_2^- levels from rat smooth muscle cells via NAD(P)H oxidase and there is evidence that reactive oxygen species (ROS) plays a role in the pathogenesis of atherosclerosis. We propose that Ang II atherogenicity may be mediated in part by ROS-dependent signals, activating mitogen-activated protein (MAP) kinases which are involved in proliferation and differentiation.

Methods and Results: Rat vascular SMC were stimulated with Ang II. The activities of mitogen-activated protein (MAP) kinases were measured by Western blot analysis or by immunocomplex kinase assay. Activator protein-1 (AP-1) binding was determined using an electrophoretic mobility shift assay. Treatment of rat SMC with Ang II resulted in rapid formation of ROS and activation of *extracellular signal regulated* (ERK), *c-Jun amino terminal kinase* (JNK) and p38MAPK, and their downstream effector, AP-1. Ang II-induced activation of p38MAPK, JNK and ERK1/2 was inhibited by the type 1 Ang II-receptor blocker losartan, but not by the type 2 Ang II-receptor antagonist PD123319. Interestingly, only the activation of ERK$\frac{1}{2}$, but not JNK and p38MAPK, was tyrosine kinase, PKC and MEK1/2 dependent. Ang II also induced the rapid formation of ROS, which could be inhibited by a specific antibody against the p22phox subunit of the NAD(P)H-oxidase. JNK and p38MAPK, but not ERK activation was inhibited by an antioxidant and an inhibitor of NAD(P)H-oxidase.

Conclusions: The results indicate that in vascular smooth muscle cells, Ang II activates MAPK and AP-1 through different pathways and suggest that ROS, generated by p22phox mediate Ang II-induced JNK and p38MAPK activation, which may contribute to the pathogenesis of atherosclerosis.

P496 TGF-β1, TGF-β2, and MCP-1 secretions respond to irradiation in a dose dependent manner in cultured smooth muscle cells

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The TGF family of cytokines is known to influence tissue fibrosis and remodeling as well as smooth muscle cell differentiation. Adventitial or medial cells are thought to trigger the restenosis process by cytokine secretion. We used a cell culture model to study the impact of radiation on cytokine secretion and cell proliferation utilizing the positron emitter Ga-68 we proposed earlier for liquid-filled balloon brachytherapy. Bovine smooth muscle cells were plated at confluence, growth arrested at 72 hourspost plating, and subsequently irradiated with Ga-68 at doses ranging from 1 to 12 Gy. The activity was delivered into cell culture wells and exposed in contact with the bottom of the insets holding cultured cells. Dosimetry was established by irradiating GAF-chromic film under the same geometry. Irradiated cells were replated at 10000/cm^2. At multiple time points, cells were counted with Trypan blue staining and media conditioned for 4 days were assayed for TGF-beta1 (TGF-B1), -beta2 (TGF-B2), and macrophage chemotactic protein (MCP-1) by ELISA. Cytokine concentrations were normalized to cell counts.

Dose (Gy)	Cell Count (1000/cm^2)	TGF-B1	TGF-B2 (pg/1000 cells)	MCP-1
0	118 ± 1.7	37.4	5.6	33
1	92 ± 2.1	42.6	10.1	31.4
3	71 ± 0.2	49.2	15.4	4.9
6	12 ± 0.2	104	75.3	0.0
12	7 ± 0.2	130	120	0.0

ED50 was approximately 5 Gy for TGF-beta1, 6 Gy for TGF-beta2, and 2 Gy for MCP-1. Irradiated smooth muscle cells in culture show growth inhibition, upregulation of TGF-beta1/2, and downregulation of MCP-1 in a dose dependent manner. We hypothesize that the efficacy of brachytherapy is in part modulated by cytokine-mediated smooth muscle cell differentiation and macrophage chemoattraction.

P497 Effects of all-trans-retinoic acid after local delivery in the rabbit carotid artery

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Retinoids regulate a variety of biological processes and play an important role in the homeostasis of cell differentiation and proliferation. The broad biological spectrum, however, leads to many severe side effects and limits the clinical use of retinoids. Local delivery of all-trans-retinoic acid (atRA) for the prevention of restenosis might be a way of exploiting the potent pharmacological properties of this compound while concurrently minimizing systemic side effects.

This hypothesis was tested in an experimental rabbit angioplasty model. After induction of a fibromuscular plaque in the right carotid artery of 45 New Zealand rabbits, 30 animals underwent balloon angioplasty of the preformed plaque formation. Subsequent local atRA delivery (10 ml, 10 μmol/L) with the double balloon catheter was performed in 15 animals. 10 animals were solely electrostimulated and 15 animals served as control group with balloon angioplasty only. 5 sham-operated animals received vehicle without atRA. Vessels were excised 7 days (n = 15) and 28 days (n = 20) after intervention. Immunocytochemistry with antibodies against alpha-actin, bromodeoxyuridine, macrophages collagen I, III and von Willebrand factor was performed.

Results: After local atRA delivery in vivo, the extent of stenosis increased slightly from 18.6 ± 7.7% (1 week) to 21.7 ± 8.3% 4 weeks after intervention compared to 31.8 ± 13.4% in balloon-dilated animals. Immunozytochemistry revealed an inhomogenous staining pattern after local atRA delivery in the α-actin- and BRDU-stained histologies indicating potential effects of atRA on cell proliferation and differentiation.

Conclusions: In this study, atRA was a potent inhibitor of smooth muscle cell proliferation in vivo. Local atRA delivery led to a better preservation of vessel shape and might be a promising strategy for the prevention of restenosis.

P498 Galectin-1 modifies growth of vascular smooth muscle cells

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We investigated the role of the matricellular protein galectin-1 (Gal-1), beta-galactoside-binding lectin, in smooth muscle cell (SMC) proliferation in atheroma and in SMC anchorage-dependent growth in cell culture.

Gal-1 expression in human coronary endarterectomy samples was visualized by tissue section immunostaining with anti-Gal-1 antibody. Anchorage-dependent growth of human vascular SMCs was determined by ^{3}H-thymidine incorporation. Recombinant Gal-1 fusion protein (Gal-1FP) binding to extracellular matrix (ECM) proteins was measured by ELISA. Gal-1 binding to SMCs and ECM of SMCs was estimated by the binding of 125I-labelled-Gal-1FP in cell culture.

Gal-1 is upregulated in endarterectomy samples cultured for 7 days in the presence of serum. Prominent Gal-1 staining coincided with the PCNA expression in SMCs. In cell culture Gal-1 FP increased anchorage-dependent growth of SMCs compared to cell growth on plastic or endogenous ECM (130% and 118%, $p < 0.01$ and $p < 0.05$ respectively). Gal-1 FP increased anchorage-dependent growth of SMCs on thrombospondin (TSP) (164%, $p < 0.01$) and osteopontin (OSP) (167%, $p < 0.01$), but decreased cell growth on laminin (LN, 73%, $p < 0.01$%). Gal-1 FP binding to ECM proteins was in the order: LN = cellular fibronectin > TSP > plasma fibronectin. The binding of Gal-1 FP to SMCs was fifty times stronger than to ECM, produced by these SMCs.

In conclusion, Gal-1 is upregulated during atherosclerotic SMC proliferation and modulates anchorage-dependent growth of SMC, with differing effects depending on the ECM protein substrate.

P499 Different kinetic properties of endothelin-1 binding between ETA and ETB receptor subtypes

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At present several studies investigated the characteristics of endothelin-1 binding in human heart but informations about cell type distribution and kinetic properties of the two endothelin receptor subtypes are laking. Aim of the present study was to investigate cell type distribution and kinetic properties of ET-1 receptor subtypes in left ventricles obtained from 5 healthy donors whose hearts were not suitable for transplantation for non cardiac reasons. [125I]-ET-1 binding studies were performed with ETA (BMS-182874) and ETB (BQ-788) selective antagonists on both ventricular membranes and enzymatically isolated cardiomyocytes. In situ hybridization studies with specific cDNA probes (ETA ATCC 105194 and ETB, ATCC 1250426) investigated cell distribution of mRNA for ETA and ETB receptors in left ventricular sections.

In competition studies BMS-182874 selectively and competitively displaced [125I]-ET-1 (2,000 Ci/mmol) binding with about 1300 times greater affinity for ETA than ETB subtypes both on ventricular membranes and isolated myocytes. The [125I]-ET-1 specific binding revealed 42,851 ± 2,546 receptors/myocyte with a prevalent proportion of ETA receptor subtypes both on myocytes (84 ± 2%) and ventricular membranes (64 ± 2%). In situ hybridization studies revealed that mRNA for ETA receptors was expressed both on myocytes and non-myocyte cells, whereas mRNA for ETB receptors was almost exclusively expressed on fibroblasts and endothelial cells.

In kinetic experiments specific binding of ET-1 to both ventricular membranes and myocytes in the presence of specific ETA and ETB receptor antagonists showed a different time course: association and dissociation phases were significantly shorter for ETB than for ETA ($p < 0.01$) without differences in the final calculated dissociation constant as confirmed by equilibrium binding studies.

In conclusion: 1) ET-1 receptor subtypes have different cell type distribution in human left ventricle because cardiomyocytes mainly express the ETA subtype. 2) the ETA subtype showes a more delayed and stable ET-1 binding than the ETB subtype. This suggests a clearance function of ETB receptors.

P500 TNFα inhibits insulin-signaling pathways in vascular smooth muscle cells

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Tumor necrosis factor alpha (TNFα) interferes with insulin signaling in adipose tissue and may promote insulin resistance. Insulin binding to the insulin receptor (IR) triggers its autophosphorylation, resulting in phosphorylation of Shc and the downstream activation of p42/p44 MAP-kinase (MAPK), which mediates insulin-induced proliferation in VSMC. Since insulin resistance is associated with vascular alterations, we examined the effects of TNFα on mitogenic signaling by insulin. In rat aortic VSMC, insulin (1 μmol/L, 5 min) induced rapid phosphorylation of the IR and Shc and caused a 5.3-fold increase in activated, phosphorylated MAPK at 10 min ($p < 0.05$). Insulin induces a biphasic MAPK-activation with a transient peak at 10 min and a sustained late phase after 2 h. Preincubation (30–120 min) with TNFα had no effect on insulin-induced IR-phosphorylation. In contrast, pretreatment with TNFα transiently suppressed insulin-induced MAPK-activation (94% inhibition after 30 min and 89% after 60 min preincubation, $p < 0.05$). After longer exposure to TNFα (90–120 min), MAPK-activation was restored. Insulin-induced phosphorylation of Shc was inhibited by TNFα in a similar pattern. Moreover did pretreatment with TNFα for 30 min suppress not only the early phase, but the entire biphasic MAPK response to insulin. Since mitogenic signaling by insulin in VSMC requires MAPK-activation, we examined the effect of TNFα on insulin-induced proliferation. Insulin alone induced a 3.4-fold increase in DNA synthesis, that was inhibited by 48% when TNFα was added 30 min before insulin ($p < 0.05$). TNFα alone was not mitogenic. Inhibition of MAPK with PD98059 (30 μmol/L) also inhibited insulin-stimulated proliferation (57% inhibition; $p < 0.05$). In contrast to insulin, TNFα did not inhibit PDGF-induced MAPK-activation or DNA-synthesis in VSMC. Thus, TNFα specifically interferes with insulin-induced mitogenic signaling by inhibiting the phosphorylation of Shc and the downstream activation of MAPK.

P501 Endothelin induces inflammatory activation of human vascular smooth muscle cells

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Acute coronary syndromes are associated with increased endothelin (ET) levels in plasma and within the atherosclerotic plaque. On the other hand, such syndromes are also characterized by systemic and local (at the site of the culprit lesion) inflammation. This study tetsted the hypothesis that ET promotes vascular inflammation by induction of cytokine release from vascular smooth muscle cells (SMC).

Methods: Human vascular SMC were stimulated with ET-1. Release of the cytokine interleukin-6 (IL-6) into the culture medium was quantified by ELISA. Levels of IL-6 mRNA in SMC were determined by RT-PCR. Activation of the proinflammatory transcription factor nuclear factor-κB (NF-κB) was examined using electrophoretic mobility shift assay.

Results: ET-1 (100 pM–1 μM) stimulated concentration-dependently IL-6 release by SMC up to 689 ± 41 pg/ml at 10 nM (control 288 ± 3 pg/ml, $p < 0.05$). This ET-1 effect was blocked by the ET receptor antagonist BQ-123, but not by BQ-788 (10 μM each), suggesting that ET-induced IL-6 release is mediated by the ET-A receptor. ET-1 also increased IL-6 mRNA indicating regulation of IL-6 release at the transcriptional level. Moreover, NF-κB, which is necessary for transcription of most cytokine genes, was activated by ET-1. The antioxidant pyrrolidine dithiocarbamate (10 μM) inhibited ET-1-induced IL-6 release indicating involvement of reactive oxygen species in ET-1 signaling.

Conclusion: The data suggest that endothelin may contribute to the pathogenesis of acute coronary syndromes by inflammatory activation of vascular SMC. Thus, inhibition of endothelin may be a novel strategy for treatment of acute coronary syndromes.

P502 The renin-angiotensin system may contribute to inflammatory activation of the vessel wall during atherogenesis

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Clinical, experimental and genetic data suggest involvement of the renin-angiotensin system (RAS) in atherogenesis. Chronic inflammation of the vessel wall mediated by cytokines is a hallmark of atherosclerosis. This study tested therefore the hypothesis that the RAS induces inflammatory signals in vascular smooth muscle cells (SMC), the most abundant cell type in atherosclerotic tissue.

Methods: Human vascular SMC were stimulated with angiotensin (ANG). Release of the cytokine interleukin-6 (IL-6) into the culture medium was quantified by ELISA. Levels of IL-6 mRNA in SMC were determined by RT-PCR. Activation of the proinflammatory transcription factor nuclear factor-κB (NF-κB) was examined using electrophoretic mobility shift assay.

Results: ANG II (10 nM-1 μM) stimulated concentration-dependently IL-6 release by SMC up to 1037 $\pm$ 63 pg/ml at 1 μM (control 423 $\pm$ 106 pg/ml, n = 3 each, $p < 0.05$). This ANG II effect was blocked by the ANG receptor antagonist losartan (1 μM), suggesting that ANG II-induced IL-6 release is mediated by the ANG-AT1 receptor subtype. ANG I similarly stimulated IL-6 release by SMC. The effect was blocked by ACE inhibitors. ANG II also increased IL-6 mRNA indicating regulation of IL-6 release at the transcriptional level. Moreover, NF-κB, which is essential for transcription of most cytokine genes, was activated by ANG II. The antioxidant PDTC (10 μM) inhibited ANG II-induced IL-6 release indicating involvement of reactive oxygen species in ANG signaling.

Conclusion: The data suggest that the RAS may contribute to atherogenesis by inflammatory activation of the vessel wall. ACE inhibitors or ANG II-receptor antagonists could exert an anti-inflammatory action on the vessel wall.

P503 Endothelin-1 and activation of mitogen-activated protein kinases in smooth muscle cells: identification of an oxygen-radical-dependent mechanism

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Background: Endothelin (ET-1) has been proposed to contribute to atherogenesis and plaque rupture in coronary heart disease. Plaque progression and destabilization has been associated with the inflammatory response of vascular smooth muscle cells (SMC). Mitogen activated protein kinases (MAPK) are strong candidate signal transducers for the activation of SMC. The present study aimed to determine if ET-1 also has a direct effect on the MAPK, c-Jun amino terminal kinase (JNK) and extracellular signal regulated kinase (ERK1/2) in addition to its traditional role in vasoconstriction.

Methods and Results: Rat SMC were exposed to ET-1 over time at concentrations from 10^{-6}-10^{-10} M and MAPK activity was quantitated. Activation of both JNK and ERK were observed, with a maximum stimulation at 10^{-7} M ET-1. Both kinases were activated by ET-1 binding to a single receptor (ET-1 1A) but differed in their downstream mechanisms: only JNK activation was sensitive to the radical scavenger N-acetylcysteine and the inhibitor of NADPH oxidase, DPI, indicating a role for reactive oxygen species (ROS). The downstream MAPK effector and proinflammatory transcription factor, the AP-1 complex, was shown to comprise mainly the JNK substrate c-Jun, and AP-1 activation was maximal at 2 h after addition of ET-1 and also dependent on ROS.

Conclusion: The data indicate a differential, ET-1 dependent mechanism of MAP-Kinase activation. Whereas JNK was preferentially activated through oxygen radicals, ERK activation appeared to be independent of radical formation. Activation of MAP-kinases in SMC may be one of the underlying mechanisms of plaque destabilization by ET-1.

P504 Atorvastatin attenuates angiotensin II-induced free radical release mediated by AT1 receptor down-regulation in vascular smooth muscle cells

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HMG-CoA reductase inhibitors (statins) significantly reduce lipid-induced cardiovascular mortality. There is evidence that these drugs exert direct effects on vascular cells independent of lowering cholesterol concentrations. Therefore, the effect of atorvastatin (ator) on AT1 receptor (AT1-R) gene expression, cell proliferation, and release of reactive oxygen species (ROS) in vascular smooth muscle cells (VSMC) was investigated.

Methods: Rat aortic VSMC in culture were incubated with 1–10 μmol/l atorvastatin. AT1-R mRNA was assessed by Northern analysis, AT1-R density was measured with ^{125}I-angiotensin radioligand binding assays, DNA synthesis was assessed by ^{3}H-thymidine and BrdU incorporation, and the effect on angiotensin II (ang II)-induced release of ROS was measured with DCF fluorescence lasermicroscopy.

Results: Preincubation with ator for 12 h reduced significantly the ang II-induced release of ROS (115.3 $\pm$ 23.7% vs 146.4 $\pm$ 29.9 of controls). DNA synthesis was decreased to 58.9 $\pm$ 5.0% of control levels after 24 h incubation, and ang II-induced cell proliferation was attenuated by 29.9 $\pm$ 8.7%. AT1-R mRNA expression was down-regulated to max. 53.7 $\pm$ 2.0% of controls after 4 h incubation, and AT1-R density was decreased to 59.5 $\pm$ 13.3% of controls after 24 h incubation with ator (B_{max} 1424 $\pm$ 474 vs 823 $\pm$ 235; no change in K_D). Mevalonate but not hydroxy-cholesterol inhibited AT1-R mRNA down-regulation by ator.

Conclusion: Atorvastatin attenuates ang II-mediated release of ROS and decreases ang II-induced cell proliferation. This is governed through a direct down-regulation of AT1 receptor expression by atorvastatin. Our findings demonstrate direct effects of statins on vascular cells independent of plasma cholesterol levels. Statin-caused therapeutic benefits may in part be mediated through these effects, since VSMC proliferation, free radical release, and AT1 receptor regulation play a major role in the pathogenesis of atherosclerosis.

P505 Angiotensin-(1–7) changes the growth of human vascular smooth muscle and endothelial cells differentially

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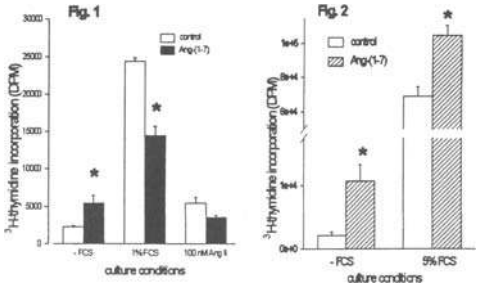
The renin-angiotensin system has two bio-active endproducts angiotensin II (Ang II) and angiotensin-(1–7) (Ang-(1–7)) which have opposite effects, compared to eachother. With respect to this, Ang-(1–7) inhibits vascular smooth muscle cells (VSMC) growth in animals. Its effects on human VSMC or on endothelial cells is unknown. We studied the effect of Ang-(1–7) on growth of human VSMC (HA-VSMC) and human endothelial cells (HUVEC).

Methods: HA-VSMC and HUVEC were made quiescent before each experiment. For HA-VSMC the effect of 1 μM Ang-(1–7) was studied under three circumstances: in absence of fetal calf serum (FCS), in the presence of 1% FCS, and in the presence of serum free medium with 100 nM Ang II. For HUVEC the effect of 1 μM Ang-(1–7) was studied under two conditions: in absence and in the presence of 5% FCS. Incorporation of [^{3}H]-thymidine was measured to quantify cell growth.

Results: Compared to serum free medium, 1% FCS induced a tenfold increase in [^{3}H]-thymidine incorporation in HA-VSMC and Ang II a 2.4 $\times$ increase (Fig. 1). In absence of FCS, Ang-(1–7) increased [^{3}H]-thymidine incorporation by 140% in HA-VSMC, whilst in the presence 1% FCS it inhibited growth by 40% (Fig. 1). In the presence of Ang II, growth was inhibited by 36% (Fig. 1). In HUVEC, [^{3}H]-thymidine incorporation was 32 times higher in cells grown on 5% FCS as compared to cells grown in absence of FCS (Fig. 2). In the absence of FCS, Ang-(1–7) increased [^{3}H]-thymidine incorporation in HUVEC by 400% (Fig. 2). In the presence of 5% FCS, it increased incorporation by 50% (Fig. 2).



Discussion: Ang-(1–7) can have a growth promoting as well as growth inhibiting effect in cardiovascular cells, depending on cell type and state. Thus, Ang-(1–7) may be involved in both the repair of endothelium and in angiogenesis, thereby fulfilling clinically benificial tasks.

P506 Hyperexpression and activation of stress-activated protein kinases/c-Jun NH2-terminal protein kinases (SAPK/JNK) in atherosclerotic lesions: role of LDL

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Hyperlipidemia alters gene expression of arterial endothelial and smooth muscle cells (SMCs) and induces atherosclerotic lesions, in which cell proliferation and apoptosis co-exist. The signal transduction pathways that mediate these responses in the vessel wall in vivo have yet to be identified. Stress-activated protein kinases (SAPK) or c-Jun NH2-terminal protein kinases (JNK) are thought to be crucial in transmitting transmembrane signals required for cell differentiation and apoptosis in vitro. In the present study, we investigated the activity, abundance and localization of SAPK/JNK in atherosclerotic lesions of cholesterol-fed rabbits. Immunohistochemical analysis revealed abundant and heterogenic distribution of SAPK/JNK, mainly localized in cell nuclei of the lesional cap and basal regions. Double-staining of the lesions demonstrated that a portion of a-actin+ SMCs contained abundant SAPK/JNK proteins. SAPK/JNK protein levels in protein extracts from atherosclerotic lesions were 2- to 3-fold higher than the vessels of chow-fed rabbits. SAPK/JNK kinase activities were elevated 3–5-fold over the normal vessel. Furthermore, LDL stimulated SAPK/JNK activation in cultured SMCs in a time- and dose-dependent manner. LDL also induced SAPK/JNK activation in vascular SMCs derived from LDL-receptor-deficient (Watanabe) rabbits. Heparin, which inhibits LDL-receptor binding, did not influence LDL-stimulated SAPK/JNK activation, indicating a LDL-receptor-independent process. Thus, SAPK/JNK persistently activated and hyperexpressed in lesions may play a key role in mediating cell differentiation and apoptosis in hypercholesterolemia-induced atherosclerosis.

P507 Urokinase induces activation and formation of Stat4 and Stat1–Stat2 complexes in human vascular smooth muscle cells

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Urokinase (uPA) and its specific receptor (uPAR), act in concert to stimulate cytoplasmic signaling machinery and transcription factors responsible for cell migration and proliferation. Recently we demonstrated that uPA activates the Jak/Stat signaling in human vascular smooth muscle and endothelial cells, namely Janus kinases Jak1 and Tyk2 and signal transducer and activator of transcription Stat1. However, the important question whether other transcription factors of the Stat family, in addition to Stat1, are involved in the uPAR-related signaling has not been addressed. In this study, we demonstrate that Stat4 and Stat2, but not Stat3, Stat5 or Stat6, are rapidly activated in response to uPA. We demonstrate further using electrophoretic mobility shift assay and confocal microscopy study, that Stat4 and Stat2 rapidly and transiently translocate to the cell nuclei where they bind specifically to the regulatory DNA elements. Analysis of Stat complexes formed in response to uPA, revealed Stat2-Stat1 heterodimer which lacks p48, a DNA binding protein known to combine with Stat1-Stat2. This new uPA-induced Stat2-Stat1 heterodimer binds to interferon (IFN)-g activation site (GAS) distinct from the IFN-stimulated response element (ISRE) to which the p48 protein containing complexes generally bind. We conclude that uPA activates a specific and unusual subset of latent cytoplasmic transcription factors in human vascular smooth muscle cells that suggests a critical role of uPA in these cells. Our finding that physiological concentration of uPA induces Stat4 activation is, to our knowledge, the first indication that there is at least one more natural ligand for the Stat4 protein beyond IL-12.

P508 Nifedipine induces a pro-atherogenic effect on smooth muscle cells in culture, incubated with LDL isolated from patients with coronary diseases

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Our previous results have demonstrated the Nifedipine ineffectiveness in prevention of atheroma formation in atherosclerotic hamsters. The aim of this study is the investigation of the effects induced by this calcium channel blocker on lipid loading of human aortic smooth muscle cells (SMC) incubated with serum or lipoproteins (LP) isolated from coronary patients.

Methods: Blood was collected from 12 male, coronary patients hospitalised with unstable angina or stable chronic ischaemic cardiopathy, and 6 subjects had no history of cardiovascular diseases. The following plasma assays were performed: glycemia, cholesterol, triglycerides and lipid peroxides. In order to study the effect of Nifedipine, patients LP were incubated for 1–5 days with SMC in culture, with cholesterol concentrations between 25–100 μg/ml medium, in the presence or absence of 10 μM Nifedipine or 10 μM Diltiazem. Quantification of cellular proliferation was done after ^{3}H-thymidine incorporation and lipid loading of the cells was visualised by Oil Red staining and examined ultrastructurally, by electron microscopy. The effect of Nifedipine was compared with that of Diltiazem.

Results: Both calcium channel blockers studied decreased the rate of human aortic SMC proliferation in culture. At similar concentrations, Nifedipine was a stronger inhibitor of proliferation than Diltiazem. The incubation with sera or LDL isolated from patients induced proliferation and lipid loading of human aortic SMC. The anti-proliferative effect of both calcium channel blockers used was maintained under LP incubation conditions. Nifedipine did not impede the intracellular lipid accumulation and SMC transformation into foam cells, by comparison with Diltiazem, that reduced SMC lipid loading significantly.

Conclusions: Nifedipine, the first calcium channel blocker of the dihydropyridine class, has pro-atherogenic effects upon human aortic SMC in culture, as our present experiments demonstrate. The transformation of SMC into foam cells, as a result of the incubation with LP in the presence of Nifedipine, offers a good explanation – at cellular and molecular level – for the aggravation of the atherogenic process, previously reported in atherogenic animal models treated with Nifedipine. The correlation of clinical and experimental data could be essential in the adequate selection of different drugs in the treatment of coronary diseases.

P509 Cyclic AMP and cyclic GMP inhibit matrix metalloproteinase-9 expression in vascular smooth muscle cells

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Introduction. Matrix metalloproteinases (MMPs) are a family of metal dependent endopeptidases, which play an important role in the resorption of extracellular matrixes. Activity of MMPs is essential for vascular smooth muscle cell (VSMC) migration and proliferation, for example in atherosclerosis. Second messengers cAMP and cGMP inhibit proliferation and migration in VSMC. Based on this, we investigated the influence of cyclic nucleotides on MMP expression in VSMC.

Method. Rabbit VSMCs were stimulated with combinations of the inflammatory cytokine, interleukin -1 (il-1), and growth factors, platelet derived growth factor (PDGF) or basic fibroblast growth factor (bFGF). The effects of 8-bromo cAMP or 8-bromo cGMP or agents that elevate endogenous cAMP or cGMP levels were then investigated. Gelatin zymography and northern analysis were used to quantify MMP-9 expression. Western analysis was used to quantify MMP-1 (Collagenase) and MMP-3 (Stromelysin) expression. Effects on the transcription factors, AP-1 and NF-kB, were investigated by electromobility shift assay.

Results. Gelatin zymography demonstrated that either 8-Br-cAMP or 8-Br-cGMP (50–800 μM) significantly reduced MMP-9 production in response to il-1 and PDGF by 94.5 $\pm$ 1.05% ($p = 0.0174$) and 66.4 $\pm$ 0.98% ($p = 0.0288$) respectively ($n = 3$), or bFGF (not shown). A similar effect was observed with forskolin, or 3-morphilinosydnonomine (SIN-1) plus 3-isobutyl-1 -methylxanthine (IBMX). This inhibitory effect was also replicated at the level of MMP-9 mRNA. EMSA demonstrated that cAMP and cGMP reduced il-1 and bFGF stimulated levels of NF-kB but not AP-1. Western analysis demonstrated that the cyclic nucleotides did not inhibit the il-1 and PDGF induced levels of MMP-1 or MMP-3.

Conclusion. Cyclic nucleotides selectively inhibit MMP-9 expression in VSMC by inhibiting NF-kB DNA binding. This mechanism may contribute to the inhibitory effect of cyclic nucleotides on VSMC migration and proliferation.

P510 Angiotensin II activates the JAK/STAT cascade via an NADH/NADPH-dependent mechanism

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Superoxide anions generated via the NADH/NADPH-oxidase system supress the endogeneous nitric oxide (NO) bio-availability, which is involved in the generation of arterial hypertension. Angiotensin II (Ang II) is a known to stimulate the NADH/NADPH-oxidase system in-vitro and in blood vessels in a variety of models in-vivo. Moreover, Ang II was shown to stimulate growth and inflammatory processes, which involve the activation of the Jak/Stat signaling cascade. Therefore, the present study investigated (A) whether Ang II induces the Jak/Stat cascade via superoxide anions and (B) whether this activation of the Jak/Stat cascade leads to an inflammatory response. Therefore, rat aortic smooth muscel (RASM) cells were stimulated with Ang II (10^{-7} M). Superoxide anions generation was blocked with dipenyleniodonium (DPI, 100 μM) and with TIRON (0.3 mM), known inhibitors of the NADH/NADPH-oxidase system. Losartan (10^{-5} M), the Ang II typ 1 (AT1) receptor antagonist was used as control. Interleukin 6 (IL-6) synthesis and release was monitored as a marker of inflammation on RNA-level. As shown previously, Ang II stimulates the rapid phosphorylation of JAK2 and STAT1/STAT3 heterodimers via its AT1-receptor.This activation leads to an increase of IL-6 on RNA-level. DPI and Tiron abolish the activation of JAK2 and STAT1/STAT3 and subsequently the synthesis of IL-6. To elucidate which subunit of the NADPH-system may be responsible for this superoxide anion dependend activation, neutralizing antibodies to p47phox were electroporated into RASM cells. The results showed that blockade of p47phox abolished the Ang II-induced activation of the Jak/Stat cascade and the synthesis of IL-6. Immunohistochemical stainings in coronary artery sections obatined from patients undergoing heart transplantation due to ischemic heart disease revealed a tight cellular co-localization of Ang II, JAK2, STAT1/STAT3, p47phox and IL-6 at the fibrous cap of stable atherosclerotic plaques.

Thus, these results demonstrate that Ang II stimulates via superoxide anions – generated by the NADH/NADPH-oxidase system- the activation of the Jak/Stat cascade. Moreover, superoxide anions seem to be responsible for the Ang II-induced synthesis of pro-inflammtory cytokines in RASM cells. Together with the immunohistochemical results, these data are consistent with the notion that Ang II induces via superoxide anions and the activation of the Jak/Stat cascade an inflammatory response in human coronary artery plaques, which may potentially contribute to the development of an acute coronary syndrome.

P511 Protein-RNA interactions in the 3′untranslated region of the AT1 receptor mRNA. RNA binding sequence and functional characterization

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Background. The expression of the angiotensin AT1 receptor which plays a pivotal role in cardiovascular physiology and pathophysiology is regulated by various agonists as well as neurohumoral and metabolic stimuli predominately via posttranscriptional mechanisms. This study investigated mechanisms involved in posttranscriptional regulation.

Methods. Interactions of the AT1 receptor mRNA and polysomal proteins isolated from rat aortic vascular smooth muscle cells in culture were assessed with UV-mRNA-protein crosslink assays. The functional characterization of these protein-RNA interactions were accomplished by transfection of appropriate AT1 receptor mRNA transcripts into VSMC. DNA-mutations were accomplished with site-directed mutagenesis and exo-nuclease III-nested deletions.

Results. The AT1 receptor mRNA interacts with polysomal proteins in its very 3′end. Multiple mutational studies demonstrated that several binding proteins associated with the AT1 receptor mRNA at base 2176–2195. This fragment is in close neighborhood to the poly(A)-tail and comprises an AUUUUA hexamer and A + U rich flanking regions. Transfection decoy assays with AT1 receptor mRNA transcripts base 1864–2213 or 2175–2213 which reduce binding of polysomal proteins to the wild type AT1 receptor mRNA led to an increased basal expression of AT1 receptor mRNA.

Conclusion. A family of at least six polysomal proteins bind to the 3′untranslated region of the AT1 receptor mRNA. Especially a 50 and a 45 kDa protein bind at the region base 2175–2195 which contains an AUUUUA hexamer. Binding of proteins to this cognate sequence cause decreased turnover of the AT1 receptor mRNA. These findings establish novel molecular mechanisms involved in AT1 receptor regulation and may contribute to the understanding of general events of posttranscriptional modulation of mRNA steady state levels.

P512 Apoptosis of smooth muscle cells stimulates platelet aggregation

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In acute coronary syndrome (ACS) and following angioplasty (PTCA), plaque rupture leads to the formation of thrombi. However, the spatiotemporal relation of platelet aggregation (PA) to vascular injury is incompletely understood. Apoptosis (A) of smooth muscle cells (SMCs) implicated in plaque rupture may contribute to increased thrombogenicity. To test this hypothesis, we examined *ex vivo* PA on A-SMCs in whole blood from healthy donors (D; n = 8), patients with ACS (n = 14) and after PTCA (n = 16).

Methods: Blood samples were obtained from D denying drug intake for at least one week and from patients under standard medication with ACS or post PTCA. A of SMCs was induced by ultraviolet irradiation and assessed by DNA laddering or by flowcytometric analysis. PA and release of platelet ATP were measured simultaneously using a Whole-Blood Lumi-Aggregometer (Chrono-Log Corp., Havertown, USA). PA was determined by the increase in impedance across paired electrodes in response to the aggregatory agent (Collagen, A-SMCs). ATP release was measured by luminescence after addition of the luciferin-luciferase reagent. Control aggregation curves remained nearly unchanged without PA agents; calibration standards were 5 ohm impedance change and 2 nmoles ATP. Intact SMCs did not induce either PA or ATP release (negative controls).

Results: A-SMCs were comparable to collagen in their stimulation of PA in all three groups, whereas only collagen induced significant ATP release. Notably, A-SMCs induced PA in patients with ACS or following PTCA, despite concomitant intensive anti-PA treatment. As also shown in the Table, anti-aggregatory comedication did not significantly diminish, but delay A-SMCs-induced PA ($x \pm$ S.D.).

Group	Agent	Final conc.	Time to PA	Impedance change	ATP release
D	A-SMCs	4000 cells/ml	8.7 ± 2.6 min	18 ± 2 ohms	0.1 ± 0.1 nmol
D	Collagen	2 μg/ml	1.1 ± 0.7	21 ± 3	1.3 ± 0.4
ACS	A-SMCs	4000 cells/ml	12.9 ± 4.6	15 ± 3	0.2 ± 0.2
ACS	Collagen	2 μg/ml	1.9 ± 0.5	16 ± 5	0.4 ± 0.2
PTCA	A-SMCs	4000 cells/ml	13.1 ± 3.7	16 ± 2	0.1 ± 0.1
PTCA	Collagen	2 μg/ml	1.8 ± 0.7	12 ± 3	0.3 ± 0.4

In conclusion, our data on *ex vivo* platelet aggregation demonstrate apoptosis of smooth muscle cells to be a novel potent stimulus that may play an important role in the thrombogenicity of the diseased vascular wall.

ATHEROSCLEROSIS

P513 Plaque temperature in acute ischaemic syndromes: an additional prognostic factor for long-term outcome?

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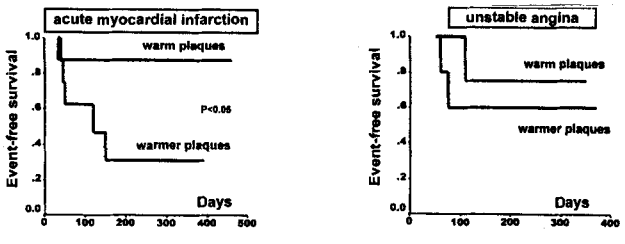
We have shown in vivo that temperature (T) heterogeneity within coronary arteries is increased in acute ischemic syndromes (*Ann Intern Med 1998;129:1079–80*). To assess the association between T and long-term outcome, 27 patients with acute ischemic syndromes (11 unstable angina, 16 acute myocardial infarction) who underwent emergency coronary intervention were followed for a mean follow-up of 6.9 months. T was measured at the time of intervention using a catheter-based technique that was developed in our laboratory and has been previously validated.

Results: Difference of plaque T from healthy vessel wall was larger in acute myocardial infarction patients compared with unstable angina (1.44 ± 0.65 and 0.72 ± 0.40 °C respectively, P < 0.01). Within each group, event (death, re-intervention, hospitalization, symptom recurrence) -free survival was worse in patients who had plaque T difference above the median value of the each study group.



Conclusions: Increased plaque T is associated with an adverse long-term outcome after coronary interventions in acute ischemic syndromes. This new prognostic factor may identify patients that are at higher risk to develop adverse events after coronary intervention.

P514 Histopathological assessment of atherosclerotic plaques by optical fiber-based Raman spectroscopy

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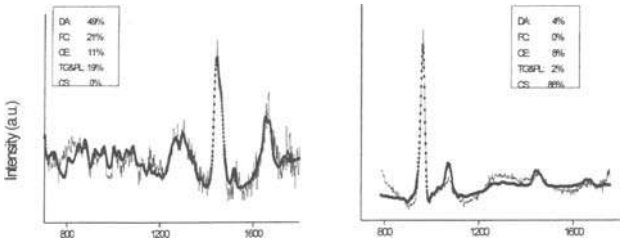
We used Raman spectroscopy to assess the chemical composition of atherosclerosis in perfused intact human coronary artery tissue.

Methods and Results: Human coronary artery samples of 5–6 cm length (n = 6) were mounted in an *in vitro* set-up and perfused with a salt solution at ~80 mm Hg. Near infrared laser light (830 nm; 100 mW) was delivered to the tissue through the central fiber of a 5F optical fiber catheter that was inserted transluminally into the artery sample. High quality tissue Raman signals were collected by surrounding fibers in 10–60 s. The spectra were modeled with Raman spectra of the chemical components comprising the artery (Figure 1). These components were free cholesterol, cholesterol esters, calcium salts, triglycerides and phospholipids, and artery protein. A diagnostic algorithm used this information to classify the examined tissue into either non-atherosclerotic tissue, atheromatous plaque, or calcified plaque.



Conclusion: Intravascular optical fiber Raman spectroscopy can provide *in situ* histopathology, which may be used to study vascular disease in the patient *in vivo*, to predict plaque rupture and to evaluate therapeutic effects.

P515 Inducible nitric oxide synthase is upregulated in ruptured infarct-related coronary plaques

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Objective: Inducible nitric oxide synthase (NOS II) produces high concentrations of nitric oxide, known as very cytotoxic. We investigated the presence of NOS II in coronary atherosclerotic lesions after acute myocardial infarction (AMI) and unstable angina pectoris (UA), and correlated this with the presence of signs of plaque rupture on coronary angiography and intravascular ultrasound (IVUS).

Methods: Patients (n = 22) with a recent AMI (n = 8) or with UA (Braunwald class IIb or IIIb) (n = 14) were examined with angiography and IVUS before directional atherectomy and stenting was performed. The angiographical and IVUS images were assessed for the presence of plaque rupture. The atherectomy specimens were immunohistochemically investigated and immunoreactive areas were quantified.

Results: The atherectomy specimens of patients with AMI contained more CD68 (macrophages) immunoreactivity (19.3 ± 7.1%) than the specimens of patients with UA (6.0 ± 2.7%) ($p < 0.05$). Also the NOS II immunoreactive area was higher in the AMI group (6.1 ± 2.2% versus 1.8 ± 0.8%) ($p < 0.05$). NOS II was present in the macrophages. A strong correlation between macrophages and NOS II ($r = 0.7$, $p \leq 0.01$) was found. Angiographic evidence of plaque rupture was observed in 7 of 8 patients with AMI. In the UA group the infarct-related lesion showed signs of plaque rupture in 8 of 14 patients. IVUS showed the presence of a ruptured cap covering an eccentric lipid pool in 40% of all (AMI + UA) patients. A correlation between IVUS lesion type and the presence of macrophages and NOS II was however not present.

Conclusion: We demonstrated that plaque ruptures related with AMI contain abundant macrophages with NOS II expression. Plaques of patients with UA contain less signs of inflammation. Excessive accumulation of NOS II containing macrophages can be a major factor in the final step of plaque destabilisation and rupture. However it can not be excluded that macrophages further accumulate in the fibrous caps after rupture.

P516 Pravastatin suppresses T-lymphocyte proliferation and interferon-gamma production

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Hypercholesterolaemia and atherosclerosis are associated with lymphocyte mediated inflammation. We have previously shown increases in lymphocyte proliferative responses and the production of the key regulatory cytokine interferon-gamma(IFN) in the hyper-cholesterolaemic apolipoprotein E deficient (apoE−) murine model of atherosclerosis. We then sought to investigate whether lymphocyte activation in apoE− mice could be suppressed by pravastatin.

Studies were performed on splenic lymphocytes from apoE− mice and on C57Bl/6j (normal cholesterol) controls. Pravastatin or placebo was administered to the mice in their drinking water. Mitogen (conA) stimulated lymphocyte proliferation was assessed by ^{3}H-thymidine incorporation and IFN production measured by ELISA of culture supernatants. Assays were performed in the presence or absence of in vitro pravastatin (100 μM).

Compared to placebo, pravastatin significantly reduced cholesterol in apoE− mice (mean 19.5 vs 30.9 μM; $p < 0.05$) but not in C57 controls (1.7 vs 2.4 μM). Ex vivo lymphocyte proliferation was decreased in pravastatin treated mice compared to placebo (stimulation index 10.6 vs 23.5; $p = 0.02$). In both C57 and apoE− mice, in vitro pravastatin was associated with suppression of cell proliferation (39.5 vs 72.0; $p < 0.001$) and IFN production (42.1 vs 71.2 U/100 μL; $p < 0.001$).

Pravastatin is able to suppress ex vivo and in vitro mitogen stimulated lymphocyte activation. These effects raise the possibility that pravastatin may modify the atherosclerotic process by direct immunomodulatory mechanisms, in addition to cholesterol lowering.

P517 Serum glucose but not insulin modulates platelet-dependent thrombosis in patients with coronary artery disease

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Previously we demonstrated that elevated blood glucose (G) is associated with augmented platelet-dependent thrombosis (PDT). High plasma insulin (I) levels are associated with enhanced risk of CAD, however, the mechanisms are unknown. We prospectively measured PDT in 36 stable CAD patients (mean age 68 ± 9 years) on aspirin with controlled lipid levels. Porcine aortic media was exposed to flowing non-anticoagulated venous blood in an ex-vivo perfusion chamber. PDT was measured by computerized morphometry. Total plasma immunoreactive I and G levels were measured after overnight fast.

Results: Initial correlation analysis between I, G and PDT demonstrated I ($r = 0.015$, $p = 0.93$) and G ($r = 0.51$, $p = 0.002$). Patients were divided into two groups: Group A ≤ and Group B > the median I level (17 μU/ml). There were no significant differences in age, serum lipids platelet count or fibrinogen levels between the two groups. PDT was not significantly elevated in Group B vs Group A (103 ± 128 vs 84 ± 74 μm^2/mm, p = NS). PDT, however, was significantly augmented in patients with G > compared to <median (90 mg/dl) level (159 ± 141 vs 67 ± 69 μm^2/mm, $p < 0.01$).

Conclusion: Elevated G but *not* I is associated with augmented PDT in stable CAD patients with controlled lipid levels. This finding suggests that the mechanism contributing to the enhanced thrombogenic risk of CAD may be related to hyperglycemia rather than hyperinsulinemia.

P518 Morphologic modelling and histopathological classification of human coronary atherosclerosis by morphology based Raman spectroscopy

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The development of an atherosclerotic plaque in arterial intima is characterized by morphological changes, which are detected by pathologists in stained tissue sections. The changes are used to determine the state of disease of the tissue. In the present study we present a classification technique for atherosclerosis based on morphological Raman microspectroscopy.

Methods and Results: Raman spectra were collected from eight morphological structures in unstained coronary artery sections with a Raman spectroscopy system (Table 1). These morphological Raman spectra were used as basis spectra in a linear fitting model, to obtain morphological information from macroscopic coronary artery Raman spectra of unknown composition, that were subsequently classified by a pathologist into three classes (normal tissue, atheromatous tissue, and calcified tissue). The results show significant changes in all morphological structures in the different artery samples.

Table 1. Fit contribution of morphological structure to artery tissue (n = 97). The data are corrected for the calcification contribution.

Structure	Normal (n = 73)	Atheromatous (n = 10)	Calcified (n = 14)
Collagen fiber	0.26 ± 0.02	0.15 ± 0.05	0.44 ± 0.07
Cholesterol crystal	0.05 ± 0.01	0.22 ± 0.03	0.09 ± 0.03
Calcification	0.01 ± 0	0.01 ± 0.01	0.68 ± 0.09
IEL (elastin)	0.07 ± 0.01	0.10 ± 0.02	0.09 ± 0.02
Adventitial fat	0.38 ± 0.03	0.24 ± 0.03	0.29 ± 0.06
Foam cell/necrotic core	0.03 ± 0.01	0.23 ± 0.04	0.07 ± 0.03
Smooth muscle cell	0.20 ± 0.01	0.05 ± 0.02	0.02 ± 0.01

Conclusion: The pathological state of human coronary artery may be assessed by determining morphological information with Raman spectroscopy. This technique may be used for histopathological classification of atherosclerosis *in situ*, and provide a better understanding of the dynamics in the evolution of atherosclerotic lesions.

P519 Association of endotoxemia with carotid atherosclerosis and cardiovascular disease: prospective results from the Bruneck study

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Objectives: Focus of the current study was on the significance of bacterial endotoxin, which shows a variety of pro-atherogenic properties and may occur at high concentration in the circulation of infected subjects. The possibility of an infectious risk factor in atherogenesis and cardiovascular disease has stimulated renewed research interest, but the nature of such process remains obscure.

Methods: We measured plasma endotoxin levels (LAL assay) in a random population of 516 men and women 50 to 79 years old at the 1990 baseline evaluation (Bruneck Study). Endpoints of this prospective survey were incident (early) atherosclerosis in the carotid arteries as assessed with high-resolution Duplex ultrasound (five-year follow-up rate, 98%) and incident cardiovascular disease (follow-up rate, 100%).

Results: Median endotoxin concentration amounted to 14.3 pg/mL with a range of 6.0 to 209.2 pg/mL. Subjects with levels beyond 50 pg/mL (90th percentile) faced a three-fold risk of incident atherosclerosis (OR 95% CI 2.9 [1.4–6.3]; $P < 0.01$). The risk associated with high endotoxin was most pronounced in subjects with chronic infections and in current and ex-smokers. Notably, smokers with low endotoxin levels and non-smokers did not differ in their atherosclerosis risk, whereas smokers with high levels almost invariably developed new lesions. All findings emerged as independent of vascular risk factors. Similar results were obtained for incident cardiovascular disease.

Conclusion: The current study yields first epidemiologic evidence that endotoxemia constitutes a strong risk factor of early atherogenesis in subjects with chronic or recurrent bacterial infections and a link in the association between cigarette smoking and atherosclerotic disease.

P520 Inflammation and increased oxidative stress as risk factors for atherosclerosis in chronic renal failure

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Atherosclerotic cardiovascular disease and malnutrition are widely recognized as leading causes of the increased morbidity and mortality observed in uremic patients. In chronic renal failure (CRF) increased concentration of acute phase proteins, such as C-reactive protein (CRP), has been associated with an increased mortality. The aim of present study was to assess the interactions between cardiovascular disease, inflammation, malnutrition and oxidative stress in CRF.

Methods: 109 predialysis patients (age 52 ± 1 years) with terminal CRF were studied. By using non-invasive B-mode ultrasonography the cross-sectional common carotid intima-media area was calculated and the presence or absence of carotid plaques was determined. Nutritional status was assessed by subjective global assessment (SGA), dual-energy x-ray absorptiometry, serum albumin, serum creatinine, serum urea and 24-hour urine urea excretion. The presence of an inflammatory reaction was assessed by CRP, fibrinogen and TNF-α. Lipid parameters as well as markers of oxidative stress (autoantibodies against oxidized LDL; vitamin E) were also determined.

Results: Compared to healthy controls, CRF patients had an increased mean intima-media area (18.3 ± 0.6 vs. 13.2 ± 0.7 mm^2; $p < 0.0001$) and a higher prevalence of carotid plaques (72 vs. 32%; $p = 0.001$). The prevalence of malnutrition (SGA 2–4) was 44%, and 32% of all patients had an acute phase response (CRP ≥ 10 mg/l). Malnourished patients had higher CRP levels (23 ± 3 vs. 13 ± 2 mg/l; $p < 0.01$), elevated intima-media area (20.2 ± 0.8 vs. 16.9 ± 0.7 mm^2; $p < 0.01$) and a higher prevalence of carotid plaques (90 vs. 60%; $p < 0.0001$) compared to well-nourished patients. During stepwise multivariate analysis adjusted for age and gender, vitamin E ($p < 0.05$) and CRP ($p < 0.05$) remained associated with an increased intima-media area. The presence of carotid plaques were significantly associated with age ($p < 0.001$), log oxLDL ($p < 0.01$) and small apo(a) isoform size ($p < 0.05$) in a multivariate logistic regression model.

Conclusion: The present results indicate that the rapidly developing atherosclosis in advanced chronic renal failure appears to be caused by a synergism of different mechanisms, including inflammation and oxidative stress.

P521 Recombinant human apo A-I adenoviruses lack hepatotropism after systemic injection in rabbits

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Stable elevation of HDL cholesterol, induced by apo A-I gene transfer, may lead to a dramatic decrease of atherosclerotic vascular disease. Recombinant adenoviruses have been shown to be hepatotropic after gene transfer in mice. In the present study, we compared systemic infusion versus portal vein injection in New Zealand White Rabbits of human apo A-I adenoviruses containing the ubiquitously active cytomegalovirus (CMV) promoter (CMV/A-I.gA-I) or the liver-specific 256bp apo A-I promoter (A-I.gA-I.4xapoE).

Results: Ear vein injection (n = 11) and portal vein injection (n = 3) of 10^{11} p.f.u. of CMV/A-I.gA-I induced human apo A-I levels of 19 ± 3.2 mg/dl respectively 18 ± 3.0 mg/dl at day 3, 14 ± 3.8 mg/dl respectively 18 ± 6 mg/dl at day 6 and 0 ± 0 mg/dl respectively 0 ± 0 mg/dl at day 10. Human apo A-I levels after gene transfer by ear vein injection (n = 3) of 10^{11} p.f.u A-I.gA-I.4xapoE were undetectable at any time point. In contrast, portal vein infusion (n = 3) of 10^{11} p.f.u. A-I.gA-I.4xapoE resulted in human apo A-I levels of 23 ± 5 mg/dl at day 3, 40 ± 1.6 mg/dl at day 6, 41 ± 1.0 mg/dl at day 10, 7.0 ± 3.7 mg/dl at day 14 and 0 ± 0 mg/dl at day 21. Portal vein infusion with 2 × 10^{11} p.f.u A-I.gA-I.4xapoE (n = 3) induced human apo A-I levels of 38 ± 6.3 mg/dl at day 3, 65 ± 5 mg/dl at day 6, 64 ± 16 mg/dl at day 10, 15 ± 15 mg/dl at day 14 and 0 ± 0 mg/dl at day 21.

Conclusion: Successful human apo A-I gene transfer in rabbits with recombinant human apo A-I adenoviruses containing a liver-specific promoter is strictly dependent on portal vein infusion, indicating absence of hepatotropism of adenoviruses in rabbits. Because we observed human apo A-I expression for more than 6 months after gene transfer with A-I.gA-I.4xapoE in C57BL/6 mice, the rapid decline of human apo A-I levels after day 10 in rabbits suggests a cellular and/or humoral immune response against human apo A-I.

P522 A novel Ca^{2+}-independent pathway for NO synthase activation in endothelial cells via Akt-dependent phosphorylation

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Fluid shear stress enhances nitric oxide (NO) production by activating the endothelial nitric oxide synthase (eNOS). The enhanced activity of eNOS is thought to be regulated by phosphorylation, although the signalling pathway involved is unclear. Since shear stress has been shown to stimulate the serine/threonin kinase Akt via the phosphoinositide-3 kinase (PI3K), we examined the contribution of the PI3K/Akt-pathway in regulation of eNOS phosphorylation and activity.

Phosphorylation of eNOS was determined by two-dimensional amino acid analysis of eNOS immunoprecipitated from ^{32}P-labelled human umbilical vein endothelial cells. The application of fluid shear stress (1 h) to endothelial cells resulted in a 2-fold increase in the serine phosphorylation of eNOS, which was abrogated by the PI3K inhibitor wortmannin (20 nM). Moreover, the shear stress-stimulated increase in cyclic GMP (186 ± 50%), which reflects eNOS activation, was also prevented by wortmannin (104 ± 23%). Furthermore, Akt directly phosphorylated eNOS in vitro. To test whether the phosphorylation of eNOS by Akt regulates eNOS activity, the two serine residues (S633 and S1177), matching the consensus sequence for Akt, were mutated into phospho-mimetic aspartic acid residues and the mutants were overexpressed in endothelial cells. The S1177D mutant revealed a 2-fold increase in enzyme activity as measured by the L-arginine assay compared to eNOS wild type (wt)-transfected cells ($p < 0.007$), whereas mutation of S633 did not affect eNOS activity. Moreover, mutation of the S1177 enhanced the sensitivity of eNOS towards calcium.

Conclusion: These results demonstrate a novel pathway for activation of the eNOS, which may have important therapeutic implications.

P523 n-3 Polyunsaturated fatty acids decrease intracellular production of reactive oxygen species and endothelial activation: a link to their anti-atherogenic and anti-inflammatory properties

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We have previously shown that the n-3 polyunsaturated fatty acid (FA) docosahexaenoate (DHA) and, to a lesser extent, other unsaturated FA, inhibit the expression of adhesion molecules and chemoattractants in cultured endothelial cells after interleukin (IL)-1 stimulation, and subsequent monocyte recruitment onto endothelium. These properties were shown to be a function of the number of unsaturation in the FA carbon chain. In investigating potential mechanism(s) for these effects, we incubated increasing concentrations (5–50 μM) of DHA, or stearate and palmitate as control saturated FA, with cultured saphenous vein endothelial cells for 24–72 h, followed by IL-1 (1 ng/mL) stimulation. DHA, but not stearate inhibited VCAM-1 mRNA levels at Northern analysis. Actinomycin-D studies indicated that DHA inhibits VCAM-1 expression at a transcriptional level. In transient transfection experiments with plasmid constructs consisting of a functional −1.8 kb VCAM-1 prommoter linked to the chloramphenicol acetyl transferase (CAT) reporter gene, DHA inhibited IL-1-stimulated VCAM-1 promoter activity by 70%. Electrophoretic mobility shift assays indicated that DHA suppresses IL-1-induced nuclear factor (NF)-κB activation. Since NF-κB activation is thought to occur via the generation of reactive oxygen species, particularly H_2O_2, we assessed the EC redox state by using a permeable oxidant-sensitive probe, dichlorofluoresceine (DCF). DHA suppressed IL-1 or TNF-induced increase in DCF fluorescence in a concentration-dependent fashion. Thus, a highly unsaturated FA, known for its susceptibility to peroxidation, paradoxically decreases the intracellular generation of reactive oxygen species, possibly preventing the dismutation of superoxide to H_2O_2, in intracellular compartments critical for cytokine signal transduction. These findings indicate that n-3 FA inhibit endothelial activation via inhibition of the oxidant-sensitive transcription factor NF-κB. These "antioxidant" properties of polyunsaturated FA may be one mechanism by which they are beneficial in atherosclerosis or inflammation.

P524 Advanced glycation end-products as pro-inflammatory cytokine equivalents for vascular endothelium

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Background: Advanced glycation end-products (AGEs) play a pivotal role in chronic disease such as diabetes and atherosclerosis. We investigated whether AGEs isolated *ex vivo* from patients or produced *in vitro* affect endothelial activation, and assessed some of the mechanisms involved. We also tested the co-expression of AGEs and products of endothelial activation in human inflammatory tissues.

Methods: AGEs were affinity-purified from plasma of uremic patients or prepared by incubating serum albumin in buffered saline with ribose at 37°C for 4 weeks, and characterized by fluorimetry and binding by specific antibodies. The expression of endothelial leukocyte adhesion molecules (VCAM-1, ICAM-1, E-selectin) and constitutive endothelial antigens were assessed by cell surface EIA and flow cytometry on cultured saphenous vein endothelial cells. Monocytoid cell or neutrophil adhesion to endotheliums was assessed by rotational adhesion assays. Specific mRNA levels were evaluated by Northern analysis.

Results: AGEs from both sources induced a concentration-dependent increase in expression of all adhesion molecules assayed, and monocytoid cell and neutrophil adhesion, which were completely and specifically blocked by anti-RAGE IgG. Northern analysis indicated a concomitant increase in adhesion molecule mRNA levels, which again was completely blocked by anti-RAGE IgG. Inflammatory tissues from rheumatoid synovia co-expressed adhesion molecules, AGEs and RAGE.

Conclusions: AGEs induce a generalized state of endothelial activation, which may contribute to inflammatory vascular changes also occurring in non-diabetic conditions.

P525 Extracellular matrix remodelling in diabetic vascular injury

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Diabetes mellitus is associated with excess atherosclerotic vascular fibrosis. Mechanisms leading to interstitial remodelling following angioplasty are not known.

Methods. NZ white rabbits (n = 12) were injected with a single IV dose of alloxan monohydrate (100 mg/kg), to induce chemical-diabetes. Four weeks later, diabetic animals and another group of control, non-diabetic rabbits (n = 10) underwent atherogenic diet and barotrauma injury in the right iliac artery. Left iliac was sham operated. All rabbits were sacrificed after 40 days of injury and vessels analyzed by RT-PCR (messenger RNA), biochemical (proteins, hydroxyproline, DNA), and computerized histomorphometric measurements (H&E, picrosirius red staining).

Results. Serum glucose was 200–400 mg/100 ml in the diabetic rabbits, accompanied by a 3–6 times higher conc. of triglyceride and total cholesterol level compared to non-diabetics ($p \leq 0.001$). A substantial increase in both procollagen type I (2 folds higher) and TGFb1 (5 folds higher) gene expression ($p < 0.001$) was associated with a moderate rise in vascular fibrillar collagen conc. (~31%), and a 15% reduction in cross-sectional area in the diabetic injured arteries. Matrix degradative enzyme mRNA (collagenase 1, and 9) were quantitated 3 times higher ($p \leq 0.01$) in diabetes. AT1 Ang II receptor mRNA was also 2 times higher in diabetic rabbits.

Conclusions. We conclude that a major up-regulation in levels of vascular TGFb1 is associated with enhanced remodelling and expansion of extracellular matrix leading to interstitial vascular fibrosis in diabetes mellitus.

P526 Evidence for cyclooxygenase-2-dependent prostacyclin production in atherosclerosis

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©Prostaglandins (PGs) play a major role in the regulation of platelet and vascular function. Ischaemia reperfusion injury, seen in patients undergoing revascularisation surgery, causes a rise in PG production. We examined the generation of PGs in 35 patients undergoing vascular surgery, using assays for the analysis of the principle endothelial product prostacyclin (PGI2) and the principle platelet product thromboxane A2 (TxA2). We hypothesised that selective cyclooxygenase-2 (COX-2) inhibition would significantly reduce the post-operative rise in PG production.

Previous work in our laboratory, using balloon angioplasty in rat carotid arteries, has demonstrated COX-2 expression in neo-intimal tissue. We have also shown that COX-2 expression is present in human atherosclerotic plaque, localised to the vascular smooth muscle cells, in endarterectomised patients.

Methods: In this study, patients undergoing revascularisation surgery for aortic or peripheral vascular disease were randomised to receive: i) no treatment ii) aspirin alone iii) nimesulide (a selective COX-2 inhibitor) alone or iv) aspirin and nimesulide. The stable urinary metabolites of PGI2, 2,3 dinor-6-keto PGF1alpha (PGI-M) and thromboxane A2, 11-dehydro thromboxane B2 (Tx-M) were measured using mass spectrometry. Measurements were made pre-operatively and for up to 48 hours post-op.

Results: Patients on nimesulide alone or in combination with aspirin showed a marked reduction in post-op production of PGI-M relative to those on no treatment [334 ± 107 to 2029 ± 818 for nimesulide alone and 139 ± 41 to 1013 ± 307 for nimesulide+aspirin vs 738 ± 246 to 4299 ± 1566, $p < 0.05$]. Patients on aspirin showed a marked reduction in Tx-M post-op compared to those on no treatment or on nimesulide alone [1093 ± 342 to 4178 ± 1169 vs 3566 ± 764 to 22760 ± 12197 for no treatment and 2501 ± 694 to 15365 ± 7996 for nimesulide alone, $p < 0.01$]. Nimesulide alone had little effect on Tx-M production [$p > 0.5$]. All results are expressed as pg/mg creatinine, mean values ± s.e.m.

Conclusion: These results indicate that in patients with widespread atherosclerotic disease, the rise in TxA2 formation after revascularisation surgery is primarily COX-1 dependent. The rise in PGI2 production, however, shows significant COX-2 dependency. As PGI2 is a potent vasodilator and inhibitor of platelet aggregation, the use of selective COX-2 inhibition in patients with atherosclerotic disease may expose these patients to the potentially harmful effects of unopposed TxA2 production.

P527 Hyperhomocysteinaemia and progression of coronary atherosclerosis

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Background: Hyperhomocysteinemia (HHCY) is an independent risk factor for the development of coronary artery disease (CAD) although the mechanisms responsible for the atherogenic or thrombogenic effects of homocysteine (HCY) have not yet been determined. Aim of this study was to evaluate the effect of HHCY on angiographic progression of coronary atherosclerosis.

Methods: To assess the effects of HHCY on progression of coronary atherosclerosis, HCY was determined after an overnight fast in 216 male patients who participated in the placebo group of the Regression Growth Evaluation Statin Study (REGRESS). These patients had normal to mildly elevated total cholesterol and were scheduled for coronary arteriography. Two years after enrollment a second coronary arteriography was performed. Progression of coronary atherosclerosis was assessed by quantitative coronary angiography (QCA). Progression was expressed as a decrease in average Mean Segment Diameter (MSD) and average Minimum Obstruction Diameter (MOD) of all available coronary segments.

Results:

HCY μmol/l	Changes MSD/SD	Change MOD/SD
<11.2	−0.0618 mm 0.1876 (ns)	−0.0703 mm 0.1605 (ns)
11.2–13.1	−0.1283 mm 0.2145 (ns)	−0.1390 mm 0.2278 (ns)
13.1–15.4	−0.1385 mm 0.2344 (ns)	−0.1514 mm 0.2610 (ns)
>15.4	−0.1261 mm 0.1963 (ns)	−0.1122 mm 0.2016 (ns)

Conclusion: There is no significant correlation between HCY levels and decrease of MSD and MOD, suggesting that the mechanism responsible for the reported higher mortality of patients with HHCY and CAD is not the progression of atherosclerosis.

P528 Vastatins compete with norepinephrine for the alpha receptor in aorta

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Previous studies from our laboratory have shown that vastatins, in particular simvastatin (SV), inhibit the contraction of aortic rings by Angiotensin II and Norepinephrine (NE). These effects of SV appears to be due to depletion of $InsP_3$- sensitive Ca^{+2} pools because the drug releases CA^{+2} from these stores in a manner similar to that of thapsigargin, a SERCA type Ca^{+2} pump inhibitor. An additional mechanism by which vastatins could inhibit the contraction of aortic rings by various agonists could involve an interaction with receptors on the cell surface because pravastatin (20 uM), a vastatin that does not affect aortic ring contractility, displaces NE-concentration response curve to the right. The latter effect suggest a competition between the drug and NE for receptor binding. To evaluate this point further, NE concentration-response curves (10^{-10} to 10^{-5}) were performed in the presence and absence of 5 uM vastatins. From these studies EC_{50} values were obtained and the results areas follows (nM): None = 1:01 ± 0.3, Simvastatin 11.1 ± 1.6 ($P < 0.05$), Lovastatin (LV) = 15.6 ± 2.7 ($p < 0.05$), Mevastatin (MV) = 10.1 ± 3.3 ($P < 0.05$) and Pravastatin = 0.78 ± 0.2 (N.S.). These data suggest that (5 uM) SV, LV, and MV, but not PV, compete with NE for receptor binding. SV was the only drug that in addition to induce a right shift in NE-concentration response curves, significantly reduces the maximal contraction by this agonist (29%, $P < 0.05$). Altogether these results indicate that vastatins could affect the NE-induced contraction by two different mechanisms: 1) by affecting intracellular Ca^{+2} release, and 2) by competing with NE at the alpha-receptor. SV (uM) possesses both of these effects whereas at similar concentrations LV, and MV, display only the alpha-receptor antagonism.

P529 Statin-sensitive dysregulated at1 receptor function and density in hypercholesterolaemic men

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Background: Hypercholesterolemia causes a significant up-regulation of vascular AT1 receptor expression in cell culture and animal models and is a well established risk factor for cardiovascular disease. The presented studies were undertaken to examine AT1 receptor overexpression in hypercholesterolemic men and therapeutic interventions thereof by HMG-CoA-reductase inhibitors (statins).

Methods: Effects of AT1 receptor activation were measured by assessing the blood pressure following infusion of angiotensin II in normo-(cholesterol 181 ± 11 mg/dl, low density lipoprotein 100 ± 7 mg/dl) and hypercholesterolemic (cholesterol 294 ± 10 mg/dl, low density lipoprotein 215 ± 9 mg/dl) men (n = 19/20). AT1 receptor expression was assessed in the same population on isolated platelets. In addition, patients were investigated before and after cholesterol-lowering therapy with statins.

Results: Hypercholesterolemia led to a significant increase of angiotensin II-induced blood pressure elevation. In contrast, norephinephrine-caused blood pressure enhancement was similar in normo- and hypercholesterolemic individuals. AT1 receptor expression was significantly enhanced in hypercholesterolemic individuals (B_{max} = 5.2 ± 1.2 fmol/mg protein) compared to normocholesterolemic men (B_{max} = 2.1 ± 0.2 fmol/mg protein). Cholesterol-lowering treatment with statins reversed the elevated blood pressure response to angiotensin II infusion and remarkably down-regulated AT1 receptor density

Conclusions: Hypercholesterolemia induces AT1 receptor overexpression and enhances biological effects of angiotensin II in men. These findings provide novel insights in the pathogenesis of hypertension and atherosclerosis and may initiate rational and new therapeutic concepts which could potentially prevent complications under these conditions. In addition, statin-caused modulation of AT1 receptor expression may be involved in beneficial therapeutic effects irrespective of plasma cholesterol-lowering.

P530 Oestrogen decreases angiotensin II mediated free radical production in vascular smooth muscle cells via AT1 receptor modulation

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In postmenopausal women, hormone replacement therapy influences lipid metabolism and potentially exerts direct effects on vascular cells. In order to elucidate those effects of estrogen on vascular smooth muscle cells (VSMC), angiotensin II mediated reactive oxygen species (ROS) production and AT 1 receptor (AT1) expression were investigated in the presence of 17β-estradiol (E_2) in VSMC.

Methods: In female rat VSMC, intracellular ROS levels were measured by confocal laserscanning microscopy using the fluorescent probe H_2DCF-DA. AT1 expression was determined by Northern analysis, and radioligand binding studies with ^{125}I-angiotensin II.

Results: After 3 h, angiotensin II caused significantly increased intracellular ROS levels in VSMC. 12 h pre-treatment with 1 μmol/l E_2 decreased the angiotensin II mediated ROS production ($p < 0.05$). E_2 led to a dose and time dependent downregulation of AT1 with a maximum of 40 ± 6% at 4 h treatment with 1 μmol/l E_2 ($p < 0.05$). In accordance, AT1 receptor density was decreased to 58 ± 4% after 12 h. Incubation of VSCM with the stereoisomeric 17 α-estradiol (1 μmol/l) or the estrogen receptor antagonist tamoxifen (1 μmol/l) did not influence AT1 mRNA expression, but tamoxifen completely prevented E_2 induced AT1 modulation ($p < 0.05$ vs. E_2 alone). Experiments performed under transcriptional blockage showed that E_2-induced AT1 downregulation was mediated through destabilsation of AT1 mRNA.

Conclusion: AT1 receptor activation is one major pathway leading to ROS release in the vessel wall. This free radical release is inhibited through estrogen-induced AT1 receptor downregulation via posttranscriptional mechanisms. These data may explain the role of estrogen in the pathophysiology of atherosclerosis and hypertension because oxygen derived free radicals and the local RAS of the vascular wall are important for the pathohysiology of both diseases.

P531 An in vitro study on the antioxidant capacity of statins

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The remarkable results achieved by statins on the various end-points (stroke, total and cardiovascular mortality rate) have lead to the theory whereby these drugs may have a 'stabilising' mechanism on the atherosclerotic plaque, independent of reduced blood cholesterol levels, which are involved, however, in the progression of the disease.

Purpose: The purpose of this study was to assess the total antioxidant capacity of four known statins: Atorvastatin, Simvastatin, Pravastatin and Fluvastatin.

Methods: The total antioxidant capacity of Atorvastatin, Simvastatin, Pravastatin and Fluvastatin was calculated. The efficiency of these molecules as free radical scavengers was compared against peroxyl and hydroxyl radicals obtained through thermal decomposition of an azo-bis precursor and a modified Fenton reaction, respectively, measured by gas-chromatography. The results achieved with the drugs under analysis were expressed in TOSC (Total Oxyradical Scavenger Capacity) units and compared with the specific TOSC value per mg of certain classical antioxidants such as glutathione, ascorbic acid, uric acid and Trolox (the hydrosoluble analogue of Vitamin E).

Results: All the drugs analysed showed a good total antioxidant capacity towards the reactive oxygen species. In particular, Atorvastatin and Simvastatin proved to be exceptional scavengers of hydroxyl radicals with specific TOSC values of 2296 and 3375, respectively (TOSC/mg of tablet at 148 and 337, respectively), greater than that shown by Pravastatin (TOSC/mg active principle = 931; TOSC/mg of tablet = 45), by Fluvastatin (TOSC/mg of active principle = 875; TOSC/mg of tablet = 89) and by the classical antioxidants such as reduced glutathione (TOSC = 358), uric acid (TOSC = 1249) and Trolox (TOSC = 759) used as controls.

Conclusion: Atorvastatin and Simvastatin show a high capacity in neutralising OH−. Their TOSC values (referring to the active principle alone) are not only the highest among the various drugs analysed but are also higher than that of classical antioxidants (Glutathione, Uric Acid and Trolox).

P532 Inhibition of nuclear factor-κB-binding activity by hormone replacement therapy in vivo

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Hormone replacement therapy (HRT) in postmenopausal women is associated with a reduced risk for cardiovascular disease. A well documented antioxidant capacity of estradiol may be partially responsible for this beneficial effect. Because increased expression of the oxidative stress sensitive transcription factor nuclear factor$_\kappa$-B (NF-$_\kappa$B) is closely linked to development of cardiovascular disease, we studied the effect of HRT on NF-$_\kappa$B activity in vivo as well as on levels of NF-$_\kappa$B dependent markers of endothelial dysfunction.

Methods: To determine the NF-$_\kappa$B activity in vivo a Electrophoretic Mobility Shift Assay (EMSA) based detection system in ex vivo isolated blood mononuclear cells (PBMC) was used in 20 postmenopausal women before and after 6 weeks under HRT. Seum levels of lipidhydroperoxides (Lpx), as well as levels of soluble adhesion molecules vascular cell adhesion molecule-1 (sVCAM-1) and sE-selectin were measured by ELISA and lipidhydroperoxides were measured by an colorimetric method.

Results: After 6 weeks therapy NF-$_\kappa$B binding activity was reduced by 41% ($p < 0.001$). This was paralleled by reductions in serum lipid hydroperoxides (−19.69%; $p < 0.0081$) as a marker of oxidative stress and decreases in levels of NF$_\kappa$-B controlled sVCAM-1 (−15.48%, $p < 0.0002$) and E-selectin (−18.49%, $p < 0.0009$).

Conclusions: The present results indicate that estrogen replacement therapy inhibits transcription factor NF-$_\kappa$B activity in vivo. This may represent a novel mechanism for the vasoprotective effects of HRT.

P533 Intramuscular administration of oestrogen induces collateral artery augmentation in a rabbit model of chronic limb ischaemia

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We tested the hypothesis that estrogen (Estr) can induce collateral artery augmentation in a rabbit model of chronic limb ischemia (I).

Methods: I was induced in the hindlimb of 16 oophorectomised New Zealand White rabbits by excision of the femoral artery. Ten days (D) after the induction of I (D 0), they were randomized into 3 groups according to the intramuscular treatment in the I limb: controls (n = 4) receiving saline at D 0; Estr 1 group (n = 6) receiving estradiol valerate, modified release (EVMR) 1 mg/kg at D 0; and Estr 2 group (n = 6) receiving EVMR 1 mg/kg at D 0 and D 15. Revascularization in the I limb was evaluated by calf blood pressure measurement and expressed as I/normal limb ratio (BPR), and capillary (Cap) density to muscle fiber ratio, after examination of light microscopic sections taken from the abductor muscle of the I limb at the time of death (D 30).

Results:

Mean ± SD	Controls	Estr 1	Estr 2
Cap/Muscle	0.83 ± 0.06	1.08 ± 0.14*	1.01 ± 0.14*
Calf BPR, D 30	0.37 ± 0.02	0.52 ± 0.11	0.65 ± 0.14*#
βEst D 15, pg/ml	13 ± 4	19 ± 1*	18 ± 3*
βEst D 30, pg/ml	8 ± 1	11 ± 2	27 ± 12*#

*$p < 05$ vs control; #: $p < 0.05$ vs Estr 1; βEst: 17-β-estradiol plasma levels.

Conclusion: Administration of Estr augments limb perfusion and is accompanied by evidence of increased collateral formation in I rabbit hind limbs. This study thus supports the hypothesis that administration of Estr to stimulate angiogenesis may represent a new therapeutic modality in the management of arterial insufficiency.

P534 C-reactive protein and atherogenesis – C-reactive protein is chemotactic for monocytes in vitro and its accumulation in the arterial intima precedes monocyte infiltration in early atherogenesis

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There are several arguments suggesting that C-reactive protein may be intimately involved in atherosclerotic lesion formation. Thus, C-reactive protein aggregates lipid particles, for example LDL and VLDL. Furthermore, CRP interacts with specific receptors on inflammatory cells and activates the complement system via the classical pathway.

CRP has repeatedly been demonstrated to be present in advanced atherosclerotic lesions of humans. Recently, it has been demonstrated in early atherosclerotic lesions of humans for the first time and shown to colocalize with the terminal membrane attack complex of human complement suggesting that CRP may be the major complement activating molecule in atherosclerotic lesions.

In this study we have investigated the effects of purified human CRP on the chemotaxis of freshly isolated human blood monocytes in a modified Boyden microchemotaxis chamber. Additionally, we have stained the earliest stages of atherogenesis, so called insudative areas, in human coronary arteries by means of immunohistochemistry with monoclonal anti-CRP- and anti-CD68-antibodies in order to investigate whether CRP-deposition in the arterial wall precedes monocyte infiltration in atherogenesis.

Purified human CRP is chemotactic for human blood monocytes in a modified Boyden microchemotaxis chamber. The effect is CRP-dose-dependant and the maximum chemotactic response is observed at a CRP-concentration of 40 μg/ml. Higher CRP-concentrations result in a decrease of chemotactic activity. Checkerboard-analysis revealed that the effect is truely chemotactic rather than chemokinetic. CRP deposits in the arterial intima of human coronary arteries in the earliest stages of human atherogenesis preceding monocyte infiltration.

We conclude that CRP may be centrally involved in human atherogenesis. In addition to lipid aggregation and complement activation in the arterial wall, CRP may be one of the major chemoattractants for human blood monocytes in early atherogenesis.

P535 Coronary artery expression of $VEGF_{165}$ after balloon angioplasty correlates with vasa vasorum angiogenesis: potential role in arterial remodelling

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Vascular endothelial growth factor (VEGF) is an endothelial cell (EC) specific mitogen that induces angiogenesis in response to myocardial ischemia. We have recently demonstrated that regression of adventitial vasa vasorum after porcine coronary balloon injury parallels arterial lumenal narrowing. Therefore, in balloon injured porcine coronary arteries we sought to determine 1) changes in adventitial microvessel number (MVN) using image analysis and 2) VEGF expression. Pigs were sacrificed 60 min and 3, 7, 14 days after injury. Most abundant VEGF protein expression was immunodetected in the adventitia at early time points (60 min, 3 and 7 days) after arterial injury. Non-injured arteries (as well as the intima or media of all injured arteries) did not express VEGF protein. Using RT-PCR only the transcript corresponding to the 165 amino acid form of VEGF was identified. Adventitial angiogenesis occurred early in response to arterial injury, indicated by EC labeling index (EC LI) and MVN which were highest on days 3 and 7 respectively.

	Control	1 Hour	Day 3	Day 7	Day 14
EC LI	<1%	N/A	12–15%	3–16%	0–10%
MVN	16 ± 4	<5	38 ± 6*	39 ± 5*	28 ± 5

[*$p < 0.05$ injury vs. control]

VEGF165 expression after coronary angioplasty correlates with the angiogenesis of vasa vasorum and may be an important component of arterial repair, possibly by modulation of arterial remodeling.

P536 Vascular endothelial growth factor-induced chemotaxis of monocytes is attenuated in patients with diabetes mellitus: A potential predictor for the individual angiogenic response

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Vascular endothelial growth factor-A (VEGF) is a potent angiogenic growth factor. In vitro, VEGF is acting on endothelial cells as well as on monocytes, two cell types participating in the angiogenic process *in vivo*. So far, it has not been possible to identify and assess differences in the individual angiogenic response.

We report about a chemotaxis assay using isolated monocytes from individual patients and from healthy volunteers, who served as normal and age-matched controls. The chemotactic response of individual monocyte preparations to VEGF (mediated via Flt-1, the VEGF-receptor 1) was quantitatively assessed using a modified Boyden chamber. While the migration of monocytes from healthy volunteers (n = 14; age 56.4 ± 4.0 years) could be significantly stimulated with VEGF (1.0 μM) to 148.4 [136; 170]% of the control value, monocytes from diabetic patients (n = 16; 68.3 ± 10.4 years; median HbA1c 8.5%) could not be stimulated with VEGF in this assay (91.1 [83; 98]% of unstimulated control; $p \ll 0.0001$). In contrast, the response of monocytes to the chemoattractant fMLP remained intact in diabetc patients (304% versus 235% in control group). The VEGF-inducible kinase activity of Flt-1 remained fully intact in monocytes from diabetic patients as assessed by in vitro kinase assays.

In conclusion, the cellular response of monocytes to VEGF is attenuated in diabetic patients, based on a signal transduction defect. Therefore, we predict that the use of VEGF for the therapeutic stimulation of angiogenesis should give better results in patients not suffering from diabetes mellitus.

P537 Augmentation of plasminogen activator inhibitor type-1 in adipocytes by glucose: implications for diminished fibrinolysis in obese insulin-resistant subjects

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Background: Vasculopathy is accelerated in type II diabetes mellitus (DM). Mechanism(s) responsible have not yet been completely elucidated. We have shown previously that plasminogen activator inhibitor type-1 (PAI-1) in blood, the primary physiological inhibitor of tissue-type or urokinase-type plasminogen activator, is increased in non-insulin dependent DM (NIDDM) accounting for an unfavorable shift in the balance between thrombosis and fibrinolysis. Adipose tissue PAI-1 is a source of circulating PAI-1.

Methods: To determine whether the concentration of glucose and insulin consistent with the hyperglycemia and hyperinsulinemia seen in NIDDM can increase PAI-1 elaboration from adipocytes, 3T3-L1 mouse preadipocytes were differentiated into adipocytes and co-incubated with selected concentrations of glucose with or without insulin for 5 days. The conditioned media were assayed for PAI-1 by Western blotting and for plasminogen activator (PA) activity by zymography.

Results: Glucose stimulated PAI-1 production in a dose-dependent manner (100 ± 22 at 5 mM, 321 ± 12 at 20 mM, 399 ± 21 at 30 mM glucose; mean ± SEM; n = 6), and PA activity was decreased in proportion to the increased PAI-1. Concomitant stimulation of insulin (2 nM) with glucose boosted PAI-1 production in adipocytes (100 ± 22 at glucose 5 mM, 165 ± 13 at glucose 10 mM, 225 ± 29 at glucose 10 mM with insulin 2 nM).

Conclusions: Production of PAI-1 by adipocytes is augmented in response to glucose and insulin in concentrations seen in obese patients with NIDDM. These results indicate that increased PAI-1 is likely to be attributable to direct effects of glucose on the synthesis of PAI-1 by adipose tissue. Because insulin can augment the effect of glucose on PAI-1 production in adipocytes, it might be suggested that cytoplasmic glucose level is more important at least in adipocytes than that of outside of the cells. The increased PAI-1 may account for the diminished fibrinolytic capacity that can exacerbate atherogenesis in patients with NIDDM.

P538 Microsphere loaded monocytes: new insights into monocyte kinetics in collateral artery formation

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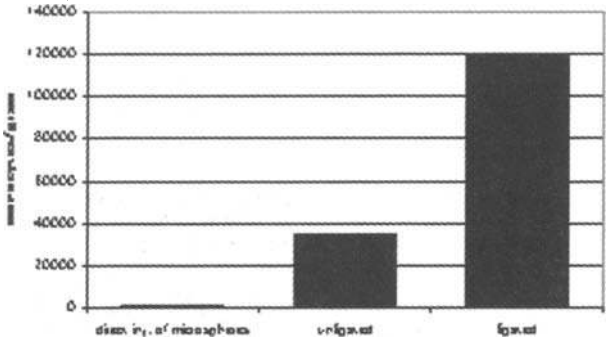
Introduction: Ligation of the art. femoralis in the rabbit leads to rapid proliferation of collateral arteries (arteriogenesis). This effect is mediated by circulating monocytes that attach to and penetrate activated endothelium in the collateral arteries under conditions of elevated shear stress. In the present study we evaluated the kinetics of monocytes in collateral artery via monocyte loading with fluorescent microspheres.

Methods: The right art. femoralis was ligated. Isolated rabbit monocytes were loaded with fluorescent microspheres (*2 mm) and reinfused intravenously. 48 hours after reinfusion animals were killed and biopsies were taken of the adductor and quadriceps muscle in both hindlimbs whereby the biopsies of the left hindlimb served as control. In a second control group microspheres were directly infused. With FACS analysis the total number of monocytes per gram muscle tissue was quantified.

Results: Number of monocytes/gram muscle tissue: direct infusion of microspheres = 1000 ± 725, unligated hindlimb = 35000 ± 7200; ligated hindlimb = 120000 ± 10500 (see figure). All differences were significant.



Conclusion: This is the first report evaluating the kinetics of monocytes in collateral artery formation by loading these cells with fluorescent microspheres. It is shown that accumulation of small microspheres in the hindlimb muscle tissue only occurs when they are loaded into monocytes. Furthermore the quantified number of monocytes is significantly higher in the ligated hindlimb as compared to the unligated hindlimb, indicating that monocyte invasion is an obligatory and highly selective step in collateral artery formation.

P539 Sustained transmyocardial loading with bFGF following single intrapericardial delivery: local kinetics and tissue penetration

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Recent data have demonstrated angiogenesis in the context of continuous or repetitive local delivery of bFGF protein. We wished to determine pharmacokinetics and myocardial penetration of bFGF following a single intrapericardial delivery; and we developed and tested a novel mathematical model for myocardial penetration from the pericardial space. Two doses of bFGF (30 ug, 200 ug) admixed with either 131-I- or 125-I-bFGF were delivered, with or without adjunctive heparin, into the porcine pericardial space by a transmyocardial route using a helix-needle catheter. Washout was assessed over 24 hours by serial scintigraphy and by direct activity measurement to define agent loss from the region of interest. Epi-to-endocardial concentration gradients (n = 5) established 1 hour and and 24 hours after delivery were assessed by gamma-counting of myocardial tissue series obtained by cryosectioning tangential to the epicardial surface. A mathematical model was developed based on a reaction-diffusion equation describing agent transfer into myocardium as a function of interstitial diffusion and transcapillary washout. The data revealed substantial transmyocardial concentration gradients, with penetration half-depths ranging from 0.5–1.5 mm; these profiles were closely fit by our mathematical model using reasonable parameters (typical r = 0.95). After intrapericardial delivery, epicardial bFGF levels were 164 ± 59 (mean ± SEM) fold and endocardial levels were 15 ± 9 fold increased over serum concentations; and these gradients were maintained for 24 hours. Adjunctive heparin did not markedly alter these results. Pericardial delivery of bFGF results in well-modeled, prolonged transmyocardial loading. These data provide a clearer understanding of the pericardial space as an advantageous administration route for angiogenic peptides.

P540 Non-invasive prediction of angiographic progression of coronary artery disease by dipyridamole stress echocardiography

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Background: coronary angiography is the currently accepted gold standard to assess progression of coronary artery disease. Dipyridamole stress echo (DSE) might provide an alternative non-invasive method for this purpose, since the extent and severity of anatomic coronary artery disease (CAD) are mirrored by the extent and severity of stress-induced wall motion abnormalities.

Aim: to assess whether variations in serial DSE match variations in angiographically assessed CAD.

Methods: from the IFC-CNR 15 years stress echo data bank (1983–1998), we selected 60 pts meeting the selection criteria of 2 repeat coronary angiography and DSE, each test performed and interpreted independently and within one week of each other. The second angiographic-stress echocardiographic assessment was repeated 45.1 ± 30.2 months after the initial one. Angiographic progressors were defined a priori, according to Kaski, as patients with any stenosis progressing to occlusion and/or any significant stenosis with >20% stenosis progression. Stress echocardiographic progressors were defined as patients with a previously negative test becoming positive or with a positive test with increase in peak Wall Motion Score Index > 0.12 (1 = normal to 4 = dyskinetic in a 16 segment model) at repeat testing.

Results: of the 60 patients, 44 were angiographic "progressors" and 16 "non-progressors". Stress echo response was concordant with angiographic identification in 39/44 progressors and 15/16 non progressors, with an overall concordance of 90%. The greatest rate of concordance was achieved with a positive DSE response becoming negative (4/4, 100% concordance with angiographic "non progressors") and with a negative DSE becoming positive (18/19, 95% concordance with angiographic "progressors").

Conclusions: dipyridamole stress echo response allows to efficiently separate angiographic "progressors" and "non progressors", simply taking into account the presence, extent and severity of stress-induced wall motion abnormalities.

P541 Quantification of aortic atherosclerosis by dynamic three-dimensional echocardiography

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Atherosclerotic plaques in the thoracic aorta are visualized by transesophageal echocardiography (TEE). The ability to render the volume of desired structure by three-dimensional echocardiography (3-D) provides the opportunity for quantitation.

To determine whether 3-D could be used for the evaluation of aortic atherosclerosis we performed serial volumetric calculations of the thoracic aorta in three levels using rotational TEE acquisition.

Group of consecutive 38 patients (26 men, 54 ± 14 y.) referred for TEE was studied. TEE probe was placed at the depth of 30 cm, 35 cm, and 40 cm from incisors and volumetric datasets were sampled using 3° intervals. The reformatted datasets were reviewed and the border between the aortic wall, plaque and lumen was determined. Two-cm segments of the thoracic aorta were analyzed to calculate the volume of protruding aortic plaques, and maximal and minimal volume of the aortic lumen – the difference being aortic pulsation.

The results of volumetric measurements in cm^3 are presented in three levels of aorta are:

	Range	30 cm	35 cm	40 cm
Aortic lumen – max	7.2–19.7	12.0 ± 3.2	11.5 ± 3.1	10.9 ± 2.5
Aortic lumen – min	4.2–19.5	10.9 ± 3.4	10.3 ± 2.9	10.0 ± 2.6
Aortic pulsation	0.0–3.4	1.1 ± 0.9	1.2 ± 0.7	1.0 ± 0.6
Aortic plaque	0.0–2.8	1.3 ± 0.5	1.2 ± 0.7	1.1 ± 0.6

There was a correlation between plaque volume and aortic volume in all three levels ($r = 0.81$, $r = 0.72$, $r = 0.73$, all $r = 0.75$, $y = 0.17x - 0.74$, $p < 0.001$). There was no correlation between the aortic pulsation and plaque volume ($r = -0.04$, p = NS). The correlation coefficients of inter-and intraobserver variability ranged from 0.89 to 0.98, $p < 0.05$, being the highest for intraobserver off-line volume calculation.

Conclusions: Aortic atherosclerosis of the thoracic aorta can be reproducibly quantitated using three-dimensional transesophageal echocardiography by aortic plaque volume and aortic pulsation calculation. Both aortic plaque volume and aortic pulsation represent different indicators of aortic physiology. There is an evidence for aortic remodeling with aortic enlargement corresponding to increase of plaque volume.

CONSEQUENCES OF HYPERTENSION: ARTERIES AND VASCULAR FUNCTION

P542 Enalapril improves aortic energetics in hypertensive patients

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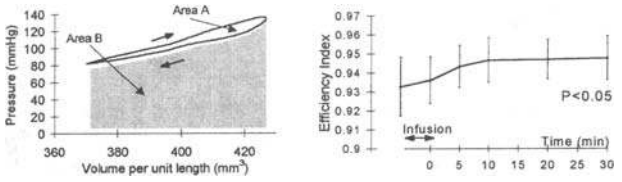
The aorta (Ao), by virtue of its elastic nature, stores a considerable amount of the LV power generated during cardiac systole, which is returned by Ao recoiling during diastole. To study the effect of ACE inhibitors on regional Ao energetics, serial pressure (P)-volume (V) loops were obtained from simultaneous recordings of the thoracic Ao V per unit length and P, before and for 30 min after the i.v. administration of enalaprilat (EN, 1.25 mg over 5 min.) in 10 hypertensives. Ao V was measured by an intravascular dimension catheter, developed in our institution (Circulation 1995; 92: 2210–9) and Ao P by a Millar micromanometer. The area under the systolic (ascending) portion of the clockwise loop (left fig., areas A + B), represents the energy stored by the Ao, the area under the diastolic (descending) portion of the loop represents the energy returned by the Ao (area B), whereas the area within the loop (area A) the energy dissipated by the Ao due to its viscosity.

Results: Efficiency index of the Ao (= energy returned/stored) was increased with EN (right fig.), indicating decreased Ao energy loss.



Conclusions. Ao energetics are improved and energy loss is reduced after EN administration. This effect may contribute to the beneficial effects of enalapril on hypertensive patients.

P543 Microalbuminuria is associated with greater large elastic-type artery stiffening in untreated essential hypertensive patients

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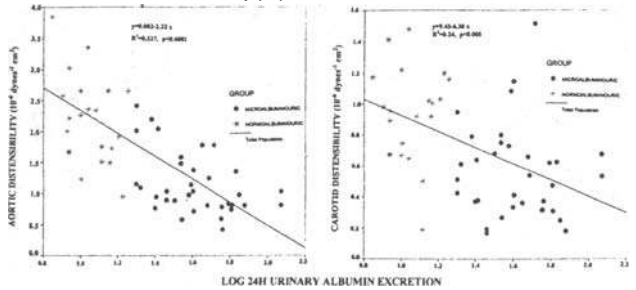
Microalbuminuria (MA) is a marker of increased cardiovascular risk in essential hypertension, but the mechanisms underlying its prognostic significance have not been elucidated. Large artery elastic properties represent an important determinant of left ventricular pulsatile load and coronary blood flow and are impaired in hypertensive patients (pts).

Methods: To investigate any possible relations between MA and large artery mechanic performance in this setting, we measured the distensibility of the ascending thoracic aorta (AoDist) and common carotid arteries (CCADist) in 83 non-diabetic pts (50 men, 33 women, aged 53 ± 10 years) with untreated JNC-VI stage 2 or 3 essential hypertension. Thirty-five pts had MA (mean urinary albumin excretion [UAE] of 20–200 mg in 3 consecutive 24-hour urine collections) and 48 pts were normoalbuminuric. AoDist and CCADist were calculated by use of the formula: 2 × (pulsatile change in diameter)/([diastolic diameter] × [pulse pressure]). Arterial diameters were measured by ultrasonography, while arterial pressure was measured simultaneously by sphygmomanometry at the brachial artery.

Results: The 2 patient subgroups did not differ significantly with respect to age, sex, smoking habits and plasma lipid values. Both AoDist and CCADist were significantly lower in pts with MA compared with normoalbuminuric pts (1.2 ± 0.4 vs. 2.3 ± 0.7 and 0.6 ± 0.3 vs. 0.9 ± 0.3 dyne^{-1} cm^2 × 10^{-6}, respectively, $p < 0.005$). Forward multiple linear regression analysis identified a significant association between the logarithm of 24-hour UAE and both AoDist and CCADist in the entire study population (scatterplots).



Conclusions: Our findings support the view that MA is a renal manifestation of widespread arterial damage rather than of damage confined to the renal vascular bed alone. The additional increase of left ventricular pulsatile load and offsetting of left ventricular-vascular functional coupling induced by greater large artery stiffening proposes one explanation for the increased cardiovascular risk of pts with essential hypertension and MA.

P544 Angiotensin-(1–7) and lisinopril act in synergism to inhibit angiotensin II-induced vasoconstriction in rat aorta

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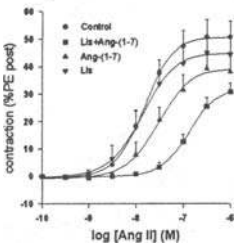
From experimental studies it is evident that angiotensin-(1–7) (Ang-(1–7)) is involved in vascular functions, e.g. by decreasing Ang II-induced vasoconstriction and angiotensin-converting enzyme (ACE) activity. Thus, Ang-(1–7) acts as a modulator of the renin-angiotensin system (RAS). The RAS is an important target for treatment of cardiovascular diseases, e.g. by ACE inhibitors. Strikingly, ACE inhibitors increase plasma and tissue Ang-(1–7) concentrations, which might further inhibit the RAS. Therefore, we investigated whether the ACE inhibitor lisinopril potentiates antagonism of Ang II-induced vasoconstriction by Ang-(1–7) in vitro.

Methods: The effect of pretreatment with either 10 μM Ang-(1–7), 1 μM lisinopril, or both on Ang II-induced constrictions of isolated rat aortic rings was measured in parallel rings from each of 7 rats. After Ang II, a single dose of 1 μM phenylephrine was given (PE post). All experiments were performed in the presence of 0.1 mM L-nitromonomethyl-arginine to inhibit Ang-(1–7)-induced vaso-dilatation by nitric oxide release. Responses to Ang II were expressed as a percentage of PE post, and statistical significance tested with ANOVA for repeated measure. The potency of Ang II (EC_{50}) was calculated via logistic curve fitting, and statistical significance tested by one-way ANOVA with Bonferroni correction.

Results: Only combined treatment with Ang-(1–7) and lisinopril inhibited dose-dependent vasoconstrictions to Ang II significantly (Fig. 1) and also decreased the potency of Ang II tenfold from −7.84 ± 0.10 (control) to −6.82 ± 0.12 (Ang-(1–7) + lisinopril) log M.

Fig. 1



Discussion: Lisinopril potentiates antagonism of Ang II-induced vasoconstriction by Ang-(1–7). Considering the RAS inhibiting and vasodilator properties of Ang-(1–7), it may be an important contributor during treatment of cardiovascular disease with ACE inhibitors.

P545 Evaluation of endothelial function in essential hypertension

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Endothelial dysfunction is detected at early stages of essential hypertension. Abnormal endothelium-dependent vascular relaxation is largely related to reduced activity of nitric oxide (NO). In the target cells NO increases concentration of cGMP by activation of soluble guanilatcyclase and causes vascular relaxation. Membrane mechanisms of vascular response can be detected by measurement of Ca,ATPase activity that is also cGMP-dependent. The purpose of our study was detection of endothelial dysfunction by vascular response to NO inhibition and evaluation of Ca,ATPase activity.

Methods: We performed randomized trial on 25 hypertensive patients (stage I, mean age 42 ± 5 yrs) and age-matched 10 healthy subjects. NO activity was estimated by vascular response to oral administration of methylene blue (5 mg/kg) – NO activity blocker. Ca,ATPase activity was measured in red blood cell membranes (Vincenzi and Raess method).

Results: Our study revealed that oral administration of methylene blue caused elevation of arterial blood pressure, especially diastolic blood pressure. Vasoconstrictive response was less significant in hypertensive patients. Basal Ca,ATPase activity did not differ significantly in both groups while after administration of methylene blue Ca,ATPase activity decreased in normotensive patients (0.62 ± 0.04 mcmol Pi/mg*h vs 1.15 ± 0.07 mcmol Pi/mg*h, $p < 0.01$) and did not change significantly in hypertensive patients (0.94 ± 0.05 mcmol Pi/mg*h vs 1.10 ± 0.06 mcmol Pi/mg*h, $p > 0.05$).

Conclusion: Patients with essential hypertension have impaired endothelium-dependent vasoconstrictive response to NO inhibition that may be partially due to inadequate changes in Ca,ATPase activity.

P546 Concentric remodelling is accompanied by an impairment of aortic distensibility and an increased urinary albumin excretion rate in untreated patients with essential hypertension and normal left ventricular mass

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The prognostic contribution of left ventricular (LV) geometry in the presence of normal LV mass in hypertensive patients (pts) has not been well defined.

Methods: Towards this end, in 210 untreated, non-diabetic, newly diagnosed patients (pts) with stage I–II (JNC VI) essential hypertension (mean age 53 ± 8 years), LV mass index (LVMI), relative wall thickness (RWT), aortic distensibility (Ao-Dist) and urinary albumin excretion (UAE) were evaluated. Ao-Dist was calculated as a function of changes in aortic diameter (d) (determined by echocardiography) and pulse pressure (determined sphygmomanometrically in the brachial artery) by the use of the formula: Ao-Dist = 2 × (pulsatile changes in d)/[(diastolic d) × (pulse pressure)]. UAE was evaluated in three non-consecutive 24 h-urine samples.

Results: In the entire study population, office systolic and diastolic BP was 155 ± 17/99 ± 9 mmHg, LVMI was 100.9 ± 22 g/m^2, Ao-Dist was 1.83 ± 1.1 dyne^{-1}cm^{2}10^{-6} and UAE was 26.6 ± 24 mg/24 h. LVMI was positively correlated with UAE ($r = 0.49$, $p < 0.001$) and negatively correlated with Ao-Dist ($r = -0.21$, $p < 0.005$). LVMI was within normal values (<125 g/m^2) in 176 pts. From these pts, 105 had LV normal geometry (NG) (LVMI 90.7 ± 16 g/m^2 and RWT 0.39 ± 0.03) while 71 had LV concentric remodeling (CR) (LVMI 98.7 ± 14 g/m^2 and RWT 0.49 ± 0.03). The group with CR compared to the group with NG, had significantly increased age (56 vs 48 years), BSA (1.93 vs 1.87 m^2), office systolic BP (157 vs 149 mmHg) and UAE (34.5 vs 15.5 mg/24 h) and significantly decreased Ao-Dist (1.49 vs 2.17 dyne^{-1}cm^{2}10^{-6}).

In conclusion, hypertensive patients with LV CR exhibit a reduction in Ao-Dist and an increase in UAE. These findings may contribute in the unfavorable prognosis of hypertenive pts with CR and normal LV mass.

P547 Effects of doxazosin and atenolol on endothelin-1 and von Willebrand factor in hypertensive middle-aged men

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The endothelium plays an important regulatory role in hypertension. Elevated levels of endothelin-1 (ET-1) and von Willebrand factor (vWF), both markers of endothelial function, are associated with hypertension.

In a randomized study we have investigated the effect of antihypertensive treatment with the α-blocker doxazosin (n = 23) or the β-blocker atenolol (n = 22) for 22 weeks on circulating levels of ET-1 and vWF in middle-aged men with essential hypertension.

Blood pressure reduction was satisfactorily achieved with both drugs. A reduction in the levels of vWF occurred in both groups being more pronounced in the α-blocker group than the decrease on β-blockers: median values 148% to 124% ($p = 0.004$) versus 170% to 143% ($p = 0.056$), respectively. In the α-blocker group, there was a significant correlation between the reduction in blood pressure and the decline in vWF; $r = 0.57$ ($p = 0.074$) for SBP and $r = 0.50$ ($p = 0.022$) for DBP. A highly significant decrease in plasma ET-1 was obtained during β-blockade (0.67 pg/mL to 0.60 pg/mL, $p = 0.007$), whereas no significant change occurred within the α-blocker group. There was no significant correlation between the fall in blood pressure and the reduction in ET-1 in the β-blocker group.

The different effects of α- and β-blockers on endothelial function expressed as vWF and ET-1, could indicate that the effects are probably not only related to the blood pressure *per se*, but also to the different pharmacological mechanisms of the drugs.

P548 Antihypertensive and vascular effects of omapatrilat, a vasopeptidase inhibitor, in salt-induced hypertension

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The involvement of natriuretic peptides in salt-sensitive hypertension is still unclear. Our objective was to determine the effects of a new, orally available dual inhibitor of neutral endopeptidase (NEP) and angiotensin-converting enzyme (ACE), omapatrilat, on systolic blood pressure (SBP) and structure of small resistance arteries in a model of salt-induced hypertension. Dahl salt-sensitive (DS) rats were treated for 8 weeks with 4% NaCl alone or in combination with either omapatrilat (35 mg/kg/day) or captopril (100 mg/kg/day). Placebo-treated rats served as controls (n = 5–6/group). Small mesenteric arteries (SMA; 270 μm) were isolated and their geometry was studied in vitro under perfused and pressurized conditions.

Chronic salt administration increased SBP by 56 ± 2 mmHg in DS rats, as compared to 7 ± 2 mmHg in control DS rats ($P < 0.05$; tail cuff method). This increase was in part prevented by concomitant omapatrilat or captopril administration (23 ± 5 mmHg and 20 ± 7 mmHg, respectively; $P < 0.05$ vs salt-treated DS rats). The media/lumen ratio of the SMA increased in the DS rats on 4% NaCl diet by hypertrophic remodeling (growth index: 19 ± 2%, $P < 0.05$). Omapatrilat prevented the structural changes (−4 ± 6%; $P < 0.05$ vs salt-treated DS rats). In contrast, captopril did not significantly affect vascular structure (11 ± 3%) despite lowering in SBP. The media/lumen ratio of SMA was significantly correlated with SBP ($r = 0.80$, $P < 0.0001$, linear regression).

These findings suggest that inhibition of the degradation of natriuretic peptides together with ACE-inhibition by omapatrilat may be therapeutically useful to lower arterial pressure and to prevent vascular remodeling of resistance arteries in salt sensitive individuals.

P549 Activation of extracellular signal-regulated kinases is essential for pure transmural pressure-induced vascular smooth muscle cell proliferation

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Background: Vascular wall is constantly exposed to mechanical forces such as transmural pressure, stretch and shear stress. In hypertension, increased transmural pressure directly affects vascular smooth muscle cells (VSMCs), which results in cell proliferation, and finally causes atherosclerosis. Little is known, however, about mechanisms by which transmural pressure promotes proliferation of VSMCs. We have developed a system with which to investigate the effect of pure transmural pressure on cell functions without effect of shear stress or stretch. In the present study with this system, we investigated the possible involvement of several protein kinases in the mechanisms underlying transmural pressure-induced proliferation of VSMCs.

Methods: DNA synthesis and cell number were measured by [^{3}H]-thymidine incorporation and a cell proliferation kit, respectively. Pressure was applied to quiescent rat VSMCs in culture for 1–30 min by compressed helium gas in the loading apparatus in which the partial pressure of oxygen was kept constant. The cells were then incubated in a CO_2 incubator for determination of DNA synthesis and cell number. Phosphorylation of ERKs was measured by Western blotting, and ERK activity was measured by an enzyme assay kit.

Results: Transmural pressure up to 120 mmHg increased [^{3}H]-thymidine incorporation (220 ± 42.5%, $p < 0.05$) in a pressure-dependent manner. Transmural pressure (120 mmHg) also significantly increased cell number. Protein kinase C inhibitors H7 (3 μM) and Bisindolylmaleimide I (1 μM) both inhibited pressure (120 mmHg)-induced [^{3}H]-thymidine incorporation. A tyrosine kinase inhibitor genistein (5 μM) also inhibited pressure (120 mmHg)-induced [^{3}H]-thymidine incorporation, whereas a stretch-activated mechanosensitive channel blocker $GdCl_3$ (10 μM) did not cause any effect. Transmural pressure (120 mmHg) increased phosphorylation (1.6 fold) and activation (3.1 fold) of ERK. Further, an ERK kinase inhibitor PD98059 (25 μM) completely blocked pressure (120 mmHg)-induced [^{3}H]-thymidine incorporation.

Conclusions: These results suggest that activation of ERK is essential for pure transmural pressure-induced proliferation of VSMCs, in addition to PKC and tyrosine kinase activation, and these multiple activation of protein kinases could be involved in the pathogenesis of atherosclerosis induced by transmural pressure in hypertension.

P550 Parallel unfavourable effects of essential hypertension on arterial pressure waveform, large arteries elasticity and urinary albumin excretion rate

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Although hypertension induces structural and functional changes in both arterioles and large arteries, the interaction between arterial pressure wave (APW) contour, carotid distensibility (CD), aortic distensibility (AoD) and urinary albumin excretion (UAE) rate has not been adequately described.

Methods: For this purpose, in 81 untreated, newly diagnosed patients (pts) with stage I–II (JNC VI) essential hypertension (aged 54 ± 10 years, office BP 154 ± 18/97 ± 12 mmHg), the LV mass index (LVMI), relative wall thickness (RWT), APW, AoD, CD and UAE were evaluated. APW was recorded by carotid applanation tonometry and waveform shape was expressed by the augmentation index (AI). Subjects were classified to group 1 (with a dominant early systolic peak, AI ≤ 0) and group 2 (with a dominant late systolic peak, AI > 0). AoD and CD were calculated as a function of changes in Ao and C diameter (determined by echocardiography) and pulse pressure (determined sphygmomanometrically in the brachial artery) by the use of the formula: Distensibility = 2 × (pulsatile changes in diameter)/[(diastolic diameter) × (pulse pressure)]. UAE was evaluated in three non-consecutive 24-h urine samples.

Results: In the entire study population LVMI was 92 ± 19 gr/m^2, RWT was 0.48 ± 0.06, AI was 0.11 ± 0.25, AoD and CD was 1.6 ± 1.1 and 1.2 ± 0.9 dyne^{-1}cm^{2}10^{-6} respectively and UAE was 25 ± 24 mg/24 h. Group 2 (54 pts, AI = 0.16 ± 0.1) compared to group 1 (27 pts, AI = −0.001 ± 0.3) were older (49 vs 56 years) and had significantly increased office BP (158 ± 18/100 ± 12 vs 145 ± 15/91 ± 9 mmHg), LVMI (98 vs 82 gr/m^2), RWT (0.49 vs 0.45) and UAE (29 vs 14 mg/24 h) and significantly impaired AoD and CD (1.2 ± 0.1 vs 2.6 ± 0.1 and 0.9 ± 0.1 vs 1.4 ± 0.1 dyne^{-1}cm^{2}10^{-6}, respectively). In the entire study population, AI was positively correlated with age ($r = 0.38$, $p < 0.05$), LVMI ($r = 0.44$, $p < 0.001$) and UAE ($r = 0.29$, $p < 0.005$) and inversely correlated with AoD and CD ($r = -0.23$, $p < 0.05$ and $r = -0.22$, $p < 0.05$ respectively).

Conclusion: Hypertension induced changes in APW shape are closely related with changes in both the physical properties of large arteries and the UAE rate.

P551 Uteroplacental perfusion and vascular endothelial growth factor in normotensive and pre-eclamptic pregnancy

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Aim: Preeclampsia is characterised by impaired uteroplacental perfusion. Vascular endothelial growth factor (VEGF), important in vasculogenesis, is upregulated by hypoxia. This study examined placental VEGF distribution in relation to uterine artery blood flow.

Methods: Third trimester Doppler recordings of uterine artery flow velocities were performed in 11 normotensive women (*NT*) and 9 women with preeclampsia *HT* matched for age and gestation. Resistance index ($RI = (V_s - V_d)/V_s$) and pulsatility index ($PI = (V_s - V_d)/V_m$) were calculated, where V_m is mean flow, V_s peak systolic flow and V_d end-diastolic flow velocity. Biopsies of placental tissue following delivery were examined for the presence and distribution of VEGF with avidin-biotin-peroxidase immunohistochemistry.

Results: Uterine artery V_s was increased and V_d decreased in *HT* (V_s: *NT* mean ± S.D. 101 ± 26 cms^{-1}, *HT* 126 ± 42; V_d: *NT* 57 ± 16 cms^{-1}, *HT* 53 ± 21). *RI* and *PI* were thus significantly increased in *HT* (*RI*: *NT* 0.44 ± 0.05, *HT* 0.58 ± 0.11, $p = 0.002$; *PI*: *NT* 0.62 ± 0.10, *HT* 1.05 ± 0.37, $p = 0.023$). Placental VEGF was increased in intensity and distribution in *HT* in both the extravillous trophoblast of the decidua (65 ± 25% cells stained for VEGF in *HT* vs 36 ± 23% in *NT*, $p = 0.014$) and in the villous syncytiotrophoblast (circumferential staining score 1.9 ± 0.4 in *HT* vs 1.4 ± 0.3 in *NT*, $p = 0.023$).

Conclusions: Impaired uteroplacental blood flow in preeclampsia is associated with abnormal uterine artery Doppler waveforms. The relative hypoxia characterising preeclampsia may be responsible for the increase in placental VEGF. Increased VEGF may act as a compensatory mechanism by promoting vasculogenesis to restore blood flow towards normal.

P552 Endothelium-dependent relaxation in rabbit mesenteric arteries: role of calcium

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Agonist-induced Ca^{2+} entry is a major determinant for the vascular endothelial release of relaxing factors. In particular, the release of nitric oxide (NO) and EDHF is associated with an increase of free intracellular calcium in the Ca^{2+} rise occurs through influx from extracellular space or through the release from intracellular stores. The aim of the present study was to characterize the Ca^{2+} mobilization process involved on vasodilating responses to carbachol in rabbit mesenteric artery (RbMa).

Methods: Ring segments of superior mesenteric artery from male New Zeland rabbits were suspended in a 20 ml bath with oxygenated krebs solution containing 0.01 mM indomethacin. Isometric responses of the vessels contracted with noradrenaline (NA, 1 μmol) were recorded. Drugs were added to the bath in a cumulative manner. In some vessels endothelium was mechanically removed.

Results: In the presence of intact endothelium carbachol (0.01–10 μmol) elicited dose related relaxing responses. In the presence of the NO-synthase L-NNA, 10 mM or with hyperpolarizing solution (K^+ 30 mM) caused a rightward shift of the dose-respone curves. In the combined presence of high K^+ and L-NNA carbachol failed to elicit any relaxing response. Removing calcium from the bathing solution shifted to the right the concentration respose curves and the addition of L-NNA to the Ca^{2+} free solution completely prevented the vasodilator effects of carbachol. The combined presence of the specific inhibitor of endoplasmic reticulum Ca^{2+} ATPase thapsigargin (1–10 μmol) and L-NNA into the bathing solution abolished the carbachol induced relaxation.

In conclusion the present data demonstrate that carbachol relax RbMa by inducing the release of both NO and EDHF from the endothelium. Moreover it is suggested that: 1) NO production does not depend on extracellular calcium and 2) EDHF-induced effects require Ca^{2+} influx from extracellular space and depend on refilling of intracellular Ca^{2+} stores.

P553 Differing benefit of haemodialysis on aortic mechanics in normotensive versus hypertensive patients with chronic renal failure

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Aortic elastic properties represent an important determinant of left ventricular pulsatile load and coronary blood flow. Aortic mechanics are markedly impaired in patients (pts) with chronic renal failure (CRF), while evidence has appeared of an acute beneficial effect of hemodialysis (HD) on this physiological parameter. Little is still known, however, regarding the magnitude of this effect in different subgroups of CRF pts.

Methods: In an attempt to further clarify this issue, we measured the distensibility of the proximal ascending thoracic aorta (AoDist) in 48 CRF pts (31 men, 17 women, aged 45 ± 14 years) undergoing regular HD, before and immediately after a mid-week dialysis session. Twenty-eight pts were hypertensive (17 men, 11 women, aged 51 ± 14 years) while the remaining 20 pts were normotensive (14 men, 6 women, aged 38 ± 11 years). AoDist was calculated as a function of changes in aortic diameter and pulse pressure, using the formula: 2 × (pulsatile change in diameter)/([diastolic diameter] × [pulse pressure]). Aortic diameters were measured by transthoracic echocardiography, while arterial pressure was measured simultaneously by sphygmomanometry at the brachial artery.

Results: The 2 groups did not differ with respect to the prevalence of coronary risk factors other than hypertension, neither regarding body mass index, body weight before and after HD, ultrafiltration volume, EPO therapy, plasma fibrinogen, plasminogen, fibronectin, creatinine and calcium/phosphorus ratio values. AoDist was significantly lower in hypertensive compared with normotensive CRF pts both before (1.7 ± 0.7 vs. 2.2 ± 0.6 $cm^2.dyn^{-1}.10^{-6}$, $p < 0.01$) and immediately after completion of the HD session (2.1 ± 1.1 vs. 3.2 ± 0.9 $cm^2.dyn^{-1}.10^{-6}$, $p < 0.001$). A significant improvement of AoDist was noted in both groups of pts after HD; The magnitude of the improvement, however, was significantly greater in normotensive compared with hypertensive pts (0.9 ± 0.6 vs. 0.4 ± 0.5 $cm^2.dyn^{-1}.10^{-6}$, $p < 0.001$).

In conclusion, our findings are in accordance with previous data indicating an acute beneficial effect exerted by HD on the aortic mechanical performance of pts with CRF. In addition, it is shown that hypertensive CRF pts gain less than normotensive CRF pts in this respect, possibly due to more severe structural changes of the aortic wall in the former. Improvement of aortic mechanics after HD, although likely passive in nature and possibly of limited duration, may however add considerably to the overall hemodynamic benefit offered by regular HD in CRF pts.

HYPERTENSION: PERSPECTIVES ON THERAPY

P554 Sildenafil citrate is a well-tolerated treatment for patients with erectile dysfunction taking concomitant antihypertensive therapy

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Erectile dysfunction (ED) is a common problem in patients with hypertension and in those receiving antihypertensive agents (anti-HTNs). Oral sildenafil is effective in restoring erectile function in response to sexual stimulation in patients with ED. This retrospective subanalysis assessed the safety of sildenafil in men with ED receiving various classes of anti-HTNs [ie, diuretics, β blockers, α blockers, ACE inhibitors (ACE-I), and calcium channel blockers (CCB)].

A total of 4274 men (1393 of whom were receiving anti-HTNs) received sildenafil (5–200 mg) or placebo for 6 weeks to 6 months in 18 double-blind, placebo-controlled studies, with a dose taken approximately 1 hour before sexual activity. The combined incidences of all adverse events (AEs) and AEs potentially related to decreased blood pressure between the beginning and the end of treatment for men taking each of the anti-HTNs are shown below.

	Incidence of Treatment-Related AEs for Sildenafil-Treated Patients					
	Diuretic n = 123	β blocker n = 137	α blocker n = 124	ACE-I n = 303	CCB n = 278	None n = 1837
Exposure (patient-yr)	80	34	38	87	80	430
All AEs	35%	34%	31%	36%	33%	38%
Hypotension	0%	0%	<1%	<1%	0%	<1%
Flushing	11%	11%	11%	16%	10%	14%
Dizziness	2%	3%	2%	2%	2%	2%
Syncope	0%	0%	0%	0%	0%	0%

The overall incidence of treatment-related AEs in patients taking sildenafil and anti-HTNs (34%) was comparable to that observed in patients taking sildenafil only (38%). The incidences of headache, dyspepsia, and abnormal vision also were comparable for all sildenafil treatment groups.

The results indicate that sildenafil is a well-tolerated treatment for ED in patients taking various classes of antihypertensive medication.

P555 Control of hypertension in patients with coronary artery disease – Polish Hypertension Survey

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Hypertensive patients with coronary artery disease are at very high risk for cardiovascular mortality. Appropriate blood pressure control may be of particular importance in such patients. The aim of the present study was to determine awareness and control of hypertension in patients with coronary artery disease (CAD).

Methods: We studied 355 154 subjects enrolled in the Polish Hypertension Survey in 1997. Hypertension was defined as SBP > 140 mm Hg and/or DBP > 90 mm Hg, or taking antihypertensive treatment. Drug compliance was assessed by questionnaire. In treated hypertensives, control of hypertension was defined as SBP < 140 mm Hg and DBP < 90 mm Hg.

Results: Prevalence of CAD in the studied cohort was 17.1% (n = 60 882). Among patients with CAD, 67.7% had hypertension. In comparison to general population, patients with CAD had higher rates of hypertension awareness (76.4% vs 58.0%; P < 0.001) and higher rates of anti-hypertensive drug compliance (85.1% vs 76.8%; P < 0.001). However, control of hypertension in drug compliant patients with CAD (27.4%) was similar to that observed in general population (26.9%).

Conclusion: Despite relatively high rates of hypertension awareness and drug compliance, blood pressure control in hypertensive patients with CAD is poor. Nearly three fourths of treated hypertensives with CAD have their blood pressure uncontrolled. These findings may have important implications for prevention of future cardiovascular events in hypertensive patients with CAD.

P556 Study on cognition and prognosis in the elderly (SCOPE): design, objectives and baseline characteristics

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Intervention studies have demonstrated the prognostic benefit of antihypertensive treatment in the elderly. However, there is currently little data in patients above 70 years of age with mild hypertension. In addition to being a risk factor for cardiovascular events, hypertension also appears to play a role in the evolution of cognitive impairment in the elderly.

SCOPE is a multinational, double-blind, prospective study which will evaluate the ability of antihypertensive treatment to improve cardiovascular prognosis and prevent cognitive impairment in elderly patients with mild hypertension. The primary objective is to assess the reduction of major cardiovascular events, which is defined as a combined end-point of cardiovascular deaths, non-fatal myocardial infarction and non-fatal stroke. Secondary end-points include cognitive function measured by the Mini Mental State Examination (MMSE), total mortality, renal function, hospitalisation, quality of life and health economics.

A total of 4964 patients from 15 countries have been randomly assigned to treatment with the long-acting angiotensin II antagonist, candesartan cilexetil, or to placebo and will be followed for an additional 2 years. Any previous antihypertensive treatment was standardised, at enrolment, to hydrochlorothiazide 12.5 mg once daily with the study drug given in addition. The starting dose of candesartan cilexetil is 8 mg once daily, which is increased to 16 mg once daily if needed to control blood pressure. In patients with a blood pressure repeatedly above 160/90 mm Hg, in either treatment group, additional antihypertensive treatment is recommended.

Baseline characteristics for the randomised population is given below.

Age (years)	76	Treated at enrolment (%)	52
Male/Female (%)	36/64	MMSE at randomisation (score)	28
Previous MI (%)	4	SBP/DBP at randomisation (mmHg)	166/90
Previous stroke (%)	4		

P557 An Italian intervention study on the quality of the antihypertensive treatment based on jointly produced, field-tested guidelines

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Aim of the study was to assess the feasibility of improving blood pressure (BP) control and the choice of antihypertensive therapy with evidence-based guidelines produced and tested with the participation of doctors concerned.

Methods: Forty-eight doctors – 38 general practitioners (GPs) and 10 hospital specialists – agreed to monitor the implementation of the collectively produced guidelines for one year on a random sample of their treated hypertensive patients (intervention group). A control group of 42 GPs recruited and followed-up for one year a random sample of their treated hypertensive patients in the framework of an observational epidemiological survey on the current status of treatment and control of hypertension.

Results: At the 12-month follow-up, the 722 hypertensives of the control group presented no changes in any of the variables evaluated. In the 1049 hypertensives enrolled in the intervention group both systolic and diastolic BP control improved (<140 mmHg from 23 to 40%; <90 mmHg from 65 to 87%; both $p < 0.001$); the prescription of poorly tolerated drugs decreased (from 12 to 7%; $p < 0.001$); the use of drugs with documented preventive efficacy – diuretics and β-blockers – increased (from 48 to 58%; from 22 to 30%, both $p < 0.001$); hypertensive patients receiving indicated drugs (with no contraindications) increased from 66 to 73% ($p = 0.006$); savings amounted to approximatively 1.5 Euro per patient/month of treatment ($p < 0.001$).

Conclusion: An intervention strategy based on collaboratively produced guidelines tested for applicability in a representative sample of patients appear to be effective in improving the quality of antihypertensive therapy.

P558 Quality of life after PTCA or CABG in hypertensive patients with coronary heart disease

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Aim: The aim of the study was to assess quality of life in hypertensive males and females with coronary heart disease (CHD) 1 year after PTCA or CABG.

Material: Study population consisted of 189 subjects with essential hypertension (H) (129 males and 60 females, aged 54.1 ± 7.2 and 56.2 ± 8.7 years respectively), who underwent PTCA (75 males and 30 females) or CABG (54 males and 30 females). Mean time interval after PTCA was 14.6 ± 2.5 months, and after CABG was 16.1 ± 3.8 months. Mean duration of H and CHD were similar in both groups – 12.5 years and 7 years, respectively. Control group consisted of 100 patients with H and CHD (50 males and 50 females, aged 52.6 ± 8.1 and 55.3 ± 9.1 respectively), without revascularization. Mean duration of H in controls was 11.6 ± 3.1 years, and mean duration of CHD was 5.5 years.

Methods: All the patients were randomly selected from the population of ambulatory treated hypertensives with CHD and completed the Psychological General Well-Being Questionnaire (PGWB) and the Health Complaints Scale in CHD (HCS) – disease specific – during their visit in the clinic. Data about BMI, education, concomitant diseases, complication of H and CHD during last year, consumed drugs, cholesterol level and systolic and diastolic BP were collected. Statistical analyses were performed (parametric and non-parametric).

Results: In all groups women had lower total quality of life indexes (in PGWB and HCS) than men ($p < 0.01$). Women were also more depressive, felt less healthy and vital in PGWB. There was no difference between PTCA, CABG and control groups in general quality of life perception. In PTCA group 38.1% of the patients underwent re-PTCA during the last year. Males and females after PTCA or CABG had lower frequency of health complaints in HCS (cardiovascular, fatigue, sleep) than controls ($p < 0.05$). As compare to controls, worrying about disease was higher in PTCA pts (especially in restenosis subgroup) and negative impact of CHD on everyday activity was most frequently reported by CABG pts.

Conclusions: Male gender is associated with better general quality of life. Both PTCA and CABG improve health perception in hypertensives. However, PTCA may diminish well-being due to risk of restenosis and CABG due to worsening ability to everyday activity in both sexes.

P559 Prognostically important coronary artery disease in patients with hypertensive reaction and myocardial ischaemic episodes during cardiac catheterization

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Aim of our study is the evaluation of prognostically important coronary artery disease (piCAD) and its correlation with strongly hypertensive reaction and simultaneous myocardial ischaemic episodes (MI) appearance during cardiac catheterization (CC) in hypertensive and normotensive patients.

Methods: Files of 1085 patients (M = 930, F = 498, mean age 51.2 ± 8.8 years), 589 hypertensive and 496 normotensive, have been studied. All of them underwent LCA catheterization, RCA catheterization and left ventriculography (hypertensive patients under treatment). As hypertensive reaction was defined the elevation of systolic blood pressure-SBP > 200 mmHg (width of elevation more than 60 mmHg) and the elevation of diastolic blood pressure-DBP > 110 mmHg. The time point just before the onset of procedure was defined as BP baseline-point and the time point just after the RCA catheterization was defined as BP end-point. As piCAD was defined the disease for which early by-pass surgery might be considered purely on prognostic grounds irrespective of symptom status. Patients with symptomatic heart failure (EF ≤ 40%), chronic renal failure and heavy valve diseases were excluded.

Results: 1) 242 (22.3%) patients, out of 1085 patients had piCAD and 153 (63.2%) of them were hypertensive whilst 89 (36.8%) were normotensive. 2) 95 (16.13%) patients, out of 589 hypertensive patients, and, 39 (7.86%) patients, out of 496 normotensive patients, expressed myocardial ischaemic episodes 3) 62 (42.3%) patients, out of 144 hypertensive patients, and, 26 (34.65%) patients, out of 74 normotensive patients, with strongly hypertensive reaction, demonstrated signs of MI. 4) 41 (42.8%) patients, out of 95 hypertensive patients with signs of MI, and, 112 (25.3%) patients out, of 494 hypertensive patients (total 153), without signs of MI, demonstrated piCAD. 5) 17 (42.3%) patients, out of 39 normotensive patients with expressed MI episodes, and, 72 (15.7%) patients, out of 457 normotensive patients (total 89), without signs of MI, demonstrated piCAD. 6) 41 (26.8%) patients, out of 153 hypertensive patients with piCAD, experienced MI episodes during CC and 30 (73.2%) of them did elevate the BP significantly at the BP end-point. 7) 17 (19.1%) patients, out of 89 normotensive patients with piCAD, expressed MI episodes during CC and 12 (70.5%) of them showed significant BP elevation at the BP end-point.

Conclusion: a) The existence of prognosticaly important coronary artery disease in hypertensive patients is almost twice as in normotensive patients. b) The incidence of piCAD in patients who expressed MI episodes on the ground of BP elevation is almost three times over the incidence of piCAD in patients with MI episodes but without BP elevation.

HYPERTENSION: LIPID AND METABOLIC ASPECTS

P560 Sex-specific associations of hypertension with lipid levels in a representative sample

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Through associations between hypertension (HT) and other risk factors, hypertensive subjects are burdened with a greater risk of premature cardiovascular disease (CVD) than that imposed by their blood pressure alone. The aim of this study was to investigate the relationship of HT with lipid levels in a random sample of the French population aged 35–64 years. Risk factors, medication use, blood pressure (two measurements), fasting serum total cholesterol (TC), HDL-cholesterol (HDL-C), triglycerides (TG) and glucose were measured according to standard protocols in 1654 men and 1625 women from Northern, Eastern and South-western France in 1995–97. The prevalence of HT (blood pressure ≥ 160/95 mmHg and/or drug treatment) was 29.9% in men (14.2% untreated and 15.7% treated HT) and 24.9% in women (7.1% untreated and 17.8% treated HT). After adjustment for age, centre, body mass index, tobacco and alcohol consumption, glycemia and TC lowering drugs, untreated hypertensive women had higher levels of TC (6.14 vs 5.85 mmol/L, $p < 0.05$), LDL cholesterol (3.95 vs 3.71 mmol/L, $p < 0.05$), and TG (1.07 vs 0.93 mmol/L, $p < 0.01$) than normotensive women; treated hypertensive women had lower levels of HDL-C (1.59 vs 1.67 mmol/L, $p < 0.05$) than normotensive women. Normotensive and hypertensive (untreated and treated) men had similar levels of TG, LDL and HDL cholesterol. In conclusion, the greater than normal CVD risk of hypertensive subjects could be partly due to abnormal lipid levels in a sex-specific manner. Further studies are needed to explain the HDL-C lowering effect of antihypertensive treatment.

P561 Peroxide lipid oxidation status in erythrocytes of hypertensive patients

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Activation of peroxide lipid oxidation (PLO) reactions is considered as one of the main mechanisms of cell membranes destruction. Since, arterial hypertension (AH) is connected with structural and functional defects of cell membranes it was interesting to look for any changes in PLO status of erythrocytes in patients with AH. Erythrocytes were selected because of more intensive PLO processes in them in comparison with plasma.

Methods: there were examined 252 patients both sexes with different forms of AH aged between 32 and 60. 86 patients had mild AH. 84 – moderate AH and 82 were with severe AH, complicated with stroke and 26 healthy persons of the same age and sex as control group. PLO status of erythrocytes was evaluated by defining of malone dialdehyde (MDA) level, superoxidedismutase (SOD) and katalase (Ka) activities with using standard methods.

Results: it was revealed that even mild AH was characterized by activation of PLO reactions, especially of MDA concentration, but efficacy of antioxidant defense was rather strong in these patients, because SOD and Ka activities didn't differ so significantly from control group levels. Moderate AH was accompanied with more marked changes in all studied parameters than mild AH. Two opposite processes, influencing on erythrocyte state, received subsequent development: damaging coercion of PLO products on cell membrane, on the one hand, and the opposing to it antioxidant system, on the other hand. It was established MDA level rise on 86.2% in comparison with control group and significant suppression of SOD activity. In the third group of patients this strengthening of radicalproducing reactions achieved its maximum level. The accumulation of MDA concentration composed 260.7% and the state of antioxidant system was defined as the most depressed (SOD activity was 62.3%). It was determined that the activity of PLO processes in membranes was especially increased in patients in the nearest period after crisis therefore hypertensive crisis may be regarded as peroxide-lipid crisis on a level of cell membranes.

In conclusion, we can state that AH is characterized with disturbance of balance of oxidant-antioxidant systems, antioxidant defense failure and accumulation of PLO products.

P562 Polymorphism of angiotensin-converting enzyme gene, thrombomodulin and tissue factor pathway inhibitor levels in untreated hypertensive patients

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The association of the angiotensin converting enzyme (ACE) gene polymorphism with essential hypertension (EH) is still controversial. Increased tissue factor pathway inhibitor (TFPI) levels have been reported in acute ischaemic episodes. Moreover, thrombomodulin (TM) is known to have inhibitory effects on thrombin. This study examined the possible association between ACE gene polymorphism TM and TFPI levels in untreated hypertensive patients (pts).

Methods: The I/D polymorphism of ACE gene was determined in 104 hypertensives aged 56 ± 12 yrs. Forty-two pts had DD genotype (Group A), 30 pts had ID genotype (Group B) and 32 pts had II genotype (Group C). The TM and TFPI levels were determined (ELISA method) in the whole population. The three groups are matched for age, sex and body mass index.

Results: The results are shown in the table:

	Group A	Group B	Group C
TM ng/ml	33.16 ± 10	38.4 ± 8.3	38.6 ± 7.1
TFPI ng/ml	113.4 ± 28	99 ± 25	98 ± 22

TM: A–B, $p < 0.01$; A–C, $p < 0.01$; B–C, p = NS
TFPI: A–B, $p < 0.05$; A–C, $p < 0.05$; B–C, p = NS

Conclusions: Our findings suggest that DD genotype of ACE gene polymorphism is associated with significantly decreased levels of TM and increased levels of TFPI, supporting the hypothesis that ACE gene polymorphism through this mechanism plays an important role in the development of cardiovascular events.

P563 Platelet activity and immune factors interaction in hypertension

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Previous studies showed that there are abnormalities in the humoral immunity system in the hypertensive patients, which are characterized by increased serum levels of various types of Ig. The data suggest that IgE and IgG benefit not only in the development of vessels spastic reaction, but also influence on the platelet functional properties. The aim was to study the relationship between platelet functional activity and IgE, IgG levels in the patients with mild hypertension.

Methods: 28 male with mild hypetension and 10 healthy male, aged 20.3 ± 2.3 years have been examined. IgE and IgG serum levels was determined using IFA method. Platelet activity was assessed by means of platelet adhesion and aggregation degree with parallel measuring the time maximum index aggregation. Exercise test with computer devices have been performed in all persons.

Results: This study indicated statistically increase serum IgE levels (17.5 ± 0.9 g/l) and IgG (218 ± 12 ME/l) in the patients with mild hypertension as compared to control group (12.7 ± 0.9 g/l, 115 ± 10 ME/l). Platelet adhesion percentage (13.8 ± 2.6%) and aggregation degree (8.9 ± 2.7%) increase in the patients with mild hypertension as compared to control group (13 ± 1.0% and 7.7 ± 1.2 accordingly). Platelet aggregation was activated by exercise test, and resulting in increase of aggregation degree in the patients with mild hypertension – 14.5 ± 1.1% ($p < 0.05$), the time maximum index decreased simultaneously (26.9 ± 2.2 sec and 24.4 ± 1.0 sec accordingly). Adhesion percentage increase after exercise test was insignificant. Increased Ig levels rate after exercise in the patients with mild hypertension was higher IgG 45.2% – initial, 56.2% after testing, IgE 7.25% – initial, 84.7% – after testing.

Conclusion: Obtained data demonstrate that exercise testing causes more significant platelet aggregation and immune response in hypertensive patients as compared to control group. We consider relationship these factors associated with hemodynamic vascular damage contribute to the thrombogenic complications.

P564 Prognostic implications of plasma renin activity in essential hypertension: role of oxidative stress

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High plasma renin activity (PRA) as well as oxidative stress (OS) have both been linked to increased risk of atherosclerotic complications in essential hypertension (EH). The aim of this study was to investigate the parameters of OS, a potential source of endothelial injury, as well as some markers indicative of endothelial dysfunction, in association with PRA in patients with EH.

Methods: Diene conjugates (DC), basal and Fe-stimulated levels of thiobarbituric acid reactive substances (TBARS, Fe-TBARS) and serum antioxidative capacity (AOC) as markers of OS were measured in 32 patients with uncomplicated EH (DBP 95–114 mmHg, mean age 32.4 ± 7.2 yr). Assessment of PRA related to concurrent 24-h urinary sodium excretion was used to define subgroups of patients with high (n = 12) and low/medium renin activity (n = 20). Urinary excretion of albumin (UAE) as a marker of endothelial dysfunction and urinary excretion of cyclic GMP (cGMP) as an indicator of endothelial nitric oxide (NO) formation were measured.

Results: Lipid peroxidation (LP) parameters were significantly ($p < 0.05$) elevated in patients with high PRA (DC 37.9 ± 8.1 vs. 34.3 ± 6.5 mmol/ml; TBARS 0.90 ± 0.16 vs. 0.61 ± 0.11 nmol/ml; Fe-TBARS 1.34 ± 0.17 vs. 1.11 ± 0.11 nmol/ml), while serum AOC was decreased in high PRA group (30.1 ± 1.8 vs. 35.2 ± 2.1%, $p < 0.05$), in comparison to the low/medium renin group. Urinary cGMP excretion was positively related to both basal TBARS (r = 0.468, p = 0.044) and Fe-stimulated TBARS (r = 0.568, p = 0.036), suggesting more pronounced NO formation at higher serum LP levels, which is consistent with previous evidence about reduced efficacy rather than decreased formation of NO in face of enhanced LP. Serum AOC was inversely related to UAE (r = −0.402, p = 0.01), indicating that impaired antioxidant status might contribute to higher UAE. Also, UAE was positively related to PRA (r = 0.473, p = 0.03) and high-renin patients had significantly higher UAE when compared to the low/medium PRA group (16.1 ± 2.1 vs. 9.8 ± 3.6 mg/min, $p < 0.05$).

Conclusions: High-renin EH patients display more pronounced abnormalities suggestive of oxidative stress. The associations between oxidative stress markers and indices of endothelial dysfunction (UAE and urinary excretion of cGMP) may point to the role of oxidative stress in the development of early vascular injury, thus potentially contributing to the higher risk of atherosclerotic complications previously reported in the high-renin subgroup of patients with EH.

P565 Decreased myocardial mRNA expression of insulin-dependent transmembrane glucose transporter in human hypertension. A key for the interdependence of disturbed glucose metabolism and hypertension?

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Transmembrane glucose transport, cellular metabolism and thus the contractile state of the cardiovascular system as well as H_2O distribution in the compartments depend largely on the insulin resposnsive GLUT 4 isoform of the transmembrane glucose transport molecule.

Here we investigate probes (60–150 mg) of right atrial auricle from non diabetic patients subjected to cardiac surgery which were snap frozen in liquid NO and stored at −70°C until homogenisation. Total RNA was isolated using guanidium thiocyanate, phenolchloroform extraction and alcohol precipitation (for details see our earlier paper Mol Cell Biol 8: 2394–2400, 1988). Total RNA was hybridised with 32P labelled human GLUT 4 cDNA and re-hybridised with a human G3PDH cDNA probe to correct for equal amounts of RNA. Quantification was performed by a laser scanner.

Our results represent the first measurements of GLUT 4 mRNA in human myocardial tissue. Sixteen patients had systemic hypertension (RR ≥ 140/90 or ≥ 160/90 if aged over 65), 24 served as controls. GLUT 4 mRNA expression was 56.2 ± 2.5 (± SEM) in the control group and 42.5 ± 3.7 (± SEM) in the hypertensive group (P = 0.0028).

Our results are in agreement with similar findings in hypertensive rats and clearly show that myocardial mRNA expression of GLUT 4 isoform is decreased in myocardium of patients with systemic hypertension. The data indicates that altered cellular GLUT 4 expression of the cardiovascular system occurs with the development of systemic arterial hypertension and may constitute a missing link between disturbed cellular glucose metabolism and systemic hypertension.

P566 11β-hydroxysteroid dehydrogenase deficiency blunts nitric oxide-mediated endothelial function: a novel mechanism in hypertension?

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Background: Mineralocorticoid receptors derive specifity for aldosterone over cortisol from co-expression of the enzyme 11β-hydroxysteroid dehydrogenase (11β HSD) that inactivates cortisol to inactive metabolites. In patients with liquorice-induced and low-renin essential hypertension 11β HSD activity is decreased and cortisol activates the mineralocorticoid receptor resulting in sodium retention and hypertension.

Methods: To evaluate the potential importance of endothelial factors in 11β HSD deficiency normotensive Wistar-Kyoto rats received licorice-derived glycyrrhetinic acid that inhibits 11β HSD activity in a dose-dependent manner (50 mg/kg bodyweight i.p. for one week; saline in the controls; n = 7). Endothelium-dependent and -independent function were assessed as response to acetylcholine (ACh, 0.01–300 μmol/L) and sodium nitroprusside (SNP, 0.01–300 μmol/L) in isolated aortic rings. Aortic tissue levels of nitric oxide were assessed by nitrate/nitrite conversion. In addition, endothelial nitric oxide synthase (eNOS) protein levels were determined by western blot analysis.

Results: Glycyrrhetinic acid induced a significant blood pressure increase (157 vs 127 mmHg in the controls; $p < 0.01$), while heart rate remained unchanged. ACh-induced endothelial nitric oxide release was blunted ($p < 0.05$ vs controls) and completely blocked by NO-synthase inhibitor L-NAME, while responses to SNP remained unchanged. Similarly, eNOS protein and nitric oxide tissue levels (1120 vs. 490 mg/g protein; $p < 0.05$ vs controls) were decreased indicating blunted nitric oxide bioavailability in 11β HSD deficiency.

Conclusions: These data show for the first time that decreased 11β HSD activity results in an attenuated bioavailability of nitric oxide and may thus contribute to the development of hypertension in patients with 11β HSD deficiency.

MECHANISMS OF HYPERTENSION: NEUROHUMORAL AND AUTONOMIC ABNORMALITIES

P567 Chronic imidazoline-1 receptor agonism with moxonidine: effect on sympathetic reflex responses in patients with essential hypertension

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Microneurographic studies have demonstrated increased resting muscle sympathetic nerve activity (MSNA) in essential hypertension. Although some antihypertensive agents increase sympathetic drive, which may have prognostic implications, we have recently shown that chronic moxonidine therapy reduces resting MSNA in essential hypertension. This preliminary study was designed to investigate the effects of oral moxonidine on sympathetic reflex responses.

Methods: Nine newly diagnosed essential hypertensives (DBP > 95 mmHg) were examined before and after 4 weeks of oral moxonidine (200/400 mcg od). Following the acquisition of resting haemodynamic and neural data, the cold pressor test (CPT) was used to stimulate sympathetic reflex responses. Heart rate (HR) and blood pressure (BP) were recorded from an ECG and Finapres device, and venous occlusion plethysmography was used to derive calf vascular resistance (CVR) in arbitrary units (U). Peroneal microneurography was used to quantify MSNA as bursts per 100 cardiac beats (b/h).

Results: There were no significant differences in the response of HR or mean BP induced by the CPT before and after moxonidine therapy (paired t tests). Moxonidine reduced the absolute and percentage change in MSNA and CVR induced by the CPT (table). Data as mean ± SEM.

	MSNA (b/h)	CVR (U)
No therapy	135 ± 31 (235% ± 48)	34.7 ± 9.7 (85% ± 19)
Moxonidine	27.8 ± 7.4* (69% ± 16)‡	21.0 ± 5.2† (60% ± 15)†

Compared to no therapy, * = $p < 0.02$; ‡ = $p < 0.03$; † = $p < 0.04$.

Conclusions: These results indicate that in essential hypertension, chronic moxonidine therapy attenuates sympathetic reflex responses and its effect on calf vascular resistance induced by noxious cold stimulation.

P568 Effects of nitric oxide synthase inhibition on baroreceptor regulation of muscle sympathetic nerve activity and haemodynamics in man

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Endothelial dysfunction, leading to an imbalance of endothelial-derived relaxing and constrictive factors, plays an essential role in cardiovascular disease. We investigated whether inhibition of nitric oxide (NO) synthesis alters baroreceptor regulation of sympathetic nervous activity.

In healthy volunteers, we recorded muscle sympathetic nerve activity (MSA) using microneurography and central hemodynamics at different levels of central venous pressure induced by lower body negative pressure (LBNP). After administration of the NO synthase inhibitor NG-monomethyl-L-arginine (L-NMMA, 1 mg/kg/min), systolic blood pressure increased by 24 mmHg (P = 0.01) while stroke volume index (measured by thermodilution) fell from 53 to 38 mL/min/m^2 ($p < 0.002$). Heart rate, but not MSA, failed to increase in response to LBNP which under control conditions led to compensatory rises in MSA and heart rate in response to falling blood pressure. The altered response of heart rate was not due to a higher blood pressure level, since heart rate responses to orthostatic stress were not altered during infusion of the alpha-1-adrenoceptor agonist phenylephrine (titrated to an equal increase of systolic blood pressure). In the presence of equal systolic blood pressure and right atrial pressure, MSA was significantly higher during phenylephrine than during L-NMMA infusion but was not different from control conditions despite higher systolic blood pressure.

This study demonstrates alterated baroreceptor regulation of heart rate but not peripheral sympathetic activity after inhibition of NO synthesis in healthy volunteers.

P569 Adrenergically-mediated low-frequency blood pressure oscillations in conscious rats

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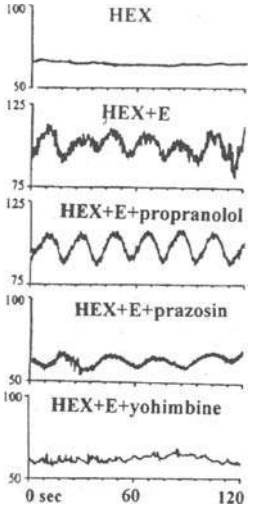
Sympathoadrenergic contribution to LF-BP oscillations is debated: we previously showed in rats that ganglionic blockade by hexamethonium (Hex) drastically lowers BP and almost entirely abolishes LF-BP spectral power (0.025–0.1 Hz, sequential FFT technique). In this study we tested in Hex-treated rats whether i) restoration of BP by an adrenergic agent also restores LF-BP power and ii) which is the adrenergic receptor involved.

Methods: in 41 conscious, instrumented rats BP was recorded for 60 min under administration of i) Hex, 1.5 $mg.kg^{-1}.min^{-1}$; ii) Hex + epinephrine (E), 4 $\mu g.kg^{-1}.min^{-1}$; iii) Hex + E + propranolol, 1 $mg.g^{-1}$; iv) Hex + E + prazosin, 0.2 $mg.kg^{-1}.min^{-1}$; v) Hex + E + yohimbine, 2 $mg.kg^{-1}.min^{-1}$.

Results: when Hex-treated rats had their BP restored by E (but not by a non-adrenergic agent such as vasopressin, data not shown), distinct LF- (period 30 to 40 sec) BP oscillations appeared; they persisted under β- or α_1-receptor blockade but disappeared after α_2-receptor blockade. Examples of the recordings obtained under each condition are shown in Figure (mean BP, mmHg). Such oscillations were shown in separate groups of rats to be similarly elicited by infusing norepinephrine rather than E and not to be abolished by administration of l-NAME or losartan (data not shown).



Thus adrenergic agonists, acting via the α_2-adrenergic receptor, have the potential to elicit vasomotor oscillations in the LF range, possibly by amplifying the intrinsic oscillatory properties of vascular smooth muscle.

P570 Vasodilator potency of proadrenomedullin N-terminal 20 peptide is apparently less than that of adrenomedullin in humans

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Adrenomedullin (ADM) and proadrenomedullin N-terminal peptide (PAMP), both of which are derived from preproadrenomedullin, are reported to have a potent hypotensive effect in animals. Plasma level of PAMP has been reported to be elevated in patients with essential hypertension ($\simeq$1 fmol/ml). However, no data are available concerning the vasodilatory potency of PAMP or comparing this potency to that of ADM in human vasculature.

Methods: We examined the effects of intra-arterial infusion of graded doses of ADM (1.25, 2.5, 5.0 and 7.5 pmol/min/100 ml of tissue) and PAMP (12.5, 25, 50 and 75 pmol/min/100 ml of tissue) on total forearm blood flow and forearm skin blood flow in 8 healthy subjects.

Results: ADM increased total forearm blood flow from 3.1 $\pm$ 0.4 to 9.3 $\pm$ 0.9 ml/min/100 ml ($p < 0.01$), and skin blood flow from 0.08 $\pm$ 0.02 to 0.15 $\pm$ 0.03 volts ($p < 0.01$). In contrast to this potent vasodilatory effect, a significant rise in forearm skeletal blood flow was seen only in response to the maximum dose of PAMP (from 3.4 $\pm$ 0.4 to 4.5 $\pm$ 0.7 ml/min/100 ml; $p < 0.05$). However, PAMP had no significant vasoactive effect on skin blood flow (from 0.07 $\pm$ 0.01 to 0.08 $\pm$ 0.01 volts; NS).

Conclusion: This study has demonstrated for the first time that the peripheral resistance vasodilator potency of PAMP is less than one tenth of that of ADM in humans. Given its calculated circulating level during PAMP infusion in the experimental arm ($\simeq 10^4$ fmol/ml), it seems unlikely that PAMP alone could significantly regulate resistance vessel tone as a circulating hormone in humans.

P571 Circadian rhythm of blood pressure and brain involvement in essential hypertension

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Objective: In order to investigate whether non-dipping is associated with more severe brain involvement in essential hypertension

Methods: Fifty five essential hypertensives, stage I and II, 26 men and 29 women, aged 30–55 underwent ambulatory blood pressure monitoring, brain MR tomography and electroencephalography with mapping of power distribution of EEG rhythms(alfa, beta, gamma and teta) in rest and during counting. ABP was recorded during 24 hours at 15 minutes interval, night time was defined as 22.00–6.00. Four types of distribution of spectral power of EEG rhythms were defined: I type – normal; II, III, IV type – mild, moderate and severe disfunction correspondently, taking into account proportion of power of slow rhythms and alfa-rhythm, abnormality of spatial distribution of power of rhythms. All patients were divided into two groups according to difference between blood pressure daytime and nighttime means: dippers (more then 10%, n = 35) and non-dippers (less then 10%, n = 20). The number of lacunae per person, subarachnoidal and brain ventricular space dimensions were significantly greater in non-dippers. Average spectral power of slow teta-rhythm was significantly higher in non-dippers ($p < 0.005$) and average power of alfa-rhythm during counting was significantly less ($p < 0.01$) in non-dippers. Significantly greater propotion of non-dippers had periventricular hyperintensity and III and IV types of power distribution of EEG rhythms. Thus, non-dipping associated with more severe brain damage according to EEG and MRI in essential hypertension.

EFFECTS OF HYPERTENSION ON THE HEART

P572 Microalbuminuria is associated with unfavourable left ventricular geometry patterns in untreated, non-diabetic, patients with essential hypertension

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Both a slightly elevated urinary albumin excretion rate and concentric left ventricular (LV) hypertrophy has been associated with increased risk for future cardiovascular events but the interaction between microalbuminuria (MA) and the spectrum of LV geometry has not been well established.

Methods: For this purpose, 249 untreated, nondiabetic, non-proteinuric patients (pts) with stage I–II (JNC VI) essential hypertension underwent echocardiography and 24 hour urine collection. Our pts were classified according to 1) the level of MA into group A (MA > 20 mg/24 h) and group B (MA < 20 mg/24 h) and 2) the relative wall thickness (RWT) and LV mass index (LVMI) into four groups [normal geometry (NM), concentric remodeling (CR), eccentric hypertrophy (EH) and concentric hypertrophy (CH)].

Results: The two groups A and B were matched for age, sex, BSA, smoking status and plasma cholesterol level. In comparison to group B (140 pts), group A (109 pts) had a significant increase in MA (42.16 $\pm$ 31 vs 9.92 $\pm$ 4 mg/24 h, $p < 0.001$), in LVMI (110 $\pm$ 22 vs 90 $\pm$ 17 g/m^2, $p < 0.0001$), in RWT (0.46 $\pm$ 0.06 vs 0.41 $\pm$ 0.04, $p < 0.001$) and in office systolic and diastolic BP (161 $\pm$ 17 vs 148 $\pm$ 15 and 101 $\pm$ 9 vs 97 $\pm$ 9 mmHg, respectively, $p < 0.005$). In the entire study population, NG, CR, EH and CH was found in 135 pts (54.2%), 76 pts (30.5%), 20 pts (8%) and 18 pts (7.3%) respectively. For the pooled population, MA was positively correlated to LVMI ($r = 0.46$, $p < 0.001$), RWT ($r = 0.47$, $p < 0.001$), and office pulse pressure ($r = 0.29$, $p < 0.001$). The incidence of NG was significantly higher in group B compared to group A (77.8% vs 23.8%, $p < 0.001$) while the incidence of CR, EH and CH was significantly higher in group A compared to group B (49.5% vs 7%, 12.8% vs 2% and 13.7% vs 3.1% respectively, $p < 0.005$ for all cases).

In conclusion, the higher prevalence of unfavorable LV geometric patterns in the microalbuminuric pts along with the increased pulse pressure may account for a worse cardiovascular outcome associated with the presence of MA in hypertensive pts.

P573 Role of insulin-like growth factor-1 in left ventricular hypertrophy in hypertensive patients

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Several lines of evidence suggest that left ventricular hypearophy (LVH) observed in hypertension (HT) occurs in response to haemodynamic and nonhaemodynamic stimulus as hormones and growth factors. A number of experimental data indicates that IGF-1 affects myocardial growth and structure. Thus in order to gain insight into the possible involvement of IGF-1 in LVH of HT the levels of this factor were measured in plasma of the patients with HT and the relation between IGF-1 and left ventricuar mass index (LVMI) as well as MBP and other neurohumoral factors were examined. **Patients and method.** The studies were carried out in 121 HT patients aged 17 to 79 (mean 48 ± 15.3) years and in 39 normotensive controls aged 18 to 73 (mean 50.21 ± 17.17) years. According to V JNC, HT patients were devided into three groups: I- 53 patients with mild HT, II- 44 pts. with moderate and III- 24 pts with severe HT. Groups I and II were derided into subgroups with and willaout LVH. All patients of group III (severe HT) had LVH. 73 out of 121 HT patients had echocardiographically documented LVH and 48 pts had no LVH. Plasma level of IGF-1, plasma renin activity (PRA), aldosterone, proendothelin-1 (proET-1) and ANP were quantitated by radioimunoassay. **Results.** MBP and the levels of IGF-1, PRA, proendothelin-1 and ANP were significantly higher in patients with severe HT compared to mild and moderate HTs. In HT patients with LVH the values of MBP and levels of IGF-1, PRA, aldosterone, proET-1 and ANP were significantly higher compared to the patients without LVH ($p < 0.001$, $p < 0.001$, $p < 0.0001$, $p < 0.001$, $p < 0.001$, $p = 0.001$ respectively). There was significant correlation between IGF-1 level and LVMI in patients with moderate HT ($r = 0.54$, $p < 0.001$) and severe HT ($r = 0.58$, $p < 0.001$) and in patients with LVH ($r = 0.7$, $p < 0.001$). Additionally only in HT patients with LVH, IGF-1 plasma levels correlated with other neurohumorals (PRA, aldosterone, proET-1 and ANP) and with MBP ($r = 0.7$, $p < 0.001$). **Conclusions.** Our results demonstrate that in HT patients LVH is associated with increased levels of IGF-1. There was significant correlation between IGF-1 level and LVMI, MBP and PRA, aldosterone, proET-1. These data suggest that circulating IGF-1 is one of the nonhaemodynamic factors involved in the development of LVH in essential HT. Additionaly our results also confirm that IGF-1 plasma levels are related to pressure load leading to cardiac remodeling in hypertension.

P574 Association between left atrial size and left ventricular geometry pattern in untreated patients with essential hypertension

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Although left atrial (LA) enlargement is thought to be an early sign of hypertensive heart disease in patients (pts) with essential hypertension, the relation between LA size and the spectrum of left ventricular (LV) geometry has not been well established.

Methods: For this purpose, 210 untreated, newly diagnosed pts with stage I–II (JNC VI) essential hypertension (mean age 53 ± 10 years) underwent echocardiography for estimation of LV, LA and aortic (Ao) dimensions. Our pts were classified according to the relative wall thickness (RWT) and the LV mass index (LVMI) into four groups [normal geometry (NM), concentric remodeling (CR), eccentric hypertrophy (EH) and concentric hypertrophy (CH)]. LA size was evaluated by calculating LA dimension (determined at its largest diameter), LA index (LA dimension/BSA) and LA/Ao ratio (LA/Ao diastolic diameter)

Results: In the entire study population LVMI was 101 ± 22 g/m^2, RWT was 0.43 ± 0.06, office BP was 155 ± 17/99 ± 9 mmHg, Ao diastolic diameter was 2.93 ± 0.3 cm, LA dimension was 3.38 ± 0.4 cm, LA index was 1.78 ± 0.2 cm/m^2 and LA/Ao ratio was 1.15 ± 0.5. Multiple regression analysis performed on demographic characteristics, BP data and LVMI, identified age and LVMI as significant predictors of LA index and LA/Ao ratio ($p < 0.005$). Furthermore, NG, CR, EH and CH was found in 105 pts (50%), 71 pts (34%), 18 pts (9%) and 16 pts (7%) respectively. LA dimension was significantly greater in pts with LV EH compared to LV NG (3.6 ± 5 vs 3.3 ± 4 cm, $p < 0.005$) and LA/Ao ratio was significantly increased in pts with LV EH compared to LV CH and LV CR (1.27 vs 1.07 vs 1.15, $p < 0.005$, respectively).

Conclusion: LA enlargement is closely related with LVMI in essential hypertension and it accompanies LV eccentric hypertrophy.

P575 Relation of ambulatory versus office pulse pressure with patterns of left ventricular geometry in essential hypertension

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Pulse pressure (PP) has been recently gaining acceptance as a predictor of cardiac risk in patients with essential hypertension. The relative value of office versus ambulatory PP measurements in this respect is an unresolved issue of considerable interest.

Methods: In 210 consecutive previously untreated patients (130 men, 80 women, aged 52 ± 10 years) in whom a first diagnosis of stage I or II essential hypertension was confirmed in our Department between January and December 1998, office PP (mean of difference between systolic and diastolic blood pressure values on 3 consecutive measurements) as well as ambulatory PP (mean of difference between systolic and diastolic blood pressure values on all measurements performed over 24 hours by standard equipment) was determined prior to initiation of treatment. These values were correlated with 4 well-defined types of left ventricular (LV) geometry categorized in order of increasing adverse prognostic significance as normal geometry, cardiac remodeling, eccentric hypertrophy, and concentric hypertrophy on the basis of LV mass index and LV relative wall thickness assessed by transthoracic echocardiography.

Results: A good correlation was demonstrated between office PP (mean ± SD: 55 ± 15 mmHg) and ambulatory PP (53 ± 9 mmHg) measurements ($r = 0.46$, $p < 0.001$). Normal LV geometry was revealed in 105 pts, the remodeling pattern in 71, eccentric hypertrophy in 18 and concentric hypertrophy in 16 pts. Office PP and ambulatory PP values correlated equally well with LV mass index ($r = 0.31$ and $r = 0.23$, respectively, $p < 0.001$ for both correlations). Both office and ambulatory PP values were lowest in pts with normal LV geometry (51 ± 15 and 51 ± 9 mmHg, respectively) and highest in pts with concentric LV hypertrophy (70 ± 14 and 57 ± 9 mmHg, respectively), with intermediate values in pts with the remodeling pattern (56 ± 14 and 53 ± 8 mmHg, respectively) and eccentric hypertrophy (57 ± 16 and 57 ± 10 mmHg, respectively). Office PP was significantly higher in pts with concentric hypertophy compared with all the other LV geometry subgroups ($p < 0.05$ for all comparisons), as well as in pts with the remodeling pattern versus pts with normal LV geometry ($p < 0.05$). Ambulatory PP was significantly higher in pts with concentric as well as eccentric hypertrophy versus pts with normal LV geometry ($p < 0.01$ and $p < 0.05$, respectively).

Conclusions: In a group of untreated hypertensive pts, increasing PP values paralleled the increasing prevalence of patterns of LV geometry associated with progressively higher cardiac morbidity. Acquisition of 24-hour ambulatory PP values revealed this relation equally well as (but not better than) plain office PP measurements.

P576 Aldosterone synthase promoter −344 C/T polymorphism determines left ventricular structure by differences in sodium handling in arterial hypertension

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Objective: High oral salt intake is associated with arterial hypertension and left ventricular (LV) structural adaptive processes. The −344 C/T polymorphism of human aldosterone synthase (CYP11B2) promoter has been found to be related to LV size, arterial hypertension, and adrenocortical function. Therefore, we questioned whether differences in sodium handling are responsible for LV structural changes in human arterial hypertension.

Methods: We enrolled 122 male, white, young (age: 26 ± 3 years) subjects with normal or mildly elevated blood pressure (but never treated for that). LV structural parameters were assessed by 2-D guided M-mode echocardiography. Urinary sodium excretion over 24 hours was measured under a standard Bavarian diet and after an additional oral sodium load (salt tablets, 6 g/day over 1 week). Serum aldosterone levels were measured by radioimmunoassay. The −344 C/T polymorphism of the aldosterone synthase promoter was determined by restriction endonuclease *Hae* III digestion after DNA amplification with polymerase chain reaction.

Results: In the entire study population, the T/T, C/T, and C/C genotype of the −344 C/T aldosterone synthase polymorphism were found in 35, 57, and 29 subjects, respectively. Baseline urinary sodium excretion and blood pressure were similar across the genotypes. After oral sodium load, hypertensive subjects with the T/T genotype had significantly higher urinary sodium excretion (291 ± 85 vs 158 ± 81 mmol/d at baseline) than hypertensive subjects with the C/C genotype (212 ± 68 *vs* 207 ± 100 mmol/d at baseline) ($p < 0.05$), with similar serum aldosterone levels at baseline and after oral sodium load. Hypertensive subjects with the C/C genotype had greater LV diastolic and systolic diameter (54 ± 2 and 34 ± 3 mm, respectively) than those with the T/T genotype (50 ± 4 and 30 ± 4 mm, respectively; all $p < 0.05$). LV mass was similar (C/C, 260 ± 53; T/T, 272 ± 57 g; n.s.), but posterior (C/C, 9.9 ± 1.6; T/T 11.0 ± 1.2 mm) and, consequently, relative LV wall thickness (C/C, 0.37 ± 0.07; T/T, 0.44 ± 0.06) were reduced in hypertensive subjects with the C/C genotype (all $p < 0.05$).

Conclusion: Our data suggest a pattern of early excentric LV hypertrophy in hypertensive subjects with the C/C genotype of the −344 C/T aldosterone synthase polymorphism. This could be caused by a reduced ability to excrete sodium and, therefore, by a higher intravascular volume load.

P577 Association between aldosterone synthase *(CYP11B2)* gene polymorphism and left ventricular hypertrophy of mechanical overload

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Aim: Aldosterone (Aldo) has been shown to be a contributing factor to myocardial growth. Since synthesis of Aldo might be influenced by *CYP11B2* promoter polymorphism, we tested the hypothesis that left ventricular hypertrophy (LVH) of pressure overload is associated with *-344CYP11B2* promoter genotype.

Methods: 78 consecutive untreated patients (pts) with essential hypertension (HBP) as well as 85 pts with aortic stenosis (AoS) were studied. Exhaustive clinical and biochemical examination was performed, including echocardographic studies (ECO) and peripheral blood determination of *CYP11B2* polymorphism by PCR amplification and restriction endonuclease digestion.

Results: The three genotype groups *-344TT, -344TC* or *-344CC* did not differ with regard to blood pressure, plasma renin activity, plasma Aldo levels (HBP group) or in severity of AoS, as assessed by Eco-Doppler. M-mode ECO measurements of septal (SWTh) and posterior wall thickness (PWTh) in mm (mean ± SD) revealed that *T* alelle was associated with a significantly greater wall thickness. Regression analysis showed that *T* alelle was an independent predictor of hypertrophy in HBP ($p = 0.003$) and in AoS ($p = 0.002$).

	Hypertension (n = 78)		Aortic stenosis (n = 85)	
	SWTh	PWTh	SWTh	PWTh
TT	12.0 ± 1.5	11.2 ± 1.2	14.6 ± 2.2	12.8 ± 1.8
CT	12.2 ± 1.5	11.1 ± 1.4	15.0 ± 2.6	13.1 ± 1.7
CC	10.7 ± 1.2	10.6 ± 1.4	12.9 ± 2.0	11.9 ± 1.8
p value	0.004	ns	0.001	0.02

Conclusions: Those findings suggests that the *T* alelle of the *-344CYP11B2* polymorphism is an independent factor associated with hypertrophy of pressure overload. Increase in Aldo synthesis might be exerted at the local myocardial level, since no association with plasma Aldo concentration was observed.

P578 Left ventricular geometry and vascular structural changes in hypertensive patients

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Arterial hypertension is associated with the presence of structural changes in the heart and both large and small arteries. It has been observed that the spectrum of geometric patterns observed in the heart of hypertensive patients (Hpts) may parallel the structural alterations detected in the carotid arteries. The relation between structural changes in subcutaneous small arteries and left ventricular (LV) geometry has never been evaluated.

Twelve normotensives (NT) and 66 Hpts with essential (n = 18) or secondary (n = 48) hypertension were included in the study. All subjects underwent an echocardiographic study for the measurement of LV mass index (LVMI) and relative wall thickness (RWT). Twelve normotensives had a normal LVMI (96.4 23 g/m^2) and geometry, 46 patients had normal RWT (RWT < 0.45) (LVMI 115.3 29 g/m^2) and 20 had concentric remodeling or hypertrophy (RWT > 0.45) (LVMI 130 31 g/m^2). All subjects were submitted to a biopsy of subcutaneous fat and morphologic characteristics of subcutaneous small resistance arteries were evaluated by a micromyographic technique (Mulvany's technique). The media/lumen ratio (M/L) was calculated.Hpts with concentric geometry had a greater M/L as compared with normotensives or Hpts with normal RWT (1.12 0.048 vs 0.06 0.01 vs 0.10 0.0031 in Hpts RWT > 0.45, NT and Hpts RWT < 0.45, respectively, $p < 0.01$).

The correlation coefficient between the M/L in subcutaneous small arteries and LVMI was 0.44, $p < 0.05$; the correlation coefficient between the M/L in subcutaneous small arteries and RWT was 0.45, $p < 0.05$.

In conclusion, the presence of a concentric geometry of the left ventricle is associated with more pronounced structural changes in small subcutaneous resistance arteries in patients with essential or secondary hypertension.

P579 Peripheral arterial disease is associated with decreased systolic left ventricular function and increased arterial stiffness: the LIFE study

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Background: Changes in LV structure and function in pts with peripheral arterial disease (PAD) & LVH have not been adequtely explored.

Methods: We studied 840 pts with hypertension and ECG LVH (Cornell Voltage-Duration product > 2,440 or $SV_1 + RV_{5-6} > 38$ mm) participating in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Trial. Of those, 37 pts had PAD and 793 did not (NO PAD). Echocardiograms were obtained by trained sonographers and read by a single central reading center.

Results: The groups were similar in age (66 vs 67 yrs), BMI (27.4 vs 26.7), systolic and diastolic BP (173/98 vs 172/97 mm Hg), septal and posterior wall thickness, LVMI (121 vs 125 gr/m^2 and relative wall thickness (0.41 vs 0.47). FS and diastolic function measures were also similar. Differences in Echocardiographic Measures between groups were as follows:

	NO PAD (n = 793)	PAD (n = 37)	p = Value
MWS (%)	0.15	0.14	0.05
SA-MWs	96.00	90.00	0.03
CO (L/min)	5.20	4.60	0.01
TPR	2028	2368	0.07
PP/STVOL	1.02	1.14	0.04

MWS = Midwall fractional shortening, SA = Stress adjusted, pp/STVOL = pulse pressure/stroke volume ration.

Conclusion: We conclude that pts with PAD and ECG LVH have early evidence of systolic LV dysfunction and increased arterial stiffness.

P580 Influence of hypertension, left ventricular hypertrophy and left ventricular systolic dysfunction on plasma cardiotrophin-1 levels

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Objective: Cardiotrophin-1 (CT-1), a member of the interleukin-6 related cytokines that acts via the gp130 signalling pathway, has been shown to stimulate the assembly of sarcomeric units in series in cardiomyocytes. Furthermore increased expression of CT-1 mRNA is evident in the hypertrophied ventricles of hypertensive rats. We set out to determine whether CT-1 was elevated in plasma of hypertensive patients (with and without left ventricular hypertrophy {LVH}) and in patients with left ventricular systolic dysfunction (LVSD) & a history of hypertension as compared to controls.

Design and Methods: A competitive immunoluminometric assay using a methyl acridinium ester to label the peptide and an in-house polyclonal antibody to amino acids 105–120 of the CT-1 sequence was developed. We compared plasma CT-1 levels between 15 echocardiographic normal controls (8 male, median age 41 yrs [range 30–76] = Group 1), 30 patients with HT, normal left ventricular systolic function and no LVH (15 male, 43.5 yrs [22–72] = Group 2), 14 patients with HT, normal left ventricular systolic function & LVH (5 male, 47 yrs [29–74] = Group 3), 18 patients with history of HT (no history of Ischaemic heart disease) and left ventricular wall motion index (WMI) between 1.9–1.3 (12 male, 74.5 yrs [56–91], median WMI 1.6 [1.–1.9] = Group 4) and 17 patients with a history of HT (no history if ischaemic heart disease) and WMI of <1.2 (10 male, 66 yrs [43–83], median WMI 0.6 [0.2–1.2] = Group 5). Medians fmol/ml [ranges] are reported.

Results: CT-1 levels were 27.8 [7.6–42.1], 51.6 [13.4–95.7], 48.6 [35.7–93.9], 54.4 [20.5–95.8] & 76.1 [28.2–130.6] for groups 1–5 respectively. Mean LogCT-1 differed among all 5 groups ($p < 0.0001$, ANOVA) and between group 1 vs group 2–5 ($p < 0.001$). Mean Log CT-1 levels were higher in group 5 compared to group 4 and group 2 ($p < 0.05$ for both). There was no difference in log CT-1 levels between group 2 & 3 ($p = 0.49$) and group 3 & 5 ($p = 0.12$). The patients in group 4 & 5 were older than those in group 1–3 ($p < 0.001$). There was no difference in ages between groups 1–3.

Conclusion: Our results suggest there is a significant rise in CT-1 levels both in HT and LVSD compared to controls. Also those patients with severe LVSD had the highest CT-1 levels. There was no difference in CT-1 levels of hypertensives with or without LVH. This is the first demonstration of significant elevation of plasma CT-1 in patients with HT and LVSD. The exact role of CT-1 in these patients remains to be defined.

P581 QT dispersion in hypertensive patients who had normal coronary angiogram with or without left ventricular hypertrophy

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The aim of this study was to investigate whether QT dispersion (QTd) was different in hypertensive patients who had normal coronary angiogram with or without left ventricular hypertrophy. The study population consisted of 61 hypertensive and 23 control subjects. All hypertensive patients had normal coronary angiogram. The electrocardiograms (ECG) of thirty-two hypertensive patients with left ventricular hypertrophy (mean age 53 ± 9), twenty-nine hypertensive patients without left ventricular hypertrophy (mean age 55 ± 2) and twenty-three normal healthy subjects were evaluated. Dispersion of QT interval was measured from 12-lead ECG at rest. Systolic (SBP) and diastolic (DBP) blood pressure, body mass index (BMI), left ventricular mass index (LVMI), QTd and QTcd were compared between groups.

(n = 23)	Hypertensive Patients		Control	p
	LVH(+) (n = 32)	LVH(−) (n = 29)		
SBP (mmHg)	147.5 ± 26.3	143.0 ± 16.3	120.6 ± 12.6	1–3*, 2–3*
DBP (mmHg)	90.8 ± 10.8	91.0 ± 7.3	76.7 ± 7.9	1–3*, 2–3*
BMI (kg/m2)	26.9 ± 4.2	26.7 ± 3.5	24.9 ± 5.3	ns
LVMI (gr/m2)	148.2 ± 31.9	96.1 ± 14.3	90.0 ± 12.3	1–3*, 1–2*
QTd (msn)	61 ± 24	64 ± 23	35 ± 10	1–3*, 2–3*
QTcd (msn)	68 ± 29	70 ± 27	38 ± 10	1–3*, 2–3*

*: $p < 0.05$, ns: non-significant

In conclusion: (1) QT dispersion was significantly increased in hypertensive patients with or without left ventricular hypertrophy.

(2) Ventricular arrythmias may be seen similarly in both left ventricular hypertrophic and non-hypertrophic hypertensive patients.

P582 Comparison of changes of heart and its function in renoparenchymal and essential hypertensive patients after more than a decade

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Although renoparenchymal disease is the most common cause of secondary hypertension there are no data in literature about its effects on heart.

Methods: We compared 35 IgA nephropathy hypertensive patients with normal renal function (IHTP) with 35 patients with essential hypertension (EHTP) all treated by combined therapy. Blood pressure was checked regularly and lab tests were taken. Heart function was measured by echocardiography.

Results: (Data are mean ± SEM) Duration of hypertension was 12.0 ± 1.02 ys and 13.1 ± 1.37 ys p: not significant. The onset of hypertension was earlier in IHTP than in EHTP (35.4 ± 1.7 ys vs. 43.0 ± 2.2 ys; $p < 0.01$). No significancy was found between left ventricle enddiastolic diameters (50.88 ± 1.07 vs. 53.8 ± 1.38) and endsystolic diameters (32.2 ± 1.1 vs. 33.7 ± 1.48) but left atrium was significantly bigger in EHTP than in IHTP (53.8 ± 1.7 ys vs. 43.0 ± 2.2 ys $p = 0.026$). The septum and posterior wall was also significantly thicker in EHTP than in IHTP (12.3 ± 0.37 vs. 11.3 ± 1.38 p $p < 0.05$ and 11.9 ± 0.33 vs. 10.9 ± 0.38 $p < 0.05$). Left ventricle mass index (LVMI) in women was also higher in EHTP than in IHTP (154.2 ± 13.1 vs. 129.3 ± 9.5) and in men (170.7 ± 7.8 vs. 149 ± 9.0). Ejection fraction was significantly higher in IHTP than in EHTP (66.7 ± 1.41 vs. 60.5 ± 1.94 $p < 0.02$). E/A also showed significant differency: in IHTP 1.03 ± 0.058 and in EHTP 0.863 ± 0.054 $p = 0.025$. Body mass index (BMI) was significantly higher in EHTP than IHTP (30.1 ± 0.66 vs. 28.1 ± 0.58 $p = 0.024$). There was a significant correlation between BMI and left atrium in IHTP ($p < 0.01$) whereas in EHTP was not.

Conclusion: Our data show that systolic and diastolic heart function is less damaged and left atrium enlargement and left ventricle hypertrophy are milder in renoparenchymal hypertensive patients eventhough hypertension existed for longer period then in essential hypertensives. The main cause is still to be found but more frequent and regular checking and follow-up because of renal disease and less degree of obesity may play role in it.

P583 Myocardial perfusion abnormalities in hypertensive patients without known coronary artery disease

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Rationale. Myocardial perfusion abnormalities may occur in hypertensive patients in absence of significant coronary artery disease (CAD). However, it is not well established whether hypertensive patients without known CAD have a higher prevalence of myocardial perfusion abnormalities compared with non hypertensive patients with similar clinical features. This study compares the prevalence and extent of rest and stress-induced myocardial perfusion abnormalities in patients with and without hypertension.

Methods. Dobutamine (up to 40 μg/kg/min) stress 99 m technetium myocardial perfusion SPECT imaging was performed for evaluation of myocardial ischemia in 350 patients (mean age = 60 ± 13 years, 146 men) without history of previous infarction or known CAD. One hundred forty eight patients were hypertensive. Rest SPECT images were acquired 24 hours after the test. Abnormal perfusion was defined as the presence of reversible or fixed perfusion defects.

Results. No significant difference was detected between patients with and without hypertension regarding gender, prevalence of symptoms, risk factors, pretest probability of CAD (52 ± 28% vs 53 ± 29%), peak rate pressure product (21040 ± 4755 vs 20774 ± 4865) or number of patients achieving the target heart rate during stress (85% vs 86%). The prevalence of myocardial perfusion abnormalities was not different between patients with and without hypertension (28% vs 31% in patients with low, 38% vs 33% in patients with intermediate and 60% vs 58% in patients with high pretest probability of CAD respectively). No significant difference was detected between both groups regarding stress perfusion defect score (1.45 ± 2.5 vs 1.50 ± 2.6) or rest score (0.72 ± 1.8 vs 0.68 ± 1.6).

Conclusion. Hypertensive patients without known CAD have similar prevalence and severity of myocardial perfusion abnormalities at rest and at dobutamine stress compared to non hypertensive patients with similar pretest probability of CAD.

P584 Ischaemic heart disease in patients with arterial hypertension

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A high incidence of hypertension and a rapid development of heart failure in elderly people account for a growing interest among research workers in this problem.

Methods: For the purpose of diagnosing IHD and studying its effect on the contractile force of left ventricular (LV) myocardium 77 elderly patients with 2nd stage hypertension (age range, 60–79 years) were investigated by means of stress testing using dipyridamole test with ECG recordings in 48 leads and transesophageal atrial electrical pacing (TAEP) of the heart. The systolic and diastolic functions of the left ventricle were studied at baseline and at each frequency of pacemaker-induced heart rate using M-mode echocardiography. On the basis of stress testing IHD was diagnosed in 87% of the patients investigated (1st group). The rest of the subjects investigated (13%) were the patients with 2nd stage hypertension without IHD (2nd group).

Results: In patients of the 1st group a decrease in contractile force of LV myocardium was observed already at rest, the ejection fraction (EF) being retained, whereas in the patients of 2 nd group the LV systolic and pumping functions remained preserved. In the patients of 1st group a pronounced disturbance of systolic and diastolic functions, and a drop of EF by 15% and over occurred during TAEP at the heart rate of 118 impulses/min. In the patients of 2nd group the contractile force of LV myocardium was retained during stress testing but a further deterioration of diastolic function proceeded. In all patients of both groups a hypertrophy of left ventricle was noted. The analysis of results obtained showed that the development of hypertrophy in 92% of the 1st group patients could be classified as such that took an eccentric way, whereas in 80% of 2nd group patients it was of concentric type.

Conclusion: The TAEP is a highly informative method of IHD diagnosing and studying the functional state of LV myocardium. In elderly patients with hypertension the IHD was detected already at early stages of the disease which determines the development of LV dysfunction and the decrease in contractile force of the myocardium.

P585 Clinical characteristics of the hypertensive patients with myocardial perfusion defects and normal coronary arteries

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Perfusion defects in myocardial scintigraphy (MPD) is a common finding in hypertensive patients with angiographically normal coronary arteries. The aim of our study was to investigate clinical, echocardiographic and electrocardiographic characteristics of the patients with essential hypertension and MPD (MPD+) and to compare them with hypertensive patients with normal scintigraphic findings (MPD-).

Methods: Fifty-seven patients (34 F, 23 M, age 59 ± 9) with MPD and angiographically normal coronary arteries and 91 hypertensive patients with normal MP (MPD-) were included to the study. Each patient underwent physical, laboratory, echocardiographic and ambulatory Holter monitoring examination. Presence of the other risk factors for coronary artery disease, left ventricular diameters, geometry, systolic and diastolic function, arrhythmic events and autonomic function were compared between the two groups.

Results: Significant clinical differences in MPD+ patients were the higher frequency of male gender, complaint of angina pectoris, smoking and longer duration of hypertension ($p = 0.006$, $p = 0.03$, $p = 0.02$ and $p = 0.01$ respectively). HDL levels were significantly lower ($p = 0.01$) and LDL was higher ($p = 0.04$) than MPD-s. In echocardiographic examination left ventricular diameters and geometry were similar in the two groups, but left ventricular internal diameter and mass index were slightly higher in MPD+s. Ejection fraction was significantly lower in MPD+ patients ($p = 0.03$), but none of the diastolic filling indexes showed significant difference in the two groups. Frequency of supraventricular and ventricular arrhythmias, dispersion of repolarization (QT-D, QTc-D, JT-D, JTc-D) were not different in both groups. Parameters of heart rate variability were slightly but significantly reduced in MPD+s.

It is concluded that MPD develops in hypertensive patients with more risk factors for coronary artery disease than MPD-s. Its frequency is similar in patients with and without left ventricular hypertrophy and its arrhythmogenic effect is not as strong as left ventricular hypertrophy.

PROGNOSIS IN MYOCARDIAL FUNCTION AND HEART FAILURE

P586 Long-term follow-up after percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy: sustained clinical and haemodynamic benefit

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PTSMA by alcohol injection into septal branches of the left coronary artery is a new treatment option for symptomatic patients (pts.) with HOCM, leading to reduction of the left ventricular outflow gradient (LVOTG) and marked clinical improvement. We analyzed the long-term follow-up in the pts. treated with PTSMA in 1996.

In 39 pts. with successful PTSMA between 1/96 and 12/96, 2 died during in-hospital stay (VF and pulmonary embolism 1 pt. each). Mean CK rise was 722 ± 401 U/l. A permanent DDD-pacemaker (DDD-PM) had to be implanted in 7 pts. Mean follow-up duration was 29 ± 4 months. Four pts. had to undergo second effective PTSMA during follow-up because of inadequate primary result. Ventricular tachyarrhythmia or late death were not observed. Further clinical and echocardiographic data are displayed in the table:

	Baseline	Follow-up	p-value
NYHA class	2.7 ± 0.5	1.1 ± 1.0	<0.001
LV enddiastolic diameter (mm)	48 ± 5	48 ± 6	n.s.
LVOTG at rest (mm Hg)	51 ± 33	4 ± 8	<0.0001
LVOTG at Valsalva (mm Hg)	141 ± 56	12 ± 19	<0.0001
Maximum workload (Watts)	76 ± 66	108 ± 39	<0.02

Conclusions: PTSMA leads to sustained and significant LVOTG reduction and symptomatic improvement without global left ventricular dilatation during long term follow-up. Possible acute complications are AV-conduction disturbances (trifascicular-block) requiring permanent DDD-PM implantation and tachycardiac arrhythmias..

P587 Prognostic value of cytokines in patients with congestive heart failure

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Elevated levels of the proinflammatory cytokines TNF-a, IL-1 and IL-6 have been reported in patients with congestive heart failure (CHF). The purpose of this study was to further assess the prognostic impact of cytokines in patients with reduced left ventricular ejection fraction (LVEF, <35%).

Plasma concentrations of IL-1, IL-6, IL-10, IL-12, sCD14 and GM-CSF were measured by ELISA in 158 patients (age: 55 ± 11 years, 87% male, 22% coronary artey disease, 78% dilated cardiomyopathy) with CHF. These patients were characterized by a LVEF of 20.3 ± 12.5% and a peak oxygen uptake (pVO_2) of 13.1 ± 7.2 ml/min/kg.

During a follow-up period of 510 ± 155 days 64 patients (41%) reached an endpoint, i.e. died and/or were hospitalized due to worsening heart failure. In comparision to clinically stable patients (n = 94), these patients were characterized by a significantly higher plasma concentration of IL-6 (9.93 ± 12.69 pg/ml vs. 4.35 ± 4.89 pg/ml, $p < 0.0001$). However, the plasma concentrations of IL-1 (1.08 ± 1.96 vs. 1.77 ± 2.85 ng/ml), IL-10 (78.4 ± 145.47 vs. 52.55 ± 89.15 pg/ml), IL-12 (3.97 ± 3.65 vs. 4.60 ± 5.73 pg/ml), sCD14 (5.75 ± 3.26 vs. 5.37 ± 3.64 mg/ml) and GM-CSF (16.67 ± 30.78 vs. 13.86 ± 34.15 pg/ml) showed no significant difference between both groups. When the patients were subdivided into quartiles according to their IL-6 concentrations, only 20% (8 out of 40 patients) of the quartile with the lowest, but 65% (26 out of 40 patients) of the quartile with the highest IL-6 concentrations reached an endpoint. There was neither a significant relationship between IL-6 and pVO_2, nor between IL-6 and LVEF, suggesting an independency of IL-6 as a prognostic marker in CHF patients.

Among all the cytokines measured in the present study only IL-6 appears to possess a prognostic value.

P588 Positive correlation between apoptosis of myocardial fibres and bad outcome after partial left ventriculectomy

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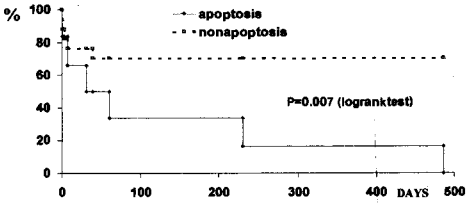
The high postoperative mortality after partial left ventriculectomy or Batista operation (BO) is the major problem in this procedure. Here we analysed if apoptosis could be involved in this problem.

Methods: We performed immunohistochemical detection of apoptotic cells using TUNEL reaction labeled with fluorescein (Boehringer-Mannheim Kit), and confocal laser microscope, in 5 μm myocardial sections from 23 patients submitted to BO. Cases were grouped in: **positive** when presenting high number of apoptotic cells – several foci of myocytes and interstitial cells; and **negative** when apoptosis was absent or only in few interstitial cells or rare (<2) myocytes, per myocardial section.

Results: The mean number of 20× microscopic fields analysed/case was 86 (±33). Apoptotic cells were seen in foci near to microvessels. There was a significant correlation between presence of cardiomyocyte apoptosis and bad outcome after BO, as showed in the above survival curve after surgery, using logrank test.



In conclusion, apoptosis seems to be an important mechanism for development of heart failure and its presence may be one important factor for bad outcome after Batista operation. As the number of myocardial fields negative for apoptosis is high, endomyocardial biopsy would not be indicated as a method to detect it.

P589 Is the prognosis of heart failure improving?

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Background and Methods: Clinical trials have suggested that a number of recent treatments for heart failure may improve mortality and prevent hospitalisation but as yet no evidence exists for this either in a community or hospital setting. We sought to determine if mortality, re-admission with heart failure and re-admission for any cause, had changed between cohorts of first-time admissions for heart failure identified in 1984, 1988 and 1992 using linked hospital discharge and mortality data from Scotland (population approximately 5 million)

Results: The number of first time admissions for heart failure increased by 30% between 1984 and 1992, from 9716 to 12640. Their mean age was 74 years and 54% were women. Over the same period 3-year mortality declined in patients < 65 years from 53% to 41% (reduction in risk 12%, 95% confidence interval 9–15%. Log rank 70.0; $p < 0.001$])and for patients ≥ 65 from 71% to 66% (reduction in risk 5%, 95% confidence interval 3–6%. Log-rank 74.5; $p < 0.0001$]). Time to death or first re-admission with heart failure also improved but not time to death or first re-admission for any cause. The total number of re-admissions increased between 1984 and 1992 but bed-days occupancy for heart failure and for any cause, adjusted for days alive, declined due to a reduction in length of stay.

Conclusions: These data suggest that the prognosis of patients with a first admission for heart failure is improving. The timing of improvements coincides with the gradual increase in the use of angiotensin converting-enzyme inhibitors for heart failure although a causal link cannot be proved from these data.

P590 Prediction of death in chronic heart failure

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Chronic heart failure (CHF) is a common condition with an adverse prognosis. Accurate identification of those most likely to die remains elusive. We hypothesised that abnormalities of ventricular repolarisation and autonomic dysfunction would predict death in CHF.

We studied 199 patients age less than 75 years with stable CHF. We determined established clinical variables: age (59 ± 9 years), aetiology of CHF (ischaemic n = 163, nonischaemic n = 36), NYHA status (2.7 ± 0.8), maximal oxygen consumption (VO_2 max 16.9 ± 4.9 ml/kg/min). Investigational variables were: plasma brain natriuretic peptide (BNP, median 48 pg/ml), 24 hour heart rate variability (HRV, median SDNN 118 msec), baroreflex sensitivity by phenylephrine bolus injection (BRS median 5.4 msec/mmHg), signal averaged ECG (SAECG 25 positive) QT dispersion by manual digitisation (QTd median 94 msec). Events were categorised by established standards using information from death certificates, autopsy findings and hospital and GP case records. Mean duration of follow-up was 971 ± 378 days. There were 54 all cause deaths, 47 cardiac deaths and 24 sudden deaths.

A Cox-proportional hazards analysis was performed with age, NYHA class, aetiology of CHF, presence/absence of bundle branch block and LVEF as forced baseline variables. QTd and SAECG did not add prognostic power. The univariate addition of plasma BNP (hazards ratio HR 3.67, p = 0.006), plasma noradrenaline (HR 3.77, p = 0.0019), HRV (SDNN-I) (HR 1.93, p = 0.0532) or baroreflex sensitivity (HR 2.94, p = 0.003), predicted cardiac death significantly. With multivariate analysis of these new variables, plasma BNP was the most significant additional co-variate and strongly predicted cardiac death (HR 3.94, $p < 0.02$). BNP retained prognostic power in patients with severe LV dysfunction (EF < 20%).

Simple venous blood sampling aids risk stratification in this common and highly lethal condition.

P591 Prognostic significance of atrial fibrillation during long-term follow-up in 409 patients with advanced chronic heart failure

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Atrial fibrillation (AF) is common in patients with chronic heart failure (CHF). It has been suggested that the presence of AF in CHF predicts an adverse prognosis, but data are scarse and inconclusive.

Methods: We studied 409 patients with moderate to severe CHF (NYHA class III–IV), who had either sinus rhythm (SR, n = 325), or atrial fibrillation (n = 84), and who were all part of a recent survival trial. At baseline the 2 groups differed with respect to age (67 vs. 70 yr, for SR and AF, resp.), etiology, duration of CHF (33 vs. 48 months, resp), blood pressure (slightly higher in SR), and plasma neurohormones (renin, atrial natriuretic peptide [ANP], N-terminal ANP, and endothelin, all higher in AF), and concomitant medication (particularly digoxin, antiarrhythmics, and anticoagulants, all higher in AF patients), but left ventricular ejection fraction (LVEF), NYHA class and gender were not significantly different. During 3.4 yr (range 2.0–5.4 yr) follow-up, 211 patients (52%) died; 52/84 patients with AF (62%), compared to 159/325 patients with SR (48%, p = 0.038, univariate analysis). On multivariate analysis, LVEF, NYHA class, renal function, age, diastolic blood pressure, and use of digoxin, were all significantly related to mortality, but AF was not (p = NS).

Conclusion: Although AF was associated with an increased mortality in the present study, AF does not appear to be an independent predictor of mortality in this patient group. The observed difference in prognosis may be due to other clinical factors, such as severity of CHF, and comparison of AF and SR will remain difficult.

P592 Prognosis of heart failure in the general population: the Rotterdam study

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There is no information on the prognosis of heart failure in the general population in the nineties. We determined the prognosis of heart failure in the large, prospective, population-based Rotterdam Study.

Methods: In 5.255 participants (age 68.9 ± 8.6 yr, 2.142 men) the presence of heart failure was assessed at the baseline visit (1990–1993) using validated criteria. Vital status and cause of death were verified during follow-up ending May 1 1996.

Results: 181 participants (age 77.3 ± 8.0 yr, 72 men) had heart failure. With an average follow-up of 4 years there were 55 deaths; 30 due to cardiovascular disease, 15 of which were sudden. Survival was 90% at one and 60% at four years.

The age adjusted hazard ratio for death in participants with heart failure was 2.1 (95% C.I. 1.6–2.8), the age adjusted hazard ratio for sudden death was 4.8 (95% C.I 2.6–8.9)

Conclusion: The prognosis of heart failure in the general population is poor. Patients with heart failure have a fivefold increase in the risk for sudden death.

P593 Prognostic value of the atrial natriuretic peptide in asymptomatic patients with Thalassemia major: ten-year follow-up

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In the present study, we evaluated the relation between Atrial Natriuretic Peptide (ANP) and long-term clinical course and survival in patients with Thalassemia Major (TM).

Purpose of our investigation was to determine the prognostic role of neurohumoral activation in this disease.

Background: when cardiac involvment, due to iron overload, becomes clinically manifest in patients with TM, clinical course evolves rapidly towards refractory heart failure.

Methods: we compared ANP levels in 31 asymptomatic patients with TM who had normal left ventricular dimensions and normal right and left ventricular systolic function, and in 30 aged and sex matched normal control subjects.

Results: ANP levels were significantly higher in patients with TM compared to control patients (65 ± 14 vs 18 ± 7 pg/ml;$p < 0.001$). Neuropeptide Y, plasmatic renin activity, aldosterone, urinary sodium and catecholamines levels did not differ significantly in the two groups ($p > 0.05$). During follow-up ranging from 72 to 120 months, 13 of the 31 study patients (42%) developed heart failure and/or left ventricular dilatation, and three of these 13 patients died of congestive heart failure.

ANP concentrations, measured at initial evaluation, were significantly higher in these 13 patients with an unfavourable clinical course than in the remaining 18 patients who were clinically stable and had normal left ventricular dimensions during follow-up (96 ± 26 vs 39 ± 34 pg/ml, respectively; $p < 0.001$).

No patients with normal ANP level at baseline experienced heart failure and/or left ventricular cavity dimensions enlargement.

Conclusions: our results show that the plasma level of ANP is a predictor of clinical course and prognosis in asymptomatic patients with Thalassemia Major who have still normal systolic function and normal left ventricular cavity dimensions.

P594 Prognostic implications of QT interval and dispersion in patients with congestive heart failure

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Background: In studies of less than 100 patients with congestive heart failure (CHF), increased QT dispersion has been associated with increased mortality. Large investigations are warranted and we have therefore studied patients enrolled in the Danish Investigation of Arrhythmia and Mortality on Dofetilide (DIAMOND-CHF) Study.

Methods: 1518 patients hospitalised with CHF and left ventricular dysfunction were enrolled in the DIAMOND-CHF Study. Technically acceptable ECGs without atrial fibrillation or bundle branch block were available in 490 patients. QT intervals were measured before randomisation using a digitizer tablet. QT dispersion was calculated as maximum minus minimum QT interval.

Results: During a minimum follow-up of one year, 188 of the 490 patients died. Table 1 below shows two Cox multivariate models of survival including either QTc interval or QT dispersion.

Table 1

	Risk ratio	95% CI		Risk ratio	95% CI
Mean QTc	1.002	0.998–1.007	QT dispersion	1.000	0.996–1.004
Age	1.054**	1.035–1.073	Age	1.053**	1.035–1.072
Heart rate	1.010*	1.000–1.020	Heart rate	1.010	0.999–1.020

**p < 0.0001 *p < 0.05. Both Cox analysis also included gender, dofetilide/placebo, beta-antagonist, diabetes mellitus, and ischaemic heart disease. None of these variables were statistically significant.

Conclusion: Prolongation of the QTc interval and QT dispersion is not associated with increased mortality in a large population of patients with congestive heart failure and reduced left ventricular function.

P595 Prognostic value of neurohumoral activation in left ventricular dysfunction: coronary heart disease versus dilated cardiomyopathy in 428 non-selected patients

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Background: Left ventricular dysfunction (LVD) is associated with neurohumoral activation. The impact of etiology on the neurohumoral activation is unknown.

Question: Are there differences in prognostic meaning of various neurohumoral parameters in patients with coronary heart disease (CHD) versus dilated cardiomyopathy (DCM)?

Methods: 428 consecutive nonselected patients with ejection fraction (EF) ≤ 45% were registrated. Follow-up time was 498 ± 287 (median 454) days. Neurohumoral parameters at discharge were measured. We compared mortality of patients with high and low levels of neurohumoral parameters. Medians of neurohumoral parameters were taken as cut-off points. Patients: 78% male, age 64 ± 11 years, EF 29 ± 9%. Etiology: 60% CHD, 29% DCM, 11% other.

Results: Mortality was 24% in CHD and 16% in DCM (p = 0.02).

n = 428		Mortality in CHD		Mortality in DCM	
	Median	>Median	≤Median	>Median	≤Median
Norepinephrine	298 pg/ml	37%	11%*	25%	9%*
ANP	314 pg/ml	32%	17%*	32%	5%*
Vasopressin	2.8 pg/ml	28%	21%*	28%	5%*
Endothelin	7.6 pg/ml	29%	20%	27%	5%*
Renin	37 μU/ml	26%	21%	20%	12%
Aldosteron	58 pg/ml	27%	21%	21%	10%

*: p < 0.05

Conclusion: 1. Increased norepinephrine- and ANP-values are associated with higher mortality in LVD caused by CHD and DCM. 2. Vasopressin and endothelin are of prognostic importance in LVD caused by DCM but not in CHD. 3. There is no prognostic value of renin and aldosteron in patients with LVD independent of etiology.

P596 A parameter of recovery after a maximal exercise is an independent predictor of survival in patients with left ventricular systolic dysfunction

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Peak VO_2 is an independent predictor of survival in patients (pts) with congestive heart failure (CHF). However, several studies have demonstrated that peak VO_2 predicts survival in pts with severe exercise intolerance. Thus, other parameters are required in order to improve the prognostic information derived from the cardiopulmonary exercise test. We prospectively analyzed the kinetics of VO_2 during exercise and recovery (Rec), in 411 consecutive pts with CHF (53 women, mean age: 53 ± 11.3 years, NYHA I–II/III–IV: 276/135, ischemic cardiomyopathy: 43%). Left ventricular ejection fraction (LVEF) was 30.5 ± 10%, peak VO_2 was 16.5 ± 5.3 ml/min/kg, % of maximal predicted VO_2 (%VO_2) was 60.8 ± 18.6%. We determined the ratio between total VO_2 during exercise and during Rec, the half Rec time of peak VO_2, the % of decrease in VO_2 at 1 min, 3 min (%Rec3), 5 min and 7 min of Rec and the slope of VE/VCO_2 during exercise and recovery. During a median follow-up period of 845 days, there were 80 cardiovascular related deaths (CD), 32 transplantations (8 were UNOS1), 11 non cardiovascular related deaths and no pt was lost to follow-up. Independent predictors of CD + UNOS1 (Cox analysis) were: %VO_2 (p = 0.0001), NYHA (p = 0.0001), %Rec3 (p = 0.0005), peak blood pressure (p = 0.003) and LVEF (p = 0.01). Cardiac event rates (CD + UNOS1) in the 4 subgroups divided according to %VO_2 (< or >50%) and %Rec3 (< or >60%) were: group 1: %VO_2 < 50% and %Rec3 < 60% = 46%; group 2: %VO_2 < 50% and %Rec3 > 60% = 19%; group 3: %VO_2 > 50% and %Rec3 < 60% = 21%; group 4: %VO_2 > 50% and %Rec3 > 60% = 10%.

In conclusion: %Rec3 is an independent predictor of survival in patients with stable congestive heart failure. %Rec3, an easy new parameter to determine, could be useful in the selection of patients at risk of cardiac events.

P597 Comparative value of plasma atrial natriuretic peptide and cardiopulmonary exercise testing to assess prognosis of patients with congestive heart failure

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Although atrial natriuretic peptide (ANP), norepinephrine (NE), and endothelin-1 (ET1)plasma levels have been recognized as valuable predictors of prognosis in patients with congestive heart failure (CHF), their measurements are rarely performed in routine. On the opposite, peak oxygen consumption (VO_2), which is considered as one of the best marker of prognosis, is widely used. Surprisingly, the comparative value of these 2 approaches has been poorly investigated.

We studied 244 patients with CHF(mean age 51 ± 11 years, left ventricular ejection fraction (LVEF) < 40%). All patients had a measurement of plasma ANP, NE, and ET-1 at rest, and underwent a symptom-limited maximal exercise with VO_2 determination.

After a mean follow-up of 868 ± 598 days, 47 deaths and 24 heart transplantations occurred. In univariate analysis, NYHA functional class (p = 0.0003), systolic blood pressure (p = 0.016), LV end diastolic diameter (p = 0.0014), LVEF (p = 0.0002), peak VO_2 (p = 0.0011), percent of maximal predicted VO_2 (p = 0.0006), plasma ANP (p = 0.0001), plasma ET-1 (p = 0.0042) and plasma NE (p = 0.0002) were associated with survival. In multivariate stepwise regression analysis, only plasma ANP (p = 0.0001), NYHA functional class (p = 0.007) and plasma NE (p = 0.035) were independent predictors of survival. Similar results were obtained for the combined end-point of death or heart transplantation, and when the analysis is restricted to patients with a determinable ventilatory threshold.

In this study, plasma ANP appears to be a stronger marker of prognosis than peak VO_2 or percent of maximal predicted VO_2. Measurements of plasma neurohormones should therefore be considered routinely for prognosis assessment in CHF.

P598 Left atrial size predicts mortality in patients with left ventricular systolic dysfunction

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Background: Atrial enlargement has long been known to be associated with increased mortality rate in general population, but little is known about its prognostic power in specific cardiac disease. Left ventricular (LV) systolic dysfunction is frequent and has a dismal prognosis, incompletely predicted by ejection fraction. The concomitant diastolic dysfunction accounts better for symptomatic status and survival. We aimed to verify the prognostic power of atrial enlargement, determined by diastolic impairment, since in pts with LV systolic dysfunction a wide range of atrial size occurs.

Method: An echo-Doppler exam was performed in 205 pts (age 59 ± 10; 85% male) between April 1993 and October 1996, subsequently followed-up through June 1998. Inclusion criteria was an EF < 50%. LA and LV dimensions and EF were taken directly from the echoreport. LA end-systolic volume (LAmax) (area-length method), LV volumes (Simpson' s method) E velocity, E/A and Dte were measured off-line. The end point was survival free from cardiac transplantation (HT).

Results: LA-d was univariately and multivariately the strongest predictor of CHF symptoms. During follow-up 43 pts did not reach the end-point Univariate analysis using a Cox model demonstrated that LA diameter (HR = 1.1; p < 0.000), LAmax (HR = 1.01; p < 0.000), LV systolic diameter (HR = 1.07; p < 0.000), EF (HR = 0.9; p < 0.000), DTe (HR = 0.99; p = 0.06) and E velocity (HR = 4.4;p < 0.005), mitral regurgitation degree (HR = 1.3; p = 0.005) and NYHA (HR = 2.2; p = 0.05) were significant predictors of outcome. However with multiple multivariate models the strongest variable significantly related to mortality remained LA diameter.

Conclusion: LA diameter, easily measured with M-mode echocardiographty, correlates with CHF symptoms and is the strongest prognostic factor in pts with LV systolic dysfunction.

P599 Insertion/deletion polymorphism of the angiotensin I-converting enzyme gene and the evolution of patients with heart failure

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We performed this study to evaluate the association between insertion/deletion polymorphism of the angiotensin I-converting enzyme gene and the time elapsed from birth until the onset of symptoms and the time of survival of patients with heart failure.

Methods: 332 patients with heart failure, aged from 13–68 (43.3 ± 10.6) years, 259 (78%) male and 73 (22%) female, were studied. The etiologies were: idiopathic dilated cardiomyopathy in 125 (37.7%) patients, ischemic cardiomyopathy in 63 (19%), Chagas' disease in 57 (17.2%), hypertensive in 41 (12.3%), alcoholic in 24 (7.2%) and other in 22 (6.6%). The DD, DI and II genotypes were determined by polymerase chain reaction. Recessive, codominant and dominant effects were analised. Kaplan-Meier method and log rank test were used in statistical analysis.

Results: DD genotype was associated with an earlier onset of symptoms in patients with alcoholic cardiomyopathy compared to those in the DI and II group (p = 0.033) as well as an earlier onset of symptoms in patients with hypertensive cardiomyopathy compared to those in the DI and II group (p = 0.024) or with the DI or II (p = 0.048) genotypes. In patients older than 50 years, the DD genotype was associated with a higher mortality compared to those in the DI and II group (p = 0.002) or with the DI or II (p = 0.007) genotypes.

In conclusion, the DD genotype may be associated with an earlier onset of symptoms in patients with alcoholic or hypertensive cardiomyopathy. The DD genotype may be associated with a higher mortality in patients with heart failure older than 50 years.

P600 Viability on combined low–high dose dobutamine echocardiography predicts improvement in LVEF, symptoms and event-free survival

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DSE can predict improvement of wall motion after revascularization. The relation between viability, improvement of function, improvement of heart failure symptoms and long-term prognosis has not been studied. This study was designed to address, in patients with severe ischemic left ventricular dysfunction, whether dobutamine stress echocardiography (DSE) can predict improvement of left ventricular ejection fraction (LVEF), functional status and long-term prognosis after revascularization.

Methods: We studied 68 patients with DSE before revascularization; 62 patients underwent resting echocardiography/radionuclide ventriculography before and 3 months after revascularization. Long-term follow-up data (NYHA functional class, CCS classification and events) were acquired up to 2 years.

Results: Patients with ≥ 4 viable segments on DSE (group A, n = 22) improved in LVEF at 3 months (from 27 ± 6% to 33 ± 7%, P < 0.01), in NYHA functional class (from 3.2 ± 0.7 to 1.6 ± 0.5, P < 0.01) and in CCS classification (from 2.9 ± 0.3 to 1.2 ± 0.4, P < 0.01); in patients with < 4 viable segments (group B, n = 40) LVEF and NYHA functional class did not improve, while CCS classification improved significantly (from 3.0 ± 0.8 to 1.3 ± 0.5, P < 0.01). A higher event-rate was observed at long-term follow-up in group B vs group A (47% vs 17%, P < 0.05).

Conclusions: Patients with substantial viability on DSE demonstrated improvement in LVEF and NYHA functional class after revascularization; viability was associated with a favorable prognosis following revascularization.

P601 Can variations of mitral regurgitation during exercise be used to predict adverse events in patients with chronic heart failure?

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Background: in patients with chronic heart failure (CHF) mitral regurgitation at rest is an important predictive marker of adverse outcome. The prognostic significance of variations of mitral regurgitation (MR) during exercise has not, however, been investigated.

Objective: this study was performed in order to evaluate MR variations during exercise and to determine the prognostic power of these changes.

Methods: 55 consecutive patients with CHF (EF 24 ± 7%) who were in sinus rhythm and in optimized medical therapy, performed transthoracic echo-Doppler at baseline and during bicycle ergometry. MR was quantified by echo-Doppler. All measurements were made at rest and during exercise. According to MR at baseline and during exercise we identified the following groups: MR− (absence MR), MR+ (presence of MR), MR↑ (MR increase). Over a follow-up of 22 ± 13 months cardiac events, defined as cardiac death, heart transplant in status 1 and heart failure requiring hospitalization, were evaluated.

Results: hemodynamic profile and functional class at baseline were similar in all subgroups. Maximal workload capacity was 50 ± 20 watts. 17/46 (37%) patients developed mitral regurgitation during exercise. 8/9 (89%) patients had increased MR and in one patient mitral regurgitation was unchanged during exercise.

	Baseline			Exercise		
	ALL	MR+	MR−	MR−	MR+	MR↑
Patients	55	9	46	29	17	8
Events	29	8	21	7	14	8
% pts	53%	89%	45%	24%	82%	100%

Logistic regression analysis showed the mitral regurgitation at baseline and its changes during exercise provided the best estimate of risk: risk ratio (95% CL): 26.6 (5.1–137).

Conclusions: in patients with CHF and without mitral regurgitation at rest, exercise induced MR in 37%. Variations of MR during exercise identified a subgroup with an increased risk of adverse cardiac events. These data need to be verified in a multicenter, prospective, clinical trial.

P602 Heart rate variability enhances the prognostic value of established parameters in patients with chronic heart failure

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Purpose: The heart rate variability assessed from the 24-hr-ECG (HRV) during sinus rhythm has been proposed as a prognostic parameter in patients with chronic heart failure (CHF). The aim of this prospective unicenter study was to evaluate if HRV has a prognostic value additional to that of the widely used parameters left ventricular ejection fraction (LVEF) and peak oxygen consumption during cardiopulmonary exercise testing ($peakVO_2$).

Methods: 222 patients (with sinus rhythm) (age 54 ± 1 yr, male:female 86:14%) with dilative ($n = 151$) or ischemic ($n = 71$) cardiomyopathy with marked LV dysfunction (LVEF < 40% measured by radionuclide ventriculography) were included. Data were analyzed by uni- und multivariate Cox regression.

Results: During a mean follow-up of 15 ± 1 months (± SE), 38 patients (17%) died (all due to cardiac events) ("†"), and 45 (20%) were hospitalized due to deterioration of CHF ("HOSP"). The HRV parameter SDNN (standard deviation of mean interval between normal beats) was lower in patients with "† or HOSP" in comparison to patients without adverse events ("free") (118 ± 6 vs. 142 ± 5 ms), as well as LVEF (18 ± 1 vs. 23 ± 1%) and $peakVO_2$ (12.8 ± 0.5 vs. 15.6 ± 0.5 ml/min/kg) ($p < 0.01$ each). *Univ*ariate analysis revealed that each of these 3 parameters was unconfounded by the two others and was a predictor for "† or HOSP" vs. "free" and for "†" vs. "alive" (SDNN: $p = 0.0001$ and $p = 0.03$, LVEF: $p = 0.0001$ and $p = 0.0002$, $peakVO_2$: $p = 0.0007$ and $p = 0.002$). In the *multi*variate analysis SDNN enhanced the prediction of "† or HOSP" vs. "free" given by LVEF and $peakVO_2$ ($p < 0.05$), but not of "†" vs. "alive". None of other traditional parameters included in the analysis, such as cardio-thoracic ratio, heart rate, plasma concentrations of sodium, atrial natriuretic peptide and norepinephrine, improved the prognostic power of LVEF and $peakVO_2$.

Conclusions: In CHF patients with sinus rhythm, HRV can be considered as an independent prognostic parameter. It enhances the power of the widely used parameters LVEF and $peakVO_2$ in the prediction of the adverse events "cardiac death or hospitalization due to worsening of CHF". Thus, the easily measurable HRV improves risk stratification in patients with CHF.

P603 Endothelin-1 is a better important prognostic predictor than atrial and brain natriuretic peptide in elderly inpatients for rehabilitation

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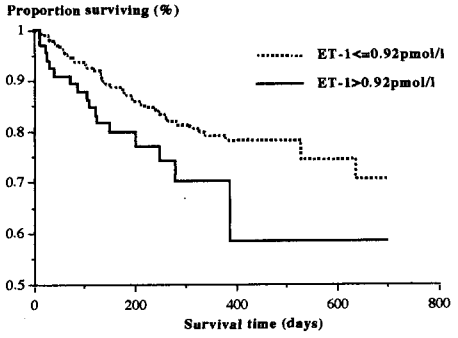
Purpose: The purpose of this prospective study was to evaluate the prognostic value of plasma endothelin-1 (ET-1) in comparison with atrial and brain natriuretic peptide (ANP, BNP) in elderly inpatients for rehabilitation.

Methods: Our 252 patients consisted of 81 men and 171 women, aged 65 to 101 years (83.9 ± 7.7 y; mean ± SD). Their diseases were cerebrovascular diseases (74%), cardiovascular diseases (23%), hypertension (34%), diabetes mellitus (14%), chronic renal failure (6%) and hyperlipidemia (11%). The endpoint was mortality due to all causes.



Kaplan-Meier survival plot for inpatients subdivided into 2 groups according to the upper normal ET-1 limit (0.92 pmol/l). (P = 0.043, Log-Rank test.)

Results: We followed up for 311 ± 119 days, during which time 56 deaths occurred (22 pneumonia, 12 heart failure, 5 cancer, 9 cerebral infarction and 8 other causes). The levels of plasma ANP, BNP and ET-1 in the cardiac deaths (n = 12) were greater than those in the non-cardiac deaths (n = 44), but these differences were not significant. A multivariate Cox proportional hazards regression analysis revealed that the following were significant independent contributors to the endpoint: ET-1, male gender, history of hypertension, serum creatinine, triglyceride and albumin. However, ANP and BNP were not prognostic indicators in this study population. Patients with an ET-1 level greater than 0.92 pmol/l had a significantly higher mortality rate than did those with a lower level (n = 65 vs 187, 26.2% vs 20.9%, P = 0.043, Log-Rank test).

Conclusion: In conclusion, plasma ET-1 may be superior to ANP and BNP as a predictor of mortality in elderly inpatients for rehabilitation.

P604 Hospitalisations and deaths in a population-based cohort of incident (new) cases of heart failure

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Background: The number of hospital admissions due to heart failure has been rising steadily in all developed countries. The factors predictive of hospitalisation on a population basis are not known.

Methods: All incident (new) cases of heart failure arising in a population of 292 000 in Bromley, South London, UK were identified by in-patient monitoring and from a rapid-access heart failure clinic over a period of 15 months. Cases were followed up for death and hospitalisation.

Results: 332 incident cases of heart failure were identified (178 M: 15 4F; median age 77 years). 211 (64%) were identified from acute admission to the hospitals serving the population and 121 (36%) from the rapid access clinic. During the follow-up period (median 14 months) there were 78 deaths (86% due to cardiovascular disease). Survival was 87% at 1 month, 81% at 6 months and 80% at 12 months. During the follow-up period there were 209 hospitalisations in 127 (38%) of the 332 patients. 78 patients had 1 subsequent hospitalisation and 49 had 2 or more hospitalisations (maximum of 5). 44% (93/209) of the admissions were related to the worsening of heart failure. The average duration of a hospital admission was 5 days (range 1–84 days). In those that survived the first 4 weeks after diagnosis, the factors independently predictive of subsequent hospitalisation for worsening of heart failure or cardiovascular death were: previous history of vascular disease (p = 0.001); serum sodium (p = 0.02); first presentation as inpatient rather than outpatient (p = 0.04); and age (p = 0.07).

Conclusions: patients with a new diagnosis of heart failure have a high rate of subsequent hospitalisation with almost half of the admissions being related to worsening of heart failure. A subgroup of patients can be identified at especially high risk of death or hospitalisation. Interventions designed to reduce hospitalisation should be targeted at this group.

P605 How right ventricular function relates to pulmonary artery pressure in advanced congestive heart failure: prognostic implications

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Aim of the study was to ascertain as to whether the evaluation of the coupling between right ventricular function and pulmonary artery pressure may improve the prognostic assessment in pts with congestive heart failure (CHF).

Methods: Between 1992 and 1998, 380 consecutive pts (mean age 51 years) with chronic CHF due to severe left ventricular systolic dysfunction (LVEF < 35%) underwent right heart catheterization; all pts received an optimized pharmacological treatment. Etiology was primary dilated cardiomyopathy (DCM) in 66% and ischemic heart disease (IHD) in 34% of pts; pts with valvular heart disease or miscellaneous etiology were excluded.

Results: In the whole population an inverse relationship was observed between thermodilution-derived right ventricular ejection fraction (RVEF) and mean pulmonary artery pressure (PAPm), with an "r" coefficient of −0.66 (p < 0.001); this relationship was similar in DCM and in IHD pts. During a follow-up period of 17 ± 9 months 104 pts died. The population was subdivided into 4 groups according to the presence or absence of pulmonary hypertension (cut-off = PAPm > 20 mmHg) and to the presence or absence of RV dysfunction (cut-off = RVEF < 30%). At the Cox survival analysis the pts in the "high PAPm-low RVEF" group (N = 209) had the worst prognosis: the hazard ratio indicated a risk 5 times larger than that of the pts in the "low PAPm-good RVEF" group (N = 97) (95% CI: 2.9–9.8, p = 0.000) and 2.4 times larger than that of the pts in the "high PAPm-good RVEF" group (N = 28) (95% CI: 1.1–5.5, p = 0.03). The prognosis of the pts in the "low PAPm-low RVEF" group (N = 44) was indistinguishable from that of the pts in the "low PAPm-good RVEF" group or in the "high PAPm-good RVEF" group.

Conclusions: In pts with heart failure due to DCM or IHD, RVEF is inversely related to PAPm. When pulmonary artery pressure is normal, RV dysfunction is uncommon and shows no clear impact on prognosis. In the presence of pulmonary hypertension however, the coexistance of RV dysfunction is clearly associated with a worse prognosis.

P606 Prognostic value of 6-minute walk corridor test in patients with congestive heart failure

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Aim of present study was to evaluate the prognostic value of 6-minute walk test in unselected patients with mild to moderate congestive heart failure (CHF) and to compare it to other indexes of cardiovascular function.

Methods: 214 patients (119 men and 95 women, mean age 64 years) with CHF who were consecutively admitted to our institution from 01.01.94 to 06.30.95 were followed-up for a median of 34 months to assess mortality

Results: At the end of follow-up 66 patients (34%) died, 63 for cardiovascular causes, 2 for cancer and 1 for stroke. 5 patients underwent heart transplantation. In patients who walked less than 300 m at 6 minute-walk test survival was 62% in comparison to 82% in patients who walked between 300 and 450 m and patients who walked >450 m.

Mortality was was significantly higher in patients with lower LV ejection fraction (<30%) and higher NYHA functional class (III-IV). At univariate analysis no significant relation was found between survival and respectively peak VO_2 and AT:

	Hazard ratio	(CI 95%)	Z	p
Age	1.007	(0.98–1.03)	0.600	0.58
Etiology	1.37	(0.82–2.28)	1.231	0.21
LVEF (%)	0.96	(0.94–0.97)	–4.37	0.000
LVFS(%)	0.92	(0.88–0.95)	–4.61	0.000
LVEDD	1.04	(1.02–1.06)	3.61	0.000
NYHA class	2.58	(1.87–3.57)	5.78	0.000
AT	0.99	(0.85–1.15)	–0.12	0.85
pVO_2	1.01	(0.91–1.11)	0.202	0.84
6 min WCT	0.995	(0.993–0.997)	–4.04	0.000
MPAP	1.03	(1.00–1.06)	2.19	0.028
E/A ratio	1.23	(0.90–1.69)	1.33	0.181

At multivariate analysis using Cox-stepwise regression model LV fractional shortening ($p < 0.009$) and the distance covered at 6 minute walk test ($p < 0.000$) were the strongest prognostic markers (table)..

Conclusion: Distance covered at 6 minute walk test is a simple and useful independent prognostic marker of subsequent cardiac death in patients with mild to moderate CHF.

P607 N-terminal proANP: a marker of clinically significant diastolic dysfunction

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Diastolic dysfunction as a cause of congestive heart failure has been considered as common as systolic heart failure. The long-term prognosis in diastolic heart failure is less severe, but no prognostic marker has been identified in this condition. In a population of patients with idiopathic congestive heart failure, we studied long-term survival and symptoms and the relation to N-terminal proANP in patients with diastolic dysfunction. Because concentration of N-terminal proANP is increased by elevated filling pressures, this peptide might reflect the degree of congestive heart failure.

Method: In a group of patients with idiopathic heart failure from western Sweden (n = 293), 60 patients with normal systolic function (EF < 40%), and concomitant signs of disturbed left ventricular function were identified. N-terminal proANP was analysed in relation to long-term survival (7 years).

Results: Patients with increased concentration of N-terminal proANP >1200 pmol/L had significantly poorer survival as compared with patients with lower values. In a multivariate analysis, N-terminal proANP was the only independent variable that correlated to mortality: RR 2.71 (95%CI 1.32–5.59), P = 0.007. A larger proportion of patients with high concentration experienced death or hospitalisation during follow-up (67% vs. 33%, P = 0.028). They also tended to develop more symptoms and to receive more diuretics (93 ± 66 vs. 55 ± 42 mg, P = 0.015).

Conclusion: Patients with diastolic heart failure and high concentration of N-terminal proANP experienced clinically significant events, with increased mortality and morbidity. We postulate that an elevation of plasma N-terminal proANP might be one of few markers of clinically important diastolic dysfunction.

P608 Prognostic value of circulating cardiac natriuretic peptides in patients with coronary artery disease

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Natriuretic peptides have been shown to be poweful prognostic indicators after acute myocardial infarction and in chronic heart failure. Whether natriuretic peptide levels are predictive of survival in patients with coronary artery disease (CAD) without symptomatic heart failure is unknown.

Methods: Plasma concentrations of atrial natriuretic peptide (ANP), N-terminal pro-atrial natriuretic peptide (N-ANP), and brain natriuretic peptide (BNP) were measured in 215 consecutive patients (mean age 60 (± 10) years, 80% male) with angiographic evidence of significant CAD. Patients with symptomatic heart failure (NYHA functional class III or IV) were ineligible for participation in the study.

Results: During a median follow-up of 52 months 10 patients died. By univariate Cox proportional hazards regression a history of diabetes mellitus, ($p = 0.002$), left ventricular dysfunction, defined as ejection fraction less than 45% ($p = 0.024$), the presence of pathological Q-waves on the electrocardiogram ($p = 0.044$) and plasma levels of N-ANP ($p = 0.025$) and BNP ($p = 0.030$) were identified as significant predictors of all-cause mortality. In multivariate models N-ANP ($p = 0.037$) and BNP ($p = 0.042$), but not ANP ($p = 0.244$) added significant prognostic information to a history of diabetes mellitus ($p = 0.0008$) and left ventricular dysfunction ($p = 0.0048$).

Conclusion: Plasma N-ANP and BNP provide prognostic information beyond that obtained from standard risk markers in patients with CAD without symptomatic congestive heart failure. Natriuretic peptide determination may have a role in risk stratification of this low-risk patient group.

P609 Chronic heart failure in the very elderly: survival and prognostic factors in 186 patients over 70 years of age

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Chronic heart failure (CHF) is a disease with high morbidity and mortality and increasing incidence and prevalence, particularly in the elderly, but little is known about prognosis in this population. Our aim is to describe survival and to assess whether there are any predictors of mortality in this subset.

Methods: we retrospectively evaluated 186 consecutive patients with CHF over 70 years of age (mean age 74 ± 4, range 70–87; 54 female). Clinical, biochemical, and echocardiographic data were recorded and cardiopulmonary exercise test was performed (peak VO_2, mean 15.1 ± 4.7 ml/min/kg). Left ventricular ejection fraction (LVEF%) was determined by radionuclide angiography (39 ± 17). The primary endpoint of the study was all-cause mortality.

Results: at the end of follow-up (42 ± 32 months, range 6–172), 55 patients (29%) had died. No patient received heart transplantation. 63% of patients had preserved systolic function, defined as LVEF>45%. Using Cox proportional hazard model, at the univariate analysis the following parameters were identified as the strongest predictors of mortality: age (HR = 1.1; $p < 0.0001$), NYHA class (HR = 3.1; $p < 0.0001$), peak VO_2 (HR = 0.88; $p = 0.014$), left ventricular end-systolic diameter on echocardiography (HR = 1.5; $p < 0.0001$), LVEF% (HR = 0.9; $p = 0.0003$) systolic blood pressure (HR = 0.9; $p = 0.0003$) and plasma sodium (HR = 0.9; $p = 0.002$). The multivariate analysis, with the most powerful model obtained combining NYHA class, age, LVEF% and peak VO_2, showed that only NYHA class ($p = 0.0028$) and age ($p = 0.03$) were independent predictors of mortality. At the log-rank test, patients with systolic dysfunction had a worse prognosis compared to those with preserved systolic function (survival at 100 months, 27% vs. 67%, $p = 0.0092$).

Conclusions: prognosis in elderly patients with CHF is poor. NYHA functional class and age are the strongest prognostic factors in this population. Patients with LV systolic dysfunction seem to be at particularly high risk of death.

MEDICAL TREATMENTS: INOTROPES, ACE INHIBITORS, AT2 BLOCKERS, VASODILATORS AND OTHERS

P610 Effects of levosimendan, a novel Ca^{2+} sensitizer, on ionic currents of human cardiac cells

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The chemical structure of levosimendan (LS) is related to pimobendan, a Ca^{2+} sensitizing and PDE III inhibitory positive inotropic agent. In experimental animals, LS was reported to exert its action by increasing Ca^{2+} sensitivity of myofilament. However, in human hearts, the mechanism of LS actions has not been clarified. The present study was undertaken to elucidate the elctrophysiological actions of LS in human cardiac cells using whole-cell voltage clamp technique. LS stimulted the nifedipine sensitive Ca^{2+} current ($I_{Ca(L)}$) which was evoked by applying step pulses from a holding potential of −40 mV. Stimulation of $I_{Ca(L)}$ by LS was dose-dependent with EC_{50} value of 0.056 μM (n_H = 1.2), which is close to the effective concentration in human subjects (i.e., 0.02 μM). Even at 0.01 μM, LS stimulated $I_{Ca(L)}$ by 14 ± 3% (n = 4). As maximal effect, $I_{Ca(L)}$ was increased by 131 ± 12% at 1 μM LS (n = 5). In the presence of 1 μM LS, application of rolipram (10 μM, a selective PDE-IV inhibitor) or IBMX (100 μM, a non-selective PDE inhibitor) produced further stimulation of $I_{Ca(L)}$ by 250 ± 45% (n = 5) and 270 ± 72% (n = 5), respectively. This suggests that LS is a selective inhibitor for PDE III. On the other hand, a higher dose (10 μM) of LS stimulated the outward currents evoked by ramp pulses, and they intersected at the expected value for E_K. Increase in the outward current (at −40 mV) was 21 ± 7 pA/pF (n = 5), and it was completely abolished by 2 μM glibenclamide, suggesting that it was ATP-sensitve K^+ (K_{ATP}) current. In conclusion, the positive inotropic effect of LS on human heart may be partly due to the increase in $I_{Ca(L)}$, because clinically relevant concentrations of LS stimulated it. Furthermore, LS might act as a cardioprotective agent by opening K_{ATP} channels in the pathophysiological conditions such as regional ischemia.

P611 Functional effects of mild hypothermia in isolated human myocardium

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Mild hypothermia increases contractility in some animals species but its direct effects in human myocardium are not characterized. We investigated the functional effects and the mechanism of action of mild hypothermia in isolated human ventricular myocardium from 5 nonfailing and from 20 end-stage failing hearts.

Methods: Isolated muscle strip preparations, isometric contractions, electrical stimulation (1 Hz). Influence of stepwise reduction in organ bath temperature from 37°C to 29°C on isometric twitch force, intracellular Ca transients (aequorin method) and sarcoplasmic reticulum (SR) Ca content (rapid cooling contractures). Furthermore, the influence of mild hypothermia (31°C) on force-frequency behavior was tested.

Results: Stepwise cooling resulted in a significant increase in isometric force to maximally 189 ± 16% in nonfailing (n = 7) and to 201 ± 23% in failing (n = 20) myocardium (37°C vs. 29°C; $p < 0.05$). The inotropic effect was associated with a significant prolongation of time-to-peak tension and relaxation times. In aequorin-loaded muscle strips (n = 10), reduction of temperature to 30°C increased force to 165 ± 22% without any increase in aequorin light emission. Likewise, the inotropic response to hypothermia was not associated with an increase in RCCs. At 37°C, the isometric force did not change with increasing stimulation rates up to 2.0 Hz and then slightly declined at 2.5 and 3.0 Hz (blunted force-frequency response in failing myocardium). However, after cooling these muscle strips to 30°C at 0.5 Hz, despite an initial inotropic effect isometric force steeply declined already at stimulation rates > 1.5 Hz (from 15.5 ± 3.9 to 6.2 ± 0.9 mN/mm², $p < 0.05$). The deterioration of force-frequency behavior at 30°C was due to a pronounced increase in diastolic tension at higher stimulation rates (by maximally 3.1 ± 0.7 mN/mm² at 37°C, and by 10.8 ± 2.2 mN/mm² at 30°C, $p < 0.05$).

Conclusion: Mild hypothermia exerts significant positive inotropic effects in human ventricular myocardium. These effects are not related to increased intracellular Ca transients or increased SR Ca content and may result from enhanced myofilament Ca responsiveness. However, at higher stimulation rates, diastolic dysfunction occurs under hypothermic conditions. Mild hypothermia may be a new therapeutical approach in patients with severe cardiogenic schock.

P612 L-NAME is effective in the treatment of cardiogenic shock

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Objective: To assess the safety and efficacy of L-NAME (a nitric oxide synthase inhibitor) in the treatment of cardiogenic shock.

Methods: Four consecutive patients with persistent cardiogenic shock despite treatment by mechanical ventilation, intra-aortic balloon pump (IABP) and high-doses of cateholamines, in whom all revasculrization options have been exhausted and were deemed beyond treatment by two expert cardiologists were enrolled in this study. All patients were continuously monitored by Swan-Ganz catheter, arterial line, pulse oxymetry and arrhythmia monitor. L-NAME (Clin-Alpha, Cal-Biochem) was administered as an IV bolus of 0.5 mg/kg and continuous drip of 1 mg/kg/hour for 6 hours. During treatment inotrope doses, fluid administration, mechanical ventilation and IABP were kept constant. Results: Within 10 minutes of L-NAME administration, mean arterial blood pressure increased from 78 ± 7 to 100 ± 8 mmHg (+28%), Urine output increased from 118 ± 100 cc/hour to 183 ± 117 cc/hour (+55%). The pulse rate has not changed 101 ± 13 versus 102 ± 31 beats/min. The cardiac output decreased at first (during the steep increase in blood pressure and afterload) from 3.1 ± 1.4 l/min. to 2.7 ± 1.2 l/min. (−13%) however it gradually increased to 2.9 ± 1.0 l/min after 5 hours of treatment (−6%). The Wedge pressure increased initially from 25 ± 15 to 27 ± 15 mmHg (+8%), however by 5 hours of treatment it decreased below baseline to 22 ± 11 mmHg (−12%). No adverse events, new ischemia nor arrhythmias were detected during L-NAME administration. Two out of four patients were able to be weaned from mechanical ventilation and IABP during L-NAME administration.

Conclusion: In this preliminary communication of an ongoing study, L-NAME administration has favorable clinical and hemodynamic effects on patients in cardiogenic shock. It increases mean arterial blood pressure and urine output with marginal effect on heart rate, cardiac output and pulmonary wedge pressure. No adverse effects could be detected.

P613 Blood pressure independent effects of AT_1 receptor blockade on left ventricular dysfunction in hypertensive transgenic (mRen2) 27 rats

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We investigated the effects of long term treatment with low dose eprosartan (E), an AT_1 receptor antagonist, and low-dose quinaprilat (Q), an ACE inhibitor, on cardiac hypertrophy and -function in transgenic rats (TGR) with renin overexpression (TGR (mRen2) 27).

Five groups of TGR and one control group of Sprague-Dawley (SD) rats (n = 12, each) were treated for 20 weeks via osmotic mini pumps implanted intraperitonealy. SD: 0.9% NaCl; TGR: 0.9% NaCl; TGR-E6: E 6 mg kg^{-1} d^{-1}; TGR-E60: E 60 mg kg^{-1} d^{-1}; TGR-Q: Q 0.1 mg kg^{-1} d^{-1}; TGR-QE6: E 6 mg kg^{-1} d^{-1} combined with Q 0.1 mg kg^{-1} d^{-1}. Body weight (BW), systolic arterial blood pressure (SBP), left ventricular weight (LVW), left ventricular enddiastolic pressure (LVEDP), systolic dP/dt (SHI), and diastolic dP/dt (DHI) were measured after treatment:

	SD	TGR	TGR-E6	TGR-E60	TGR-Q	TGR-QE6
BW (g)	581 ± 14	558 ± 10	570 ± 15	544 ± 9	527 ± 8$^{\$}$	569 ± 10
SBP (mmHg)	128 ± 3$^{*\#}$	186 ± 5	185 ± 5	129 ± 5$^{*\#}$	153 ± 5*	159 ± 3*
LVW (mg g^{-1})	2.2 ± 0.06*	2.9 ± 0.1	2.3 ± 0.06*	1.8 ± 0.05$^{\&}$	2.1 ± 0.06*	1.9 ± 0.02$^{*\#}$
LVEDP (mmHg)	4.5 ± 0.4*	8.4 ± 0.5	5.3 ± 0.4*	4.8 ± 0.4*	6.7 ± 0.8*	4.2 ± 0.2$^{*\#}$
SHI($s^{\pm1}$)	27.1 ± 0.32*	23.7 ± 1.0	26.4 ± 0.32*	26.8 ± 0.53*	27.2 ± 0.8*	27.4 ± 0.33*
DHI(s^{-1})	24.8 ± 0.64*	20.5 ± 0.5	23.3 ± 0.54*	24.4 ± 0.49*	22.4 ± 0.99*	26.1 ± 0.56$^{*\#}$

Mean ± SEM, n = 6–12, $p < 0.05^{*}$ vs R, $^{\#}$ vs Q, $^{\$}$ vs SD, $^{\&}$ vs E6

Conclusion: Low dose E did not decrease blood pressure, but still prevented left ventricular hypertrophy and -dysfunction in hypertensive TGR (mRen2) 27. Furthermore, combined E with Q had an additional effect. Therefore, this study is the first to demonstrate that left ventricular dysfunction in hypertensive Ren-2 rats can be prevented by AT_1 blockade, even without lowering blood pressure. This suggests an important role for enhanced AT_1 receptor stimulation in the pathophysiology of comparable hypertension related left ventricular dysfunction.

P614 Effect of age on outcome in the ATLAS study

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The mean age of patients (pts) with chronic heart failure (CHF) in the community is about 75 years (yrs), but few pts > 75 yrs have been randomised in the landmark studies of CHF. Age may be a major determinant not only of the likelihood of treatment with an ACE inhibitor (ACEi) but also of the dose employed.

In the ATLAS study 3,164 pts with CHF and left ventricular ejection fraction ≤ 30% were randomised to either low dose (LD) 2.5–5 mg or high dose (HD) 32.5–35 mg lisinopril (Lis) and followed for a median of 46 months. 988 (31%) pts were ≥70 yrs and 437 (14%) ≥75 yrs. Baseline characteristics of older pts revealed they were more often women, more likely to have ischaemic heart disease, atrial fibrillation, renal dysfunction and a lower body weight. Mortality and morbidity rates by age are shown in the table.

	<60 yrs (n = 990)	60–69 yrs (n = 1186)	70–74 yrs (n = 551)	≥75 yrs (n = 437)
All Cause Mortality (%)	34%	43%	52%	57%
Death or Hosp (%)	76%	82%	86%	88%
Death or CHF Hosp (%)	49%	58%	64%	69%
No.Hosp/100 pt yrs	74	89	98	108
No.CHF Hosp/100 pt yrs	24	32	31	38

Compared to LD, HD Lis showed greater reductions in the composite (principal secondary) end-point of all-cause (AC) mortality or hospitalisation (hosp), death or hosp for CHF, the total number of AC hosp (p = 0.021) and CHF hosp (p = 0.002). Trends to a reduction in AC mortality (primary end-point) with HD Lis were not significant. Analyses showed no interaction between age above or below 70 yrs (pre-specified) or above or below 75 yrs (post-hoc) and effect of Lis dose, suggesting that the benefit of HD on outcome was unaffected by age. However, HD Lis reduced the risk of AC mortality by 12% (p = 0.036) in pts < 75 yrs. Although ATLAS did not show statistical evidence for less benefit of HD Lis in older pts, few elderly patients with CHF and concomitant problems such as renal dysfunction were randomised in the ATLAS study. The results of ATLAS should be extrapolated to frail, elderly patients with CHF with caution.

P615 Ramipril reduces ischaemia only when blood pressure is lowered: results of the LORAMI trial

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ACE-inhibitors are proposed to have an antiischemic effect in patients with coronary artery disease (CAD).

Methods: To test this hypothesis we randomised (1:1:1) 346 patients with proven stable CAD and preserved left ventricular systolic function to double blind treatment for 6 months with placebo, low dose (1.25 mg/d) or high dose (5 mg/d) of ramipril. Inclusion criteria included prior myocardial infarction, PTCA, CABG or angina pectoris with ST-segment depression (STD) at a maximal exercise test. All patients had at least 10 minutes of STD at a baseline 48 h Holter. Antiischemic drug effect was measured as reduction of STD (duration and total area of ST-segment depression)between baseline and 6 months treatment.

Results: While no change in STD was found in any of the three treatment groups, a significant antiischemic effect was seen in ramipril patients with ≥20 mm Hg reduction in BP. These patients had a more pronounced antiischemic effect than patients with 10–20 mm Hg BP reduction, while patients with a reduction of <10 mm Hg had no antiischemic effect. The BP-reducing effect was partly dose-related. The ramipril effect on STD during Holter was mainly found in patients in whom heart rate (HR) increased prior to the maximal ST-segment depression. With a more increased HR (+7%, +10% or +15%) a more pronounced effect was seen on STD.

Conclusions: Six months ramipril treatment demonstrated an antiischemic effect as measured by ST-segment depressions during 48 hours Holter in patients with stable CAD and preserved left ventricular systolic function. This was seen only if ramipril induced a clear fall in systolic blood pressure and mainly in patients with increased heart rate prior to ST-segment depression. Patients with increased heart rate prior to myocardial ischemia are considered to have exercise induced ischemia.

Our results indicate, that a group of patients with expected antiischemic effect of an ACE-inhibitor may be identified in a clinically simple manner.

P616 Inhibitory effects of valsartan on angiotensin II-induced release of norepinephrine from rat atria

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The effects of valsartan and other nonpeptide angiotensin II receptor (AT_1) antagonists on the prejunctional actions of angiotensin II were investigated in the isolated left atria of rat. Norepinephrine (NE) stores in the rat atria were loaded with [^{3}H]-NE, and neuronal NE release was deduced from the radioactivity efflux. Angiotensin II (1 micromolar) enhanced (46.5%) the electrical stimulation-induced (SI) efflux of [^{3}H]-NE from the preparation. Valsartan (10 micromolar) did not affect the control SI efflux of [^{3}H]-NE, but inhibited (83.0%) the angiotensin II-mediated augmentation of the response when administered concurrently with the agonist. Comparable inhibitions of the angiotensin II-mediated responses were also effected by a similar concentration of losartan, eprosartan and irbesartan, the other AT_1 antagonists tested. Thus, there appear to be no discernable differences among the four AT_1 antagonists when tested at this concentration, as regards their effects on the prejunctional actions of angiotensin II. Pretreatment of the tissues with a lower, albeit therapeutically pertinent concentration (1 micromolar) of valsartan, also resulted in a significant inhibition (40.4%) of the angiotensin-evoked response. This indicates that valsartan indeed inhibits the prejunctional facilitatory effect of angiotensin II on the release of NE from peripheral sympathetic nerves. Thus valsartan affords the potential therapeutic benefits emanating from such an inhibition in addition to the benefits ensuing from its inhibition of the other pathophysiological actions of angiotensin II.

P617 Excessive in vivo formation of superoxide during metabolism of glyceryl trinitrate but not pentaerithrityl tetranitrate: prevention by antioxidant vitamin c

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Background: Glyceryl trinitrate (GTN) and pentaerithrityl tetranitrate (PETN) are frequently used nitrates in cardiovascular therapy. However, anti-ischemic therapy with nitrates is complicated by the induction of tolerance potentially resulting from a coproduction of reactive oxygen species (ROS) e.g. superoxide ($O_2^{\bullet}$). Until now nitrate-induced increases of formation of ROS *in vivo* have not been reported. Our aim was to analyze the *in vivo* formation of ROS induced by treatment with PETN or GTN and the modulating effect of the antioxidant vitamin C (Vit-C) using electron spin resonance spectroscopy.

Methods: 22.5 mg/kg of spin trap 1-hydroxy-3-carboxy-pyrrolidine (CP-H), which after reaction with ROS forms nitroxyl radical 3-carboxy-proxyl (CP), and 130 μg/kg of GTN or PETN were infused IV. into anesthetized rabbits. Formation of ROS was determined from contents of nitroxyl radical CP in the blood drown from the carotid artery.

Results: Both PETN and GTN show similar vasodilator effects. Formation of CP in blood after infusions of GTN or PETN were 2.0 ± 0.4 μM and 0.98 ± 0.23 μM. Pretreatment with 20 mg/kg Vit-C led to significant decreases in CP formation: 0.27 ± 0.14 μM (Vit-C plus GTN) and 0.34 ± 0.15 μM (Vit-C plus PETN).

Conclusion: *In vivo* infusions of GTN or PETN in rabbits enhance formation of superoxide radicals in the vasculature and can be detected in blood. Thus, formation of peroxynitrite (a strong oxidant) eliciting vascular dysfunction is a relevant consequence. However PETN provokes only a minimal stimulation of ROS formation. The significant effects of Vit-C on nitrate induced ROS production documented by CP formation establish Vit-C as an effective antioxidant *in vivo*.

P618 Formation of reactive oxygen species in blood during in vitro application of pentaerithrityl tetra/tri/di and mononitrate

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Recent studies on the development and prevention of nitrate tolerance report about the decisive role of reactive oxygen species (ROS) in the development of tolerance. The analyses of ROS formation during in vivo nitroglycerin (GTN) and pentaerithrityl tetranitrate (PETN) infusions showed a more favorable ROS during PETN than during GTN. Here ROS develop either through the interaction of PETN-induced NO release with the $O_2^{\bullet}$ radicals in the vessel lumen or during the oxidative metabolism of PETN. In order to test this hypothesis we studied ROS formation in blood following application of pentaerithirityl tetra/tri/di/ and mononitrate.

ROS formation was analyzed in blood of mongrel dogs using an electron spin resonance spectrometer and the ascorbate and thiol resistant spin trap l-hydroxy-3-carboxy-pyrrolidin (CP-H; 0.8 mM). The heparizined blood sample (1250 I.E. heparin/ml) was mixed with CP-H, deferoxamin (50 μM) and with PETN or with a PETN derivative (0.5 mM). Quantification of the formation of $O_2^{\bullet}$ $ONOO^-$ was performed through the inhibition of $ONOO^-$ formation following addition of DMSO (0.1%) to the probe.

The ROS release in blood increased significantly compared to control values from 7.5 ± 0.4 to 11.8 ± 0.3 a.U/min during PETriN and to 32.8 ± 0.6 a.U./min during PETN which was still 3fold less than during administration of GTN. An addition of PEMN and PEDN led to no significant increase in ROS formation. Furthermore an addition of 0.1% DMSO during PETN and its derivatives significantly inhibited ROS formation.

These results justify the statement that the efficacy and rate of release of NO during the metabolism of pentarithrityl tetra/tru/di and mononitrate in blood determines the rate of subsequent peroxynitrite formation. In contrast to GTN (e.g. significant formation of $O_2^{\bullet}$) this may explain the absence of tolerance during administration of PETN in vivo.

P619 Transforming growth factor-β-induced differentiation of cardiac fibroblasts to myofibroblasts is accompanied by an increase in angiotensin-converting enzyme activity

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Cardiac fibrosis is accompanied by an increase in the level of transforming growth factor β (TGF-β) and by the appearance of angiotensin converting enzyme (ACE) and myofibroblasts in the fibrotic tissue. Whether TGF-β induces ACE activity during TGF-β-induced differentiation of fibroblasts to myofibroblasts is investigated in the present study.

The effect of TGF-β on the ACE activity, the proliferation and the differentiation of cardiac fibroblasts (passage 2), obtained from male adult Wistar rats, is studied. Cells are characterised as fibroblasts or myofibroblasts by morphology, by Western blotting and immunostaining with antibodies to von Willebrand factor (endothelial cells), to desmin (vascular smooth muscle cells), to vimentin (fibroblasts) and to α-smooth muscle actin (α-SMA) (myofibroblasts). DNA synthesis is estimated by [^{3}H]thymidine incorporation and cells are counted with a hemacytometer. The assay for ACE is based on the conversion of Hippuryl-Histidyl-Leucine to Histidyl-Leucine which is quantified fluorometrically.

TGF-β (in a concentration range from 0.2 to 10.0 ng/ml) inhibits dose-dependently the proliferation of fibroblasts cultured for 7 days in its presence. At 10 ng/ml, TGF-β decreases the cell number by 65.0 ± 2.3% (n = 5, SEM) and the [^{3}H]thymidine incorporation by 95.4 ± 1.5%. The basal ACE activity in fibroblasts (13.4 ± 2.4 pmol/min per 106 cells) is inhibited by 94.4 ± 2.0% in the presence of 1 μM lisinopril. TGF-β does not induce ACE activity at concentrations less than 5 ng/ml. After 7 days, but not after 1–3 days, TGF-β at 5 and 10 ng/ml induces an increase in the ACE activity by 51.3 ± 7.4% and 82.4 ± 8.0%, respectively, as well as the appearance of α-SMA, a marker of myofibroblasts.

Our data show that TGF-β induces a change in the cell morphology and an increase in the ACE activity as well as in the level of α-SMA. We suggest that TGF-β induces the differentiation of fibroblasts to myofibroblasts which contain ACE activity.

P620 Long-term effects of pentoxifylline in patients with idiopathic dilated cardiomyopathy: One-year results

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We recently reported a significant improvement of left ventricular (LV) function in patients with idiopathic dilated cardiomyopathy (DCMO) treated with pentoxifylline. However, if this effect is maintained at 1 year is unknown.

Methods: in a prospective, double blind, randomized, placebo controlled trial we enrolled 49 patients (mean age 52 ± 11 years, 57% males) with idiopathic DCMO. Patients were randomized to pentoxifylline 400 mg TDS or placebo. All patients received treatment with diuretics, digoxin and ACE inhibitors. Clinical, echocardiographic and radionuclide evaluation were performed at baseline (B), at 6 months (6 m) and at 1 year (1 y) after randomization.

Results: 12 patients died (9 in the placebo group ($p = 0.05$ between groups). All deaths were due to progression of heart failure. LV ejection fraction improved from 21 ± 8% at B to 35 ± 17% at 6 m and 30 ± 16% after 1 y of treatment with pentoxifylline ($p = 0.002$ B vs 6 m and $p = 0.004$ B vs 1 y. P = NS 6 m vs 1 y). No significant changes were observed in the placebo group. TNF-α and IL 6 plasma levels significantly declined with pentoxifylline (6.4 ± 5 to 2.0 ± 1 pg/ml, $p = 0.003$; and 5.4 ± 4 to 1.8 ± 1 pg/ml, 0.001 respectively). No significant reduction in the cytokine levels were noted in the placebo group.

Conclusion: treatment with pentoxifylline is associated with a sustained improvement on LV function in patients with idiopathic DCMO.

P621 Optimal chronic intravenous therapy in managing unloading therapy and improving clinical outcome in severe congestive heart failure

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Background: In patients with severe heart failure awaiting transplantation, intravenous inotropic or vasodilator drugs are frequently employed in the attempt to obtain hemodynamic control. The choice between these treatments is often based on clinical criteria. The efficacy of chronic dobutamine (DOB) or nitroprusside (NTP) infusion have not been prospectively compared.

Aims: the aim of this study was to compare the efficacy of both drugs in managing unloading therapy and improving clinical status.

Methods: 105 consecutive patients with severe heart failure (EF 19 ± 6%) who received 7 ± 3 γ/kg/min 12 h/day of DOB (35 pts) for 9.2 ± 5 days, or 0.76 ± 0.99 γ/kg/min 12 h/day NTP (70 pts) for 10.8 ± 6 days as a first-line therapy were evaluated. Hemodynamic profile, NYHA functional class, unloading management defined as Ace-inhibitor (ACE) optimization and clinical outcome defined as weaning from intravenous therapy, heart failure requiring hospitalization, cardiac death, and heart transplantation in status 1 (HTX1) were considered in two groups.

Results: hemodynamic profile and functional class at baseline were similar in both groups. Unloading therapy was significantly greater in patients receiving NTP than in those receiving DOB (ACE: 127 ± 30 vs 80 ± 46 mg $p < 0.002$). Weaning from intravenous support was significantly more frequent among patients receiving NTP (73% vs 45% $p < 0.006$). In the NTP subgroup, cardiac death due to CHF and HTX 1 occurred less than in the DOB subgroup (36% vs 88% $p < 0.0001$). Time to adverse clinical outcome from initiation of therapy was longer among patients receiving NTP (245 ± 70 vs 117 ± 93 days $p < 0.007$). The cost of daily therapy was significantly higher in patients receiving NTP ($14.4 vs $11.5 $p < 0.03$).

Conclusions: in patients with severe congestive heart failure requiring intravenous support, NTP has a greater unloading effect and clinical benefit than DOB, used as first choice therapy. These data need to be verified in a multicenter, prospective, randomized clinical trial.

P622 Early, long-term therapy with the mixed endothelin-1 receptor antagonist, bosentan, preserves left ventricular function in dogs with progressive heart failure

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We examined the effects of early, long-term monotherapy with bosentan (BOS), a mixed endothelin-1 ET_A and ET_B receptor antagonist, on the progression of LV dysfunction and remodeling in dogs with moderate heart failure (HF).

Methods: LV dysfunction (ejection fraction, EF = 30% to 40%) was produced in 14 dogs by multiple intracoronary microembolizations. Dogs were randomized to 3 months therapy with BOS (30 mg/kg Bid, n = 7) or to no therapy at all (control, CON, n = 7). The change (Δ) in cardiac index (CI), LV EF, end-systolic (ESV) and end-diastolic (EDV) volumes between pre- and post-treatment are shown in the table. Cardiomyocyte cross-sectional area (CCSA), a measure of cell hypertrophy, and LV volume fraction of interstitial fibrosis (VFIF) were determined histomorphometrically.

Results: In CON dogs, LV EF and CI decreased and LV volumes increased after 3 months while in BOS dogs, CI increased and EF, EDV, and ESV were preserved. Compared to CON, BOS treated dogs had a smaller CCSA (699 ± 107 vs 850 ± 36 μm^2, P = 0.002) and lower VFIF (10.6 ± 0.5 vs 14.3 ± 0.7%, P = 0.017).

	Control	BOS	P-value
Δ CI (l/min/m^2)	−0.4 ± 0.1	0.7 ± 0.3	0.005
Δ LV EF (%)	−6 ± 1	5 ± 2	0.001
Δ LV EDV (ml)	13 ± 6	−4 ± 2	0.020
Δ LV ESV (ml)	14 ± 5	−5 ± 1	0.003

Conclusion: In dogs with moderate HF, early, long-term therapy with BOS prevents progressive LV dysfunction and attenuates LV remodeling. The results support the use of mixed endothelin-1 receptor antagonists in the treatment of chronic HF.

P623 Multicentre, double-blind, placebo-controlled study of long-term endothelin blockade with bosentan in chronic heart failure: results of the Reach trial

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Endothelin (ET) may play a role in the pathophysiology of chronic heart failure (CHF), but the long-term effects of ET blockade have not been studied. To do so, 370 patients with NYHA class IIIB–IV CHF (EF < 35%) receiving diuretics and an ACE inhibitor, were randomized (double-blind in a 2:1 ratio) to receive the ET_A + ET_B antagonist bosentan (target dose 500 mg BID) or placebo for 6 months. The primary endpoint was a clinical composite which assessed symptoms and major events. The trial was stopped due to concerns about elevations in hepatic transaminases when 47% of the pts (N = 173) had been followed for 6 mos. In the entire study population, there was no difference in efficacy between bosentan and placebo. However, in patients followed for the intended duration of the study (6 months), Bosentan significantly increased the likelihood of clinical improvement (bosentan 27%, placebo 19%) and decreased the likelihood of CHF deterioration (bosentan 27%, placebo 43%), P = 0.045. In these patients bosentan decreased the total number of hospitalizations for any reason by 41%. The benefits of bosentan increased with the duration of follow-up. Bosentan was generally well tolerated but produced asymptomatic, reversible elevations in hepatic transaminases and decreases in hematocrit. These results indicate that long-term blockade of ET_A and ET_B receptors with bosentan has the potential to decrease symptoms and favourably alter the progression of CHF.

P624 Clinical variables predicting the use of β-blockers in heart failure: the BRING-UP study

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BRING-UP (BetablockeRs IN patients with congestive heart failure: Guided Use in clinical Practice) is an observational study designed to guide the introduction of betablockers (BB) in the therapy of heart failure (HF) in the clinical practice of Italian cardiologists. The treatment (bisoprolol, carvedilol, metoprolol) was started according to the clinical decision of the responsible cardiologist.

Out of 2975 pts enrolled in the study, 734 (24.7%) were already on BB: these pts were not included in the analysis. 836 (28.1%) started BB therapy, while 1405 (47.2%) did not. We analyzed the baseline characteristics of the pts receiving or not BB.

NYHA IV class needing iv inotropes, hypotension, heart rate < 50 bpm and/or hypokinetic arrhythmia, respiratory insufficiency and severe peripheral vasculopathy were considered absolute contraindications to BB therapy.

At univariate analysis: (a) younger age, higher SBP and heart rate (HR), recent diagnosis of HF and a hystory of hypertension were significantly associated with a higher use of BB; (b) advanced (III-IV) NYHA class and atrial fibrillation were significantly associated with a lower use of BB; (c) gender, etiology, ejection fraction and history of diabetes did not influence BB prescription.

At adjusted analysis the only variables that resulted independently associated with BB therapy are reported in the table:

	Odds Ratio	95% CI	p
Age*	0.968	0.960–0.977	0.0001
SBP*	1.017	1.012–1.022	0.0001
HR*	1.013	1.007–1.019	0.0001
NYHA class III–IV vs I–II	0.601	0.493–0.732	0.0001

*As continuous variables.

Conclusions: In routine clinical practice cardiologists prescribe less frequently BB to patients with advanced age, low SBP, low HR and advanced NYHA class.

P625 Effects of acute administration of irbesartan on myocardial metabolism and coronary haemodynamics

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The aim of this study was to consider the effect of Ibesartan, a new Angiotensin II Receptor Antagonist, on coronary haemodynamics and myocardial metabolism, in order to clarify the mechamism underlying the beneficial effects on cardiovascular performance. We have studied eleven patients with hypertensive cardiomyopathy, without lesions of the coronary vessels. All patients underwent cardiac catheterization and measurements were made at rest and two hours after oral administration of 150 mg Ibesartan. We have calculated the following parameters: mean sistemic arterial pressure (MSAP), mean pulmonary arterial pressure (MPAP), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), anterior coronary resistances (ACR), coronary flow (CF) (determined by Doppler flow wire), and myocardial oxygen consumption (by Double Product) (DP).

Results:

Pre-Irbesartan

	MSAP (mmHg)	MPAP (mmHg)	SVR (dynes cm^{-5})	PVR (dynes cm^{-5})	ACR (mmHg) min ml^{-1})	CF (ml/min)	DP
Mean value	93.18	13.45	1321.64	197.64	40.84	210.15	9847.73
SD	± 7.47	± 0.50	± 17.93	± 20.42	± 15.92	± 71.98	± 385.90

Post-Irbesartan

	MSAP (mmHg)	MPAP (mmHg)	SVR (dynes cm^{-5})	PVR (dynes cm^{-5})	ACR (mmHg) min ml^{-1})	CF (ml/min)	DP
Mean value	76.36	8.82	1175.45	136.45	28.22	239.52	7154.55
SD	± 12.45	± 1.99	± 214.11	± 33.36	± 6.77	± 96.84	± 1264.74
Δ (pre/post)	−18%	−34%	−11%	−30%	−31%	+14%	−27%
p	= 0.01	<0.0001	= 0.03	<0.0001	<0.001	<0.001	<0.001

Our data indicate the effectiveness of Ibesartan in improving coronary haemodynamics, probabily due to the activation of receptors AT2 and to the inhibition of simpatic nervous system, independently from prostaglandin action.

P626 Effects of losartan on e-NOS and i-NOS mRNA expression and myocytes apoptosis in isolated working rat hearts

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Angiotensin II produced by endothelium through the activity of ACE plays an important role in ischemia-reperfusion (I/R) injury. Recent studies suggest that Angiotensin II-receptor antagonist may induce a cardioprotective effect against I/R damage. Apoptotic cell death might be ab integral part of the pathogenesis of cardiac dysfunction related to I/R.

The aim of our study was to evaluate in isolated working rat hearst the effects of Losartam (L) on post-ischemic endothelial dysfunction, Nitric Oxide Synthase (NOS) mRNA expression (inducible, i-NOS; endothelial, e-NOS) and myocytes apoptosis.Hearts were subdivided in 3 groups: A) control; B) ischemia and reperfusion; C)L 1 μM. hearts submitted to 15 min. ischemia and 190 min. reperfusion. The L was added to the perfusion buffer at the beginning of experiment. Hemodynamic parameters,CPK release, morphological alterations and endothelial permeability (FITC-albumin extravation) were valuad; e-NOS and i-NOS mRNA were valued by multiplex RT-PCR, and results were expressed as Glyceraldheyde-3-Phosphate Dehydrogenase (G-3PDH)/e-NOS and G-3PDH/i-NOS ratio. Detection of apoptosis was based on electron microscopy and in situ end-labeling assay (TUNEL).

In C group we detected a significant reduction of functional deterioration and coronary endothelium post-ischemic hyperpermeability and ultrastructural damage; a significant decrease of G-3PDH /e-NOS ratio also occurred respect to B group. Furthemore, in C group the electrophoretic pattern of apoptotic DNA bands was observed and confirmed by TUNEL; i-NOS expression was detected only in B group.

In conclusion our data evidenced that L may acutely induce a coronary endothelium protection against reperfusion injury by means of an e-NOS mRNA over-expression; it has no effect on myocytic apoptosis.

P627 Impact of neurohormonal antagonists on left ventricular remodelling: comparison of carvedilol versus captopril in chronic heart failure

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The independent effects of carvedilol (CAR) versus ACE-inhibitors on ventricular (LV) remodelling in chronic heart failure (CHF) are not known. We investigated 57 patients with CHF (ischaemic or non-ischaemic, NYHA II–III, EF < 40%) randomized double-blind to treatment with CAR or captopril (CAP) at maximum doses of 25 mg b.d. for 12 weeks, followed by 12 weeks of combined treatment. Serial echocardiography was performed to assess LV mass, end-systolic volume (ESV), sphericity index (SI) and systolic wall thickening index (SWTI). Medians for baseline values and changes with monotherapy versus baseline and combination therapy versus monotherapy are given below:

	Baseline		Monotherapy		Combination Therapy	
	CAR	CAP	CAR	CAP	CAR+ CAP	CAP+ CAR
LV ESV (ml)	117	100	$-10^{\dagger***}$	0	-7^{***}	-8^{***}
LV mass (g)	291	219	−20	-7.5^{*}	-16^{***}	-11^{***}
SI	1.4	1.4	$+0.04^{*}$	$+0.04^{***}$	$+0.06^{***}$	$+0.08^{***}$
SWTI	2.7	2.8	-0.25^{***}	-0.16^{***}	-0.08^{**}	$-0.25^{\dagger***}$

comparision between groups $^{\dagger}p \leq 0.05$; within groups: $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, $^{***}p \leq 0.001$

Each drug produced favourable changes in LV mass, SI and SWTI with further improvements on combined treatment. These findings suggest synergistic effect of CAR and ACE-inhibitors on LV remodelling in CHF.

ATRIAL FLUTTER

P628 A constant interval between the stimulus artifact and the local atrial electrogram: a new electrophysiological technique for radiofrequency ablation of the cavotricuspid isthmus

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Background: Previous studies performed in patients with atrial flutter (AF1) have shown a clock-wise homogeneous activation front (with conduction velocities lower than 1 m/s) through the cavotricuspid isthmus (CTI), during pacing from the coronary sinus (CS) in sinus rhythm. Thus, a constant interval stimulus artifact-local atrial electrogram (S-A) recorded with the ablation catheter (Abl C) could be useful to create a line of bi-directional block along the CTI.

Patients and Methods: In 17 consecutive patients (P) who underwent RF ablation of typical AF1 in sinus rhythm, radiofrequency (RF) linear lesions were made sequentially (with point-by-point ablation) during pacing at 500 ms from the CS. The Abl C (8-mm-tip) was positioned at the tricuspid annulus (TA) recording a bipolar electrogram with an A/V ratio $\leq$ 0.1 and a S-A between 30 and 80 ms at a paper speed of 200 mm/s. After each 30 s RF application, the Abl C was withdrawn 5 mm (in right anterior oblique view) toward the right atrium, trying to maintain a constant S-A (variation $\leq$ 10 ms). The presence of bi-directional block across the CTI was confirmed by comparing the timing and sequence of 10 standard bipolar electrograms of a catheter positioned along the TA.

Results: In all patients a constant S-A interval (mean 46 $\pm$ 15 ms) could be maintained during the RF applications. In 11 P bidirectional CTI block was created with the first RF line (mean of RF pulses 8 $\pm$ 6). Three P required 2 RF lines and 2 P 4 RF lines. In one P it was not possible to block the CTI. A good correlation was observed between the lengthening or shortening of the S-A interval and the lateral or septal displacement of the Abl C in the left anterior oblique view.

Conclusion: A constant S-A interval seems to be an useful electrophysiological tool to guide linear RF ablation of the CTI.

P629 Terminal crest permeability can prevent evaluation of isthmus block after flutter ablation

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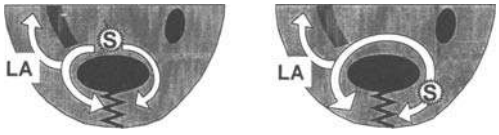
Background: Descending anterior right atrial (RA) activation pacing the low septum suggests cavo-tricuspid isthmus CTI block after typical flutter (FL) ablation.

Objective: To report 7 cases with anterior RA activation suggestive of CTI conduction, probably due to conduction across terminal crest (TC).

Methods: Anterior RA activation was compared pacing low septal and low posterior RA. Conduction through TC should produce a stimulus (S) to low anterior (LA) RA interval shorter pacing posterior RA (fig left) than low septal RA (fig right). The opposite should occur with CTI conduction.



Results: In 6 cases with anterior RA activation compatible with collision pacing the posterior RA produced the same pattern with shorter S-LARA than pacing the septal isthmus. In 2 there was apparent rate-dependent CTI block, that according to these intervals was rate-dependent TC block. In a 7th case with lateral wall scar, ablation between scar and inferior caval vein changed anterior RA activation from apparent collision to descending.

Conclusions: Conduction through TC can prevent detection of CTI block. Shorter S-LA RA intervals pacing posterior RA than pacing septal RA should suggest conduction through posterior RA-TC.

P630 Effect of restored sinus rhythm on right atrial status following radiofrequency catheter ablation of chronic atrial flutter

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Restoration of normal sinus rhythm after RF-ablation (RFA) in patients with chronic atrial flutter (AF) and cardiomyopathy has been shown to result in substantially improved left ventricular function. However, the effect of restored sinus rhythm on right atrial (RA) size and function has not been examined.

Methods: Twenty patients (59 ± 15 years old; 12 men) undergoing successful RFA of common AF underwent right atrial angiography to evaluate the size and function of the right atrium in sinus rhythm 30 minutes after the ablation procedure and at reevaluation 10 ± 2 months (range: 6–12 months) post-ablation follow-up. For comparison, 30 normal control subjects were also studied.

The linear diameter of the right atrium was measured in right anterior oblique projection and the RA function was assessed by estimating the contraction fraction measuring the end-diastolic and end-systolic areas of the right atrium by digital planimetry.

Results: The mean length of the RA diameter was larger in patients with common AF than in the control group ($p < 0.001$) (table). There were no significant differences in the dimensions of the right atrium in patients with AF measured in sinus rhythm post-ablation and at reevaluation 6–12 months later. Atrial contractility, however, improved significantly, as shown by differences in the contraction fraction obtained in both periods ($p < 0.001$). Additionally, the mean contraction fraction of the right atrium at reevaluation in patients with previous AF was similar to that previously obtained in the control group.

	Control group	AF post-RFA	AF at follow-up
RA dimensions	48.5 ± 6 mm	57.6 ± 9 mm	57.1 ± 8 mm
RA contractility	0.51 ± 0.1	0.23 ± 0.06	0.53 ± 0.1

Conclusions: 1. After ablation of patients with chronic AF there is a recovery time to achieve normal contractility of the right atrium. 2. The persistence of an enlarged right atrium after the ablation, but with normal contractility, suggests a previously dilated right atrium which may predispose to the development of atrial flutter.

P631 Incidence and characteristics of new developed atrial flutter and monomorphyc atrial tachycardia after lung transplantation

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A high incidence of "incisional" atrial reentrant tachycardia or flutter has been reported after the creation or implantation of atrial suture lines and patches during corrective surgery of congenital heart disease. Similarly, atrial anastomosis between the receptor left atrium and one or two donor pairs of ipsilateral pulmonary veins could provide a potential substrate for intra-atrial reentry after lung transplantation (LTx).

Methods: The study included 77 consecutive adult patients with LTx (30 bilateral LTx, 47 unilateral LTx). Patients were monitored during the first postoperative with continuous single lead ECG. A conventional 12 lead ECG was performed whenever a cardiac rhythm disorder was suspected. None of the patients had history of atrial arrhythmias prior to LTx and none were on antiarrhythmic drugs.

Results: 9 patients (38 ± 18 y, 7 male, 6 bilateral LTx, 3 unilateral LTx) developed atrial monomorphic arrhythmias: 7 developed non-common atrial flutter and 2 atrial tachycardia (mean cycle lenght 232 ± 66 ms). None had atrial arrhythmias in relation to graft rejection but one. Time between LTx and arrhythmia onset was 9.8 ± 6.3 days (range 1–18). All patients had the tachycardia controlled with amiodarone, which was discontinued at hospital discharge. At follow-up (8 ± 8.7 months), there were no arrhythmia recurrences.

Conclusions: 1) A high incidence of regular monomorphic atrial arrhythmias is seen in the early stage after LTx. 2) The mechanism of these arrhythmias is uncertain. However, similarly to that described after congenital heart disease surgery, left atrial suture lines could act as conduction barriers around which a circular reentry circuit can occur.

P632 Presence of preferable activation patterns during atrial fibrillation as assessed by three-dimensional mapping of the conduction velocity vectors

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Atrial fibrillation (AF) is believed to result from multiple reentrant wavefronts that wander randomly in the atria. We tested the hypothesis that atrial activations during AF are not completely random, by examining the possible presence of preferred activation patterns during AF in a chronically paced goat model.

Methods and Results: A new method, which utilizes a custom-built tripole locatable catheter, was developed to measure the atrial conduction velocity (CV) vector. The location and local activation time of each electrode (derived from the 3 recorded unipolar electrograms) is used to calculate the CV vector of each atrial activation. By recording 30 seconds of AF activity at each endocardial site, the changes in the activation direction can be analyzed by the construction of detailed CV vector direction histograms (describing the number of atrial activations for each vector angle). Four different types of histograms were noted: endocardial sites with no preferable activation direction (type 1), sites with one preferable activation direction (type 2), and sites with two preferable activation patterns positioned 180° apart with equal number of activation (type 3) or one direction being more dominant (type 4). Significant variations in the regional distribution of the different types of the CV angle histograms were found (table).

Distribution of CV Angle Histograms

	IVC	SVC	Anterolateral	Isthmus	Posterior	Septum
Type 1	0	0	6	9	58	73
Type 2	88	60	58	38	13	9
Type 3	6	13	14	15	21	9
Type 4	6	27	22	38	8	9

Conclusions: (1) Significant regional differences are present in the RA CV directional histograms. (2) The septum and posterior walls are associated with no preferable activation dirrection, indicating the presence of multiple wavefronts propagating in all directions. The tube like areas (SVC, IVC and Isthmus) and the anterolateral free wall are characterized by one or two preferable activation directions, indicating the dominance of anatomical reentry.(3) Assessment of regional differences in the activation patterns of AF may become a useful tool in evaluating the underlying mechanisms of AF and may aid in designing therapeutic strategies.

P633 Intravenous sotalol in the treatment of atrial flutter: a randomised, double-blind, placebo-controlled study

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Introduction: A prospective, randomised, double-blind, placebo controlled study was conducted to investigate the efficacy and tolerability of intravenous sotalol for the conversion of atrial flutter (AF) to sinus rhythm.

Methods: Of 70 consecutive patients (44 men, mean age 59 ± 10 years) with AF lasting from 2 hours to 28 days, 35 were randomised to receive a single intravenous dose of sotalol (1.5 mg/kg over 10 minutes) and 35 to receive an identical amount of saline solution. Baseline clinical characteristics were similar in the two groups.

Results: The number of patients that converted to sinus rhythm was significantly higher in the sotalol group than in the placebo group (17/35 vs 2/35, 49% vs 6%; $p = 0.00005$). Mean time to AF termination after initiation of sotalol was 34 minutes. As a consequence of sotalol prolonging effect on the refractory period, a rapid (within the time of infusion) reduction of arrhythmia cycle length has been observed. The resulting lower ventricular rate (from 153 ± 5 to 116 ± 11 beats per minute – $p < 0.01$) rendered the arrhythmia better tolerated during the time preceding the restoration of sinus rhythm. 18 episodes of mild, transient hypotension occurred in 11 patients treated with sotalol versus 7 treated with placebo. No severe side effects necessitating termination of drug administration were observed.

Conclusion: The intravenous administration of sotalol appears to be safe and effective for acute termination of atrial flutter. The reduction of ventricular rate induced by the drug may offer clinical benefits even in those patients in whom sinus rhythm is not obtained.

P634 IC drug induced atrial flutter during treatment of atrial fibrillation: usefulness of a combined pharmacological and ablative therapy

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It is well known that patients (pts) chronically treated with IC antiarrhythmic drugs for recurrent atrial fibrillation (AF) can experience conversion of AF to typical atrial flutter (AFl) during the follow-up. In these cases the radiofrequency catheter ablation (RF) of the inferior vena cava-tricuspid valve (IVC-TV) isthmus could theorically avoid further arrhythmic recurrences of both AF and AFl. Aim of this study was to verify the clinical efficacy of this therapeutical strategy.

Methods and Results: We studied 9 pts (mean age 58 ± 11 yrs) with frequently recurrent episodes of AF alone, without documented episodes of AFl, who were treated with IC antiarrhythmic drugs (flecainide in 6 pts and propafenone in 3 pts) to prevent AF recurrences and who experienced only episodes of typical AFl after the onset of treatment (mean 5 ± 1.5 episodes per pt during a mean period of 12 ± 0.3 months). All 9 pts underwent successful RF of AFl with the achievement of bidirectional isthmus conduction block. After the ablation procedure no pt was treated with any antiarrhythmic drug until the first arrhythmic recurrence. At least one episode of AF occurred in all pts within 1 month. After the AF recurrence IC antiarrhythmic treatment was restored at the same dosage as before RF. During a mean follow-up period of 14 ± 9 months only one pt (11%) had one recurrence of AF 7 days after the onset of therapy and no pt experienced further recurrences of AFl.

Conclusion: These results suggest that combined therapy with RF catheter ablation of IVC-TV isthmus and IC antiarrhythmic drugs may be useful in preventing further arrhythmic recurrences in AF pts who experience episodes of typical AFl during chronic treatment with flecainide or propafenone. Randomized controlled studies are needed to confirm these preliminary data.

P635 Persistent atrial flutter in patients treated for atrial fibrillation with amiodarone and propafenone: risk prediction and radiofrequency ablation

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Antiarrhythmic drugs (AAD) have been reported to promote the conversion of atrial fibrillation (AF) to atrial flutter (AFL) in patients (pts) with paroxysmal AF. The purpose of this study was to investigate the electrophysiologic characteristics, radiofrequency catheter ablation (RFCA) and determinants of persistent (>24 hours) AFL in 136 pts treated for AF with amiodarone and propafenone.

Methods: A 20-pole halo catheter was placed around the tricuspid annulus to map the activation sequence of AFL. Entrainment of the tachycardia was attempted by pacing from the low right atrial isthmus. The clinical variables including sex, age, presence of structural heart disease, presence of atrial enlargement, left ventricular ejection fraction, and maximal sinus P wave duration were analyzed in relation to the occurrence of persistent AFL.

Results: Fifteen pts (11%, mean age 65.5 ± 12.3 years) were identified to have subsequent development of persistent AFL during AAD treatment. The mean interval between the beginning of drug treatment and the onset of AFL was 5.0 ± 5.5 months. Eleven pts had counterclockwise typical AFL, and 4 had clockwise typical AFL. All 15 pts underwent successful RFCA with creation of complete bidirectional isthmus conduction block. After a mean follow-up of 12.3 ± 4.2 months, 14 (93%) of 15 pts who underwent successful RFCA and continued on AAD have remained in sinus rhythm. Univariate analysis of clinical variables demonstrated that only the atrial enlargement was significantly related to occurrence of persistent AFL.

Conclusion: In pts with AF, persistent typical AFL might occur during AAD treatment, and atrial enlargement was a risk factor for the development of such arrhythmia. RFCA and continuation of pharmacological therapy offered a safe and effective means of achieving and maintaining sinus rhythm.

P636 Initial experience with a new non-contact mapping system for catheter ablation of atrial flutter

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Catheter ablation of typical atrial flutter (AF) was performed in 13 patients (pts) using a non-contact endocardial mapping system. This new non-contact multielectrode array (MEA) enables reconstruction of 3360 electrograms using inverse solution mathematics. The MEA is a 64 wire braid woven around a 8 ml ballon, mounted on a 9F catheter. The reconstructed electrograms are superimposed onto a computer simulated 3 dimensional model of the endocardium. Using the MEA a replica of the right atrium was created enabling us to design the ablation lines and to check their completeness. In addition, conventional mapping with a "halo" catheter was performed. Aim of this study was to report the inital experience with the MEA for mapping and catheter ablation of atrial flutter.

Results: 8 pts presented with a pattern of typical, counter-clockwise AF during mapping with the Halo. However, the MEA showed a focal origin in 1 of these 8 patients in the posteroseptal region. In 2 pts with clockwise AF determined by a Halo-catheter, the MEA identified a focal activation originating from the crista terminalis. 3 pts had atypical AF. In 1 pt a focus was found at the crista terminalis, in 2 pts conventional mapping showed left atrial origin. MEA identifies the entrant point into the right atrium at the Bachmann bundle and ostium of the coronary sinus. Successful ablation was performed in all 11 AF originating in the right atrium. During ablation of typical AF, MEA was helpful to identify activation gaps in the isthmus region. The ablation catheter was navigated to the site of the activation gap and ablation was performed until MEA showed complete line of block.

Conclusions: 1. The MEA is helpful to identify different mechanism of AF, especially focal AF mimicking typical AF. 2 The MEA identifies activation gaps at the isthmus site more precisely than conventional mapping techniques.

P637 Is it worth to use radiofrequency catheter ablation as the first treatment of atrial flutter for patients with dilated cardiomyopathy?

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Clinical cases of reversible dilated cardiomyopathy (DCM) with atrial flutter (AF) have been reported after conversion to sinus rhythm. Previous reports showed that recurrent AF is more frequent after overdrive pacing, cardioversion or antiarrhythmic drugs than after radiofrequency catheter ablation (RFCA): >50% versus 10 to 20%. The aim of this study was to evaluate the left ventricular end diastolic diameters (LVDD) and function (Shortening fraction: SF) by echocardiography after successful RFCA.

Methods: We studied 30 patients (pts) with DCM and chronic AF. The DCM was idiopathic (n = 15) or secondary (n = 15, 10 ischemic, 4 valvular diseases and 1 hypertrophic). There was no significant difference between the 2 groups. Pts were 63 ± 11 years old, 97% male, with 16 months duration of AF; and a ventricular rate of 112/min. A first echocardiography was performed 48 hours after ablation and a second later during follow up (FU): mean FU = 11.4 ± 6.6 months.

Results:

	LVDD (mm)	SF (%)	LVDD FU (mm)	SF FU (%)
Idiopathic DCM	62.6 ± 6*	23 ± 8*	56.1 ± 3*	30 ± 4*
Secondary DCM	62.1 ± 5	30 ± 8	58.9 ± 5	31 ± 7

Student test: *: $p < 0.05$

In the group of idiopathic DCM, we observed a significative improvement of LVDD and SF during the FU but not in the group of secondary DCM. In the idiopathic DCM group, a total recovery of left ventricular parameters was observed in 53% of cases and for 80% of pts LVDD was normalized.

In the 2 groups, NYHA cardiac heart failure class improved from 2.5 to 1.1.

Conclusions: 1) The only predictive factor of normalization of the left ventricular function is the diagnosis of idiopathic DCM 2) AF seems to be a real and frequent cause of DCM: "tachycardiomyopathy" 3) When idiopathic DCM with AF is presumed an aggressive therapy with RFCA should be considered early.

P638 Isoproterenol to evaluate resumption of conduction following right atrial isthmus ablation in type I atrial flutter

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Following radiofrequency (RF) ablation of atrial flutter (AFL) the demonstration of bidirectional isthmus conduction (BIC) block is considered the hallmark of a successful procedure. Purpose of our study was to test the persistence of BIC block following isoproterenol administration and to evaluate the importance of this finding on AFL recurrences.

Methods: RF ablation of AFL was performed in 44 consecutive pts with type I AFL by a linear ablation of the posterior (n = 29 pts), septal (n = 4 pts) or both right atrial (RA) isthmi (n = 11 pts). Procedural endpoint was complete BIC block and noninducibility of AFL. In case of noninducibility and apparent BIC block the pacing protocol was repeated under isoproterenol infusion (1–3 mcg/min).

Results: Reversal of apparent BIC block occurred in 7/44 (15.9%) pts. Six pts had bidirectional and 1 pt unidirectional resumption of isthmus conduction. Counterclockwise AFL could be reinduced in 4 of these pts. 2–24 (median 4) additional RF applications were required to acheive a permanent BIC block. At a mean follow-up of 7.3 ± 7.6 (2–31) months 2/44 (4.5%) pts had AFL recurrences.

Conclusions: Partial linear RF ablation could possibly aggravate the pre-existing nonuniform anisotropic conduction in the RA isthmus resulting in profound conduction slowing and apparent BIC block. Isoproterenol can unmask apparent BIC block thus providing an opportunity to assess the possibility of reversal of BIC block and completeness of isthmus ablation during the same procedure. The low incidence (4.5%) of AFL recurrences at follow-up suggests that noninducibility and BIC block under isoproterenol infusion may be a better endpoint for successful AFL ablation.

P639 Electrophysiology of "class IC atrial flutter"

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A combination of class IC antiarrhythmic drug [AAD] therapy and right atrial isthmus [RAI] ablation has been effective in a subset of pts with recurrent atrial fibrillation [AF] who develop atrial flutter [AFL] on class IC AADs, the "class IC AFL".

Methods: Twenty-three pts (54 ± 12 years, 18 males) with recurrent AF who developed a "class IC AFL" underwent an electrophysiology study and linear RAI ablation. AFL induction was not attempted in 8 pts and 22 patterns of AFL (262 ± 36 ms) were documneted in the remaining 15 pts. Ablation was performed during AFL (n = 7), coronary sinus [CS] pacing (n = 12) or both (n = 4).

Results: The RAI conduction was slower in antegrade (104 ± 32 ms) than in retrograde direction (75 ± 34 ms) direction. Ten AFLs (46%) were incessant. In the remaining 12 cases AFL was initiated following spontaneous transition from ongoing AF (n = 3), programmed atrial stimulation (n = 5), catheter induced atrial premature beats (n = 1), isoproterenol infusion (n = 2) and immediately after external cardioversion (n = 1). 20/22 AFLs were sustained and predominantly counterclockwise (CCW) (n = 18, 82%). The available CS recordings (17/22 pts) suggested a AFL (n = 16) most commonly, while a AF in only 1 instance. Inadvertantly induced sustained AF (n = 12) was "organized" along the crista terminalis, cranio-caudally, during 6/12 patterns. Sinus rhythm was restored by external/internal cardioversion (n = 8), flecainide (n = 1) or overpacing (n = 1). Isthmus dependence was suggested by termination of AFL in the RAI or near CS (10/24, 42%) and noninducibility of AFL following RAI ablation (21 pts, 91%). AFL persisted despite ablating both the RAI in 2 pts.

Conclusions: "Class IC AFL" is predominantly CCW, possibly based on slow RAI conduction antegradely. Most "class IC AFL" circuits seem to be RAI dependent. Sustained AF may be frequently complicate the ablation procedure.

P640 Surface ECG characteristics and endocardial activation sequence in patients with counterclockwise and clockwise atrial flutter

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Due to the lack of high resolution mapping systems, the relations between activation patterns within the human atria and surface ECG morphology in patients with atrial flutter (AFl) have never been satisfactorily defined.

In 41 patients with AFl, (mean age 62 ± 12 years), a 64-elecrode basket catheter was deployed in the right atrium (RA). Out of 64 electrodes, 56 bipolar electrograms are derived. A decapolar catheter was inserted within coronary sinus (CS) to record from the left atrium (LA). Temporal relations between endocardial and surface ECG activity, were determined with the use of electronic calipers.

Results: In counterclockwise (Ccw) AFl, (32 patients) the impulse conduction through the lateral wall produced the upstroke component in inferior leads and positive deflection in V1. The impulse conduction through isthmus coincided with the plateau in inferior leads, which lasted until the beginning of activation in low septum area. Plateau duration (121 ± 27 ms) correlated strongly with isthmus conduction time(117 ± 23 ms), (r = 0.93). Septal and LA conduction accounted for the negative component in lead I, inferior leads and V6. In Ccw AFl, the spread of impulse in CS electrograms was invariably from proximal to distal.

In clockwise (Cw) AFl, (11 episodes) the impulse propagation through septum and posterior wall produced the first positive component in inferior ECG leads. The impulse propagation through the LA produced the second positive deflection. The distance between two deflections (60 ± 18 ms) correlated strongly with interatrial conduction time (57 ± 19 ms), (r = 0.83). Interatrial conduction interval was prolonged during AFl as compared to sinus rhythm (60 ± 18 ms vs 43 ± 13 ms, p = 0.04). The impulse spreading through lateral wall of RA produced the negative component in inferior leads. Contribution of impulse conduction through the isthmus was hidden by ongoing impulse propagation in the LA. The CS activation patterns were proximal-to-distal, simultaneous or undetermined.

Conclusions: 1) Impulse conduction through lateral and septal walls of RA and isthmus conduction time are major determinants of RA contribution to ECG morphology, 2) Sequential use of lower or upper interatrial connections, determines contribution of LA in Ccw or Cw episodes of AFl, 3)Polarity of the F wave in an ECG derivation is determined by a resultant of opposing activities generated in the lateral wall of RA and the LA.

P641 Intercaval block in atrial flutter: is there a physiologic basis?

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Typical atrial flutter in dogs is due to reentry around the caval veins and a line of functional conduction block (CB) in between. The interindividual reproducibility of this activation pattern suggests a physiologic basis for the intercaval (IC) CB. In 6 dogs, a high density patch electrode (7 × 13 bipolar electrodes, spacing 1.5 mm) was placed in the IC region, perpendicular to the IC axis. Using a computerized mapping system, epicardial activation maps were constructed during pacing (cycle-length 200 ms) from 2 different sites, eliciting a wavefront parallel and perpendicular to the IC axis, respectively. Local refractory periods (ERP) were determined at 13 adjacent electrode sites along the center row of the patch (extrastimulus technique).

Results: Local ERPs did not show any systematic pattern, but seemingly random de- and increases instead. Mean ERP was 102 ± 26 ms. The maximum local ERP gradient reached 30 ms, the mean local gradient was 10.3 ± 4.6 ms. Activation maps revealed marked anisotropic conduction patterns, with fast conduction parallel and slow conduction perpendicular to the IC axis in the crista terminalis (CT) region, as opposed to slow conduction parallel (0.5 ± 0.1 m/s) and fast conduction perpendicular (1.5 ± 0.6 m/s) to the IC axis in the pectinate muscle (PM) region ($p < 0.05$).

Conclusions: Dispersion of ERP is not likely to facilitate IC block. The location of the CT and of IC blocks suggests a causal relation, but conduction properties of the CT do not. The PMs, however, exhibit fast conduction and a reduced safety factor for propagation perpendicular to the IC axis. Thus, insertion sites of the PMs into the CT might be the crucial link providing a physiological basis for IC block.

P642 Electrocardiographic patterns of flutter wave in "Class IC atrial flutter"

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Recent reports suggest a clinical benefit following right atrial [RA] isthmus ablation in pts who experience conversion of atrial fibrillation [AF] to atrial flutter [AFL] during antiarrhythmic drug [AAD] therapy. Our aim was to study the electrocardiographic morphology of a new AFL developing after class IC AAD therapy in pts with recurrent AF, so called "Class IC AFL".

Methods: Thirty recordings of "Class IC AFL" observed in 23 consecutive pts (mean age 54 ± 12 years, 18 males) during a clinical episode (n = 8) or electrophysiological study (n = 22) were analyzed. All pts developed their AFL (paroxysmal, 12 pts; incessant 12 pts) while on class IC AADs (propafenone, 12 pts; flecainide, 11 pts) for recurrent episodes of AF. Most of the pts (96%) did not have significant structural heart disease. The mean left atrial size was 4.6 ± 0.4 cm.

Results: The mean AFL cycle length was 262 ± 32 (190–320) ms. The flutter wave (FW) polarity in the inferior leads (II,III,aVF) was: negative and angled (n = 4), negative and rounded (n = 8), positive and rounded (n = 9), flat (n = 1) or undetermined (n = 1). In lead V1 the polarity of FW was: positive (n = 19), negative (n = 8), flat (n = 1) or undetermined (n = 2). The majority of AFL patterns (n = 27, 90%) had an isoelectric interval between two consecutive FWs. Atrioventricular response was 2:1 (n = 21) or >2:1 (n = 9). Importantly, none of the AFL patterns had the combination; "saw-tooth" pattern in inferior leads, a positive or negative FW in lead V1 and no isoelectric interval between FWs, as found in "common AFL".

Conclusions: Electrocardiographically, "Class IC AFL" is pleomorphic and not entirely identical to the "common AFL". The pleomorphism of FW could be based on slow intra-atrial conduction with detours of the macro-reentrant circuit when propagating at non-isthmic atrial sites. Electrocardiographic FW patterns may have implications for proper selection and results of ablation therapy.

P643 P on T ectopics predict the occurrence of atrial fibrillation after ablation of typical flutter

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Background: Most patients with pulmonary vein ectopy initiating atrial fibrillation (AF) exhibit a P on T pattern during ectopy. We investigated the pronostic value of such ectopics in patients (pts) during the first 24 hours. after undergoing ablation of typical atrial flutter (Afl).

Methods: 53 pts (9 female, 44 male), mean age: 61 ± 2 were studied after ablation of typical Afl in the cavo-tricuspid isthmus. 22 pts had structural heart disease but only 1 had an ejection fraction < 50%. 27 had previously documented AF. After ablation, each patient underwent 24 hr holter monitoring and remained under telemetric surveillance for the 5 day duration of their hospital stay. The occcurence and frequency of P on T ectopy (a coupling interval of ≤500 ms) as well as AF was documented.

Results: Of the 17 pts who developed AF after flutter ablation; 5 did so on the first day after the procedure and the remaining later. The only significant predictive factors of post ablation AF were the presence of P on T ectopy and a previous history of AF (Table). A previous history of AF did not significantly correlate with the occurrence of post procedure P on T ectopy.

	AF post = 17	No AF = 36
P on T present*	15	13
no ectopy	2	23
History of AF†	13	14
No prev AF	4	22

*p = 0.0004, †p = 0.017

Conclusions: Most patients who exhibit a P on T pattern of ectopy after ablation of typical Afl or have a previous history of AF have a high risk of developing subsequent AF. This may indicate that the elimination of stable arrhythmia such as flutter permits a common trigger (P on T ectopy) to induce atrial fibrillation.

P644 Cavo-tricuspid isthmus width in relation to the radiofrequency ablation of the common atrial flutter

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The aim of this prospective study was to correlate the width of the cavo-tricuspid isthmus (CTI) with the immediate outcome of radiofrequency (RF) ablation for common atrial flutter (AFl).

Methods: In 15 consecutive patients (pts) undergoing their first AFl ablation, right atrial angiography was performed immediately before the RF procedure. Cineangiography of the right atrium and inferior vena cava was performed in the 30° right oblique projection with the RF catheter in place (4 mm tip electrode). The CTI width was measured manually and the true value was calculated by reference to the distal electrode of the RF catheter. After RF ablation, conduction block in the CTI was evaluated by pacing from the proximal coronary sinus and the right postero-lateral atrium.

Results: Bidirectional block in the CTI could be achieved in 13 pts. Number of RF applications was 21.2 ± 13.1. Width of the CTI was 30.8 ± 10.5 mm. Significant correlation was found between the CTI length and the number of RF applications (r = 0.62, p < 0.05). A CTI length of < 30 mm was associated with a higher success rate and a lower number of RF applications.

	CTI width <30 mm (n = 10)	CTI width >30 mm (n = 5)	*p*
RF applications	14.5 ± 8.5	31.8 ± 12.5	*<0.01*
Block achieved	10/10 pts	3/5 pts	*<0.05*

Conclusion: 1) CTI length is correlated with the number of RF applications; 2) A CTI length > 30 mm is associated with more difficult ablation procedures with 4 mm tips. Longer distal electrodes might be more appropriate for these pts.

P645 Initial experience with a novel multielectrode catheter ablation system for atrial flutter

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Catheter ablation of atrial flutter (AFl) is performed by creating bidirectional conduction block in the isthmus area. Traditionally, a catheter pullback approach is used to create linear lesions. We investigated the feasibility and efficacy of a novel temperature controlled multielectrode catheter ablation system in the treatment of AFl.

Methods: Fourteen consecutive patients were studied (mean age 57 yrs, 11 males, 3 females). Six patients had structural heart disease and six patients were in Afl at the time of ablation. The 7 F ablation catheter has four 4 mm band electrodes each with its own thermocouple (Quadrapolar Steerable Ablation Electrophysiology Catheter, IBI, CA). Power was delivered either to a single electrode or to multiple electrodes simutaneously. Radiofrequency (RF) energy was delivered via a 150 W RF generator (IBI, 1500 T) in the temperature controlled mode (set at 65°C). The ablation catheter electrodes spanned the tricuspid annulus/IVC isthmus (5.30 to 6.30 o'clock position in the LAO60° view) and a linear lesion was created without dragging the catheter.

Results: Bidirectional conduction isthmus block was achieved in all patients. In one patient a standard 7 F 4 mm ablation catheter had to be used to complete the line of block. Median procedure time was 90 minutes (range 55–180) and median fluoroscopic time was 18.1 minutes (range 6.8–65.2). A median of 15 RF applications (range 6–40) were delivered. Carbonisation on the catheter tip occurred during two energy applications. All patients were in sinus rhythm after the ablation procedure. After a mean follow up of 4 months only one patient has had a clinical recurrence of Afl.

In conclusion, these preliminary results show that bidirectional isthmus block can be induced safely with a multielectrode ablation catheter system.

P646 Critical appraisal of local double spikes analysis as criteria for achievement of complete bi-directional isthmus block during typical atrial flutter ablation

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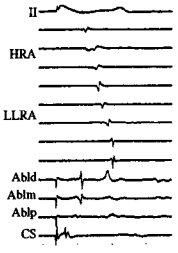
Activation mapping (AM) at the tricuspid ring-inferior vena cava isthmus (I) is the method of reference to assess achievement of complete bi-directional isthmus block (CBIB) during typical atrial flutter (AFl) ablation. It has been recently suggested that recording of widely separated double spikes (WSDS) at the ablation line could be a marker of CBIB after radiofrequency (RF) ablation. We therefore prospectively looked for WSDS during RF ablation of AFl, while simultaneously monitoring isthmus conduction using AM.

Methods: Patient population consisted of 20 consecutive patients (pts, 18 males) with a mean age of 63 ± 12 years (35–78). Seven pts had structural heart disease. In all pts, a decapolar catheter was inserted into the coronary sinus (CS), and a depolar Halo shaped catheter was positioned at the low lateral right atrium (LLRA) with the distal bipole located as close as possible to the line of ablation. AM and analysis of local WSDP were performed during LLRA and proximal CS pacing before, during and after each RF pulse delivery.

Results: CBIB was obtained in 18 patients, incomplete IB in 1 pt and procedure failed in 1 pt. In 2 pts, WSDS were recorded whereas there was either no IB (1 pt) or incomplete IB (1 pt, Fig). In 3 pts, CBIB was obtained using AM whereas WSDS could not be recorded at the site of ablation because of the presence of a wide electrically silent area. In 3 additional pts, triple spikes were recorded during LLRA pacing only, whereas AM showed CBIB.



Conclusions: WSDP recording is an adequate end point in the majority of the pts. However, WSPS does not necessarily correlate with activation mapping in assessing CBIB especially in difficult cases where high number of RF pulses are required.

VALUE OF SIGNAL-AVERAGED ECG OF P WAVE AND ATRIAL FIBRILLATION

P647 Value of the P-wave signal-averaged electrocardiogram for predicting atrial fibrillation early and long term after coronary bypass surgery

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Atrial fibrillation (AF) occurs commonly after coronary artery bypass surgery. Prolonged P-wave duration (PWD) on atrial signal averaged ECG (A-SAECG) recorded before cardiac surgery is predictor of AF following operation.

The purpose of this study was 1) to evaluate the influence of coronary artery bypass grafting (CABG) on PWD 2) to assess the relationship between PWD and prevalence of AF in one year follow up.

Methods: Study population consisted of 170 patients, 108 men and 62 women, aged 33–70 years (58 ± 8) with 2–3 vessel coronary disease who had no prior history of AF and were refered to CABG. All patients 2 days before and 14 days/1 year after cardiac surgery underwent A-SAECG recordings from orthogonal XYZ leads using digital 3-channel Holter monitoring. Filtered P wave triggered R wave signals averaging at noise level of ≤ 0.3 μV was analysed.

Results: Twenty two (13%) of the patients developed AF only 2–7 days after surgery. No one had AF during one year follow up. The P wave duration ≥ 130 msec predicted perioperative AF with sensitivity of 73%, specificity of 80%, positive predictive value of 57% and negative predictive value of 96%.

Values of P wave duration:

	PWD 1	PWD 2	PWD 3	
AF(+) 22 pts (13%)	135 + 19 ms	124 + 20 ms	125 + 24 ms	NS
AF(−) 170 pts (87%)	117 + 11 ms	119 + 17 ms	120 + 16 ms	NS
	p < 0.01	NS	NS	

PWD1-before operation; PWD2-14 days after; PWD3-1 year after

Conclusions: Prolonged P wave duration is good predictor of atrial fibrillation only in early period after coronary artery bypass grafting.

P648 Signal-averaged P-wave ECG in prediction of paroxysmal atrial fibrillation in patients with enlarged atrium

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The aim of our study was to evaluate sensitivity, specificity and positive predictive value of signal averaged P wave ECG duration (hfP) and root mean square of the signal in the first 30 ms of P wave (sRMS30) in identification the risk of paroxysmal atrial fibrillation (PAF) in group of patients with enlarged left atrium. We studied 87 patients (pts) with left atial dimension (LAD) greater then 40 mm, divided in two groups: 1. PAF – 50 (29 men/21 women) pts with PAF (62 ± 8.6 yrs old), 2. nPAF – 37 (26 men/11 women) healthy objects (62 ± 8.9 yrs old). Using an IBM PC based, special developed signal averaging system we aquire 256 PQRS complexes using P wave as a dynamical template from orthogonal, bipolar XYZ. Finally, SAP was filtered using Kaiser window 45–150 Hz. Echocardiographical measurments of LAD were carried by Hewlett-Packard Sonos 2500 in M-mode parastemal long axis examination.

Results: We determinate normal values for hfP as ≤123 ms and sRMS30 > 5.40 μV. We found in PAF group 46 pts with hfP > 123 ms, 8 pts with hfP ≤ 123 ms, 40 pts with sRMS30 < 5.4 μV and 10 pts with sRMS30 > 5.4 μV. In nPAF group we found 3 pts with hfP > 123 ms, 34 pts with hfP ≤ 123 ms, 11 pts with sRMS30 < 5.4 μV and 26 pts with sRMS30 > 5.4 μV.

	Sensitivity	Specificity	Positive predictive value
hfP	85%	91%	93%
sRMS30	80%	70%	78%

Conclusion: Both hfP and sRMS30 have value in identification pts at risk of PAF in group with enlarged atrium. However hfP has better sensitivity, specificity, positive predictive value than sRMS30.

P649 P-wave dispersion: the simple electrocardiographic marker for the detection of patients with paroxysmal atrial fibrillation

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The prolongation of intraatrial and interatrial conduction time and the inhomogeneous propagation of sinus impulses have been shown in patients with atrial fibrillation. Recently P wave dispersion (PWD), which is believed to reflect inhomogeneous atrial conduction, has been suggested to be useful in predicting patients with paroxysmal atrial fibrillation (PAF).

Methods: Eighty-one consecutive patients, 51 men and 30 women aged 43 ± 18 years with a history of idiopathic PAF and 40 healthy subject (25 men and 15 women, mean age 41 ± 19 years) were studied. Twelve leads ECG was obtained from all patients and control subjects in the supine position during sinus rhythm. The P wave duration was calculated in all 12 leads of the surface ECG. The difference between the maximum P wave duration and minimum P wave duration was calculated and this difference was defined as P wave dispersion (PWD = Pmax − Pmin). All patients and controls were also evaluated by echocardiography to measure the left atrial diameter.

Results: There was no difference between patients and controls in age (43 ± 18 vs 41 ± 19 years, p = 0.6) and left atrial diameter (3.7 ± 1.1 cm vs. 3.6 ± 1.0 cm, p = 0.8). P maximum was found to be significantly higher in patients with a history of PAF (119 ± 13 ms) than controls (101 ± 11 ms, p = 0.001). P wave dispersion was also significantly higher in patients than controls (42 ± 13 ms vs 23 ± 9 ms, p < 0.001). There was no correlation between age, left atrial diameter and P wave dispersion (p > 0.05). A P maximum value of 108 ms separated patients with PAF from control subjects, with sensitivity 66%, a specificity of 65%, positive predictive accuracy of 79% and negative predictive accuracy of 49%. A P wave dispersion value of 35 ms separated patients from control subjects, with sensitivity 71%, a specificity of 72%, positive predictive accuracy of 84% and negative predictive accuracy of 55%.

Conclusion: P maximum and P wave dispersion calculated on standard surface electrocardiogram are simple electrocardiographic markers that could be used to identify the patients with idiopathic paroxysmal atrial fibrillation.

P650 Is there any relationship between signal-averaged ECG P-wave duration and P-wave dispersion?

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P wave signal-averaged electrocardiography (SAECG) and P wave dispersion (PWD = Pmax-Pmin) have been shown to be useful to detect the patients at risk of atrial fibrillation. However the relationship between the SAECG P wave duration and PWD has not been evaluated yet.

Methods: Thirty-four consecutive patients, 19 women and 15 men, aged 49 ± 12 years with a history of idiopathic paroxysmal atrial fibrillation and 30 healthy subject (5 women and 25 men, mean age 48 ± 11) were enrolled in this study. SAECG P wave recordings and 12-lead surface ECGs were obtained from all patients and control subjects in the supine position. The P wave duration was calculated in all 12 leads of the surface electrocardiogram. The difference between the maximum P wave duration and the minimum P wave duration was calculated and this difference was defined as P wave dispersion. Filtered P wave duration was calculated on SAECG recordings.

Results: P maximum was found to be significantly higher in patients with a history of PAF (117 ± 14 ms) than controls (98 ± 9 ms, p = 0.000). P wave dispersion was also significantly higher in patients (40 ± 12 ms) than in control subjects (22 ± 8 ms, p = 0.000). Filtered P wave duration was longer in PAF patients than controls (131 ± 12 ms vs 107 ± 9.7 ms, p = 0.00). There was a positive correlation between PWD and SAECG P wave duration (r = 0.79, p = 0.000).

A P maximum value of 105 ms separated patients with PAF from control subjects, with a sensitivity 70%, a specificity of 76%, and a positive predictive accuracy of 77% and negative predictive accuracy of 69%. A P dispersion value of 30 ms separated patients from control subjects, with a sensitivity 83%, a specificity of 80%, and a positive predictive accuracy of 77% and negative predictive accuracy of 69%. These values for SAECG P wave duration > 120 ms were 79%, 86%, 87% and 78% respectively.

Conclusion: 1) There is a relationship between P wave dispersion and SAECG P wave duration. 2) P maximum, P wave dispersion and SAECG P wave duration could be useful to identify the patients with history of PAF during sinus rhythm. 3) P wave dispersion, as a simple ECG parameter, can be used instead of SAECG P wave duration.

CARDIOVERSION OF ATRIAL FIBRILLATION

P651 Left atrial appendage stunning in atrial fibrillation: comparison between pharmacological and DC cardioversion

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Background: The stunning of the left atrial appendage (LAA) and the left atrium (LA)after cardioversion (CV) is a phenomenon that could increase the embolic risk. It seems more evident after DC (DCV)than pharmacological (PCV) CV, for this reason a four-weeks of oral anticoagulation after successfull procedure is usually recommended.

Aim of the study: To evaluate the LA function, the emptying (EV)and filling velocity (FV) profiles of LAA we evaluated a group of randomized patietns (P) with recent (<6 months) onset non rheumatic AF (NRAF) with TTE and TEE immediately before and after 48 hours from DCV or PCV and with TTE alone 24 hours after CV.

Study population: Thirty P (17 females) with NRAF lasting 85 ± 34 dd, age 66 ± 9 were randomized to PCV with quinidine or DCV.

Results: Twenty P reverted to sinus rhythm (11 DCV, 9 PCV)

Comparison between DCV and PCV

	DCV	PCV	p
FV basal (cm/sec)	37 ± 18	38 ± 12	ns
EV basal (cm/sec)	26 ± 9	31 ± 14	ns
FV aft 48 h (cm/sec)	44 ± 16	39 ± 9	ns
EV aft 48 h (cm/sec)	40 ± 20	41 ± 14	ns
A 24 h aft CV (m/sec)	0.6	0.53	ns

Conclusion: 1. In P with recent onset NRAF DCV does not induce more evident

LA and LAA stunning in coparison with PCV

2. Our data demonstrate a good LAA function just 48 h after successfull CV, for this reason a four-weeks antocoagulation therapy may be unnecessary in this group of patients.

P652 Evidence of atrial stunning after acute infusion of class 1C anti-arrhythmic agents

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Restoration to normal sinus rhythm is responsible for the transient left atrial dysfunction ("stunning") observed after cardioversion of atrial fibrillation (AF). In recent onset AF class 1C anti-arrhythmic agents are often used as a first line intervention to restore the normal sinus rhythm. Aim of the study was to evaluate the left atrial and left atrial appendage (LAA) function during acute administration of these drugs in patients not converted to sinus rhythm.

Method: Using data from our registry on transesophageal echocardiography (TEE) in AF management, 41 patients were identified who underwent chemical cardioversion; 21 patients successfully reverted to sinus rhythm were excluded. 14 patients (group 1) received propafenone (P) and 6 patients (group 2) received flecainide (F). Both drugs were administered i.v. at a dosage of 2 mg/kg body weight in 10 minutes during continuous TEE monitoring. Presence and intensity of spontaneous echo contrast (SEC) (from 0 = absent to 3 = intense) and LAA function (average of peak Doppler derived outflow velocities over 5 consecutive cardiac cycles) were evaluated.

Results: Baseline characteristics (Age, AF duration, left atrial dimension, SEC and LAA function) were similar in both groups. At the end of bolus infusion, in both groups SEC was increased and LAA outflow velocities were decreased.

	Group 1 (n = 14)	Group 2 (n = 6)
Age (years)	64 ± 11	71 ± 3*
AF duration (days)	18 ± 9	28 ± 24*
Left Atrial diameter (mm)	43 ± 5	47 ± 6*
Mean SEC degree:		
Baseline	0.64 ± 0.6	0.83 ± 0.4*
End of bolus	1.29 ± 0.8+	1.17 ± 0.4**
LAA flow (cm/sec):		
Baseline	32.1 ± 18.1	25.1 ± 10.1*
End of bolus	16.9 ± 12.3#	14.8 ± 3.0†

Abbreviations: see text. *p = NS vs group 1; **p = NS vs baseline. +p = 0.007 vs baseline; #p = 0.000 vs baseline; †p = 0.028 vs baseline.

Conclusion: Left atrial stunning, a known risk of thromboembolic events, develops during acute administration of propafenone and flecainide. This phenomenon is not due to restoration to normal sinus rhythm.

P653 Measurement of atrial effective refractory period during ongoing atrial fibrillation in man allows study of anti-fibrillatory drug effects

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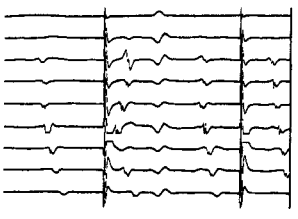
Variations in local atrial fibrillation intervals (AFI) can be due to variations in refractory period and (ERP)/or excitable gap (EG). Class I drugs are known to increase AFI. We studied the effects of a Class I drug on ERP, EG and AFI during AF in man.

Methods. In 5 patients (pts) with sustained AF, a 20 poles Halo catheter was positioned anterior to the Crista Terminalis for unipolar atrial recordings (A), and another bipolar catheter within 1 mm of the Halo catheter for pacing. After local AF entrainment was performed, pacing at a cycle length of 500 ms was delivered in an asynchronous mode. Coupling intervals (CI) of captured beats were measured at the closest electrode from the pacing site. Capture was said to occur if local A potential morphology was changed after the pacing spike, and when impulse radiated from the paced site to neighboring electrodes (Figure shows lead 1 and 8 atrial unipolar recordings). Mean CI of a minimum of 15 captured beats was taken as local AERP. Before pacing, 100 consecutive AFI were evaluated at same site. The same procedure was repeated after IV Cibenzolin (cib) injection in 3 pts.

Results. In all 5 pts, a strict correlation was found between AERP and AFI (r = 0.95, p < 0.0001). Cib prolonged AERP in the 3 pts (from 159 ms to 211 ms). After Cib, EG/AFI was shortened in 2 pts (−4 and −13%), One converted to SR and one to Aflutter. In 1 pt EG/AFI increased and AF persisted.



Conclusion. This method may be of value for the measurement of the effects of anti-fibrillatory drugs on AERP and EG during AF in man.

P654 Restoration and maintenance of sinus rhythm with amiodarone after initial unsuccessful electrocardioversion in patients with persistent atrial fibrillation

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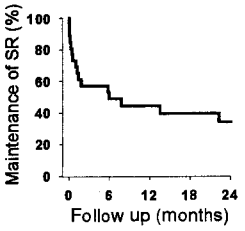
Background When external electrical cardioversion (ECV) fails to restore sinus rhythm (SR) in patients with persistent atrial fibrillation (AF), a second ECV attempt after pre-treatment with amiodarone is an option. However, the efficacy of amiodarone in restoring and maintaining SR using this strategy is yet to be established.

Methods After unsuccessful ECV 39 patients (25 male, mean age 62 ± 11 years) with AF (median duration of current episode 304 days) were treated with amiodarone 200 mg t.i.d. during four weeks before a second ECV was attempted. If SR was restored, amiodarone treatment was continued at 200–300 mg daily as a prophylactic drug, depending on amiodarone and desethylamiodarone plasma levels.

Results Five (13%) patients converted on amiodarone to SR within the four weeks prior to the second ECV. Two others (5%) did not undergo a second ECV because of unstable heart failure. The remaining 32 patients underwent the re-ECV which was successful in 21 patients. Mean follow up was 14.5 ± 17.3 months. Of the 26 patients who converted to SR, 44% were in SR after 12 months (figure) which equals an overall success rate of 30%.



Conclusions After an unsuccessful ECV 30% of patients maintained long-term SR after pre-treatment with amiodarone. Therefore, this strategy may be considered before attempting internal defibrillation or accepting AF.

P655 Pharmcokinetics and pharmacodynamics of atrial versus peripheral infusion of flecainide acetate in patients with atrial fibrillation

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Background: the automatic chemical cardioverter defibrillator may be a near future chance in the treatment of atrial fibrillation (AF). There is little knowledge about possible different antiarhythmic properties of the antiarrhythmic drugs according to rate and site of infusion.

Methods: We compared pharmacokinetics and conversion efficacy of different administration routes of flecainide (Fl) in 16 patients with paroxysmal AF in which sustained AF (>20 min duration) was induced during EP study. Pts were divided into 3 groups: A (6 pts, 2 mg/kg 5′ i.v. infusion), B (5 pts, 2 mg/kg 10′ intraatrial infusion) and C (5 pts, 2 mg/kg 5′ intraatrial infusion). We evaluated: Fl plasma concentrations at 1′–2′–5′–10′–15′–20′ after the beginning of the infusion; the samples were simultaneously drawn from pulmonary artery (PA), coronary sinus (CS), femoral artery (FA). Mean AF cycle length, efficacy to restore sinus rhythm (SR, C) and proarrhythmic events were evaluated.

Results: Significant lower peak Fl concentration in the PA blood was observed in group A vs B and C (1.7 vs 3.6 vs 2.6 mg/L, $p < 0.05$ A vs B or C respectively) while no differences were detected in the Fl concentration in CS or FA among the three study groups (p = NS). No difference in sinus rhythm conversion was observed among the three groups, but a faster sinus conversion time in the group C vs A and B (3 vs 8 and 8 min respectively, $p < 0.05$) In all 3 groups AF mean cycle lengths significantly prolonged prior to sinus rhythm conversion (A: from 156 msec to 191 msec, B: from 151 to 196 msec, C: from 155 to 197 msec; $p < 0.01$). No proarrhythmic events or hypotension were reported.

Conclusion: Fl intraatrial infusion: i) allowed a faster sinus rhythm restoration compared to peripheral infusion; ii) was not accomplished by high peripheral plasma concentration because of a strong lung first-pass absorption. This behaviour could contribute to reducing the rate of adverse events or allow a lower acute i.v. Fl dose maintaining a good efficacy rate.

P656 Once-a-day formulation of diltiazem or metoprolol to control ventricular rate in patients with permanent atrial fibrillation: a randomized, crossover, placebo-controlled study

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Calcium-blockers and beta-blockers have been successfully used to control ventricular rate (VR) in permanent atrial fibrillation (PAF). No data are avalaible about the administration of once-a-day formulation drugs in this field.

Methods. The study concerns 25 patients (pts) (mean age 63 ± 7, range 52–76 years) with stable (>6 months) PAF, without organic heart disease or with arterial hypertension only (22/25 pts; 88%), NYHA functional class I, and VR > 100 beats/min on resting ECG. The effect on VR of once-a-day formulations of Diltiazem 300 mg (DLT) or Metoprolol 200 mg (MTP) were compared to placebo (PLA) and to oral digoxin (DGX) (mean dose 0.304 ± 0.063 mg/day, serum concentration 0.8–1.4 ng/ml). Treatments were administred randomly (each for a week) in a cross-over fashion, and were assessed by 24-hour Holter during daily life and by three-minute walking-test (WT). We evaluated: mean VR (AVR) over 24 hours, minimal VR (mVR), maximal VR during WT (MVR), VR impairment (VRi) {MVR/maximal VR for age × 100}, pauses >2 sec (PAU), phases of brady < 50/min (BRD) over 4 consecutive RR cycles.

Results:

	AVR	mVR	MVR	VRI	PAU	BRD
PLA	111 ± 14	79 ± 10	164 ± 19	105 ± 14	1 ± 1	1 ± 3
DGX	93 ± 13*	65 ± 11*	147 ± 20*	94 ± 12*	13 ± 21**	23 ± 32**
DLT	88 ± 10*°	60 ± 11**	138 ± 17**	88 ± 13**	15 ± 25**	60 ± 95**
MTP	92 ± 13*^	69 ± 12*°^^	138 ± 22*°	88 ± 14*°	4 ± 10^^	19 ± 50^

p value vs. PLA: * < 0.001; ** < 0.01. p value *vs* DGX: * < 0.05; ° < 0.01. p value *vs* DLT: ^ < 0.05; ^^ < 0.001

None of the study-pts experienced either RR cycles > 3 sec or phases of bradycardia < 30/min. No seriuos adverse effects causing discontinuation of the drug-trial were noted in either group.

Conclusion. Once-a-day formulations of diltiazem or metoprolol are equally superior to DGX or PLA to control the VR during mild exercise and to minimize VRi in patients with permanent atrial fibrillation without organic heart disease. The reduction of peak VR is obtainable without critical slowing of resting VR.

P657 Intravenous amiodarone versus glucose-insulin-potassium-magnesium infusion in cardioversion of new-onset atrial fibrillation: preliminary results

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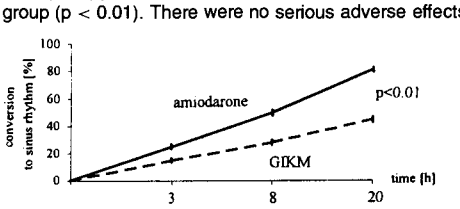
Paroxysmal atrial fibrillation (PAF) is one of the most common causes of hospitalisation. However, until now, no standard antiarrhythmic therapy has been accepted for pharmacological cardioversion of PAF. Amiodarone seems to be a promising candidate, but only a few randomized trials are available and the results are inconsistent.

Aim of the study: To compare efficacy of intravenous amiodarone with standard electrolyte supplementation in cardioversion of PAF.

Methods: 65 patients with PAF lasting less than 24 hours were randomly assigned to amiodarone group (n = 32) (5 mg/kg as a 30 min. iv infusion, followed by iv infusion of 10 mg/kg during 20 hours), or iv infusion of 10% glucose, 10 IU of rapid action insulin, 40 mEq of kalium chloride and 4 g of magnesium sulphate (GIKM) (n = 33). Patients requiring emergency DC cardioversion were excluded.

Results. Twenty hours after initiation of therapy sinus rhythm was restored in 26 (81%) patients in the amiodarone group and in 15 (45%) patients in GIKM group ($p < 0.01$). There were no serious adverse effects in either group.



Conclusion. Amiodarone is a very effective drug for termination of PAF lasting less than 24 hours, with the conversion rate much higher, than reported for spontaneous conversion of PAF. The study is ongoing and the final results will be reported after inclusion of 150 patients.

P658 Combined administration of quinidine and propafenone for atrial fibrillation: the CAQ-PAF pilot study

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The need for innovative approaches in the prevention of recurrence of atrial fibrillation (AF) is well recognized. The objective of the CAQ-PAF study was to evaluate the potential of low dose quinidine (QUI) to improve propafenone (PPF) efficacy by causing chronic inhibition of its metabolism mediated by CYP2D6. This would favor PPF instead of its 5-hydroxy metabolite as the active compound in the plasma; PPF being a product with a potentially more favorable profile including β-blocking effects. This prospective, double-blind study consisted of 102 pts (48 males and 54 females; 60 ± 11 y), with AF lasting >1 hour. All pts received PPF 150 mg TID but were randomized to combined therapy with either placebo or QUI (100 mg BID). Clinical profile, history of AF and antiarrhythmic use, CYP2D6 genotype and left atrial size were documented: 77% had ≥2 episodes of AF in the previous year, 38% had AF recurrence while on antiarrhythmics and 21% had *de novo* AF. First recurrence of AF (≥7 days), side-effects, ECG and plasma concentrations of PPF and its metabolites were monitored for 1 year. Throughout the study, PPF concentrations (ng/mL) were increased by QUI compared to patients receiving placebo ($P < 0.05$).

	1 month	3 months	9 months	End of study
PPF + QUI	115 ± 567	1013 ± 511	1073 ± 698	1033 ± 611
PPF + placebo	349 ± 282	376 ± 399	330 ± 240	328 ± 229

Thirty-five patients completed the study without recurrence of AF: 20 were receiving PPF + QUI while 15 were receiving PPF + placebo. 78% of pts with PPF levels > 1500 ng/mL were in sinus rhythm at 1 year compared to 58% when levels were >1000 ng/mL. In contrast, recurrence of AF occurred in 22/23 pts with PPF levels < 1000 ng/mL. In addition, 10/11 pts with a genetically-determined nonfunctional CYP2D6 activity and increased PPF concentrations remained in sinus rhythm and completed the study. Finally, 14% of the pts were excluded due to side-effects. In conclusion, our results indicate the potential benefits of increased plasma concentrations of PPF to prevent recurrence of AF. Strategies aimed at improving bioavailability of PPF during oral treatment could represent new avenues in the treatment of AF.

P659 Pre-treatment with verapamil in patients with persistent or chronic atrial fibrillation who underwent electrical cardioversion

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The increased vulnerability for atrial fibrillation (AF) recurrence is probably due to AF induced changes in the electrophysiologic properties of the atria. This electrical remodeling seems to be due to intracellular calcium overload. The aim of our study was to evaluate, in a prospective and randomized fashion, the efficacy of a pretreatment with Verapamil (V) in reducing recurrences of AF after electrical cardioversion (C).

Methods. One hundred-seven patients with persistent or chronic AF underwent external and or internal C. Three days before C patients were randomized in three groups. All patients received oral Propafenone (P) (900 mg per day) 3 days before and during the entire period of follow-up (3 months). In the first group patients received only the P. In the second group, in adjunct to P oral V (240 mg per day) was initiated 3 days before C and continued during the follow-up; finally, in the third group oral V was administered 3 days before and continued only for 3 days after electrical C.

Results. In 7 (6.5%) patients sinus rhythm was documented at the time of C. Eight (8%) patients were dropped from the follow-up because of pharmacological side effects. During the three months follow-up 23 patients (23.7%) had AF recurrence. Mantel-Haenszel cumulative χ^2 reached a significant level only when comparing AF free survival curves of group I versus group II and group III ($\chi^2 = 5.2$ and $\chi^2 = 4$, respectively, $p < 0.05$). Significantly, fifteen (65.2%) AF relapses occurred during the first week after C with an higher incidence in group I (10/33 patients, 30.3%) than group II (2/34 patients, 5.9%, $p = 0.01$) and group III (3/30 patients, 10%, $p = 0.04$).

Conclusions. Six days oral V administration centered on the C day, combined with P, significantly reduce the incidence of early recurrences of AF compared to P alone. The time course of AF relapses, and the lack of benefits of long-term therapy with V, strongly support the hypothesis that calcium antagonists just facilitate the recovering from electrical remodeling.

P660 High-dose i.v. amiodarone in the conversion to sinus rhythm of paroxysmal atrial fibrillation. When is it necessary?

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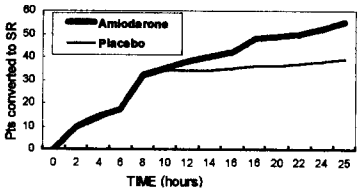
The rate of spontaneous conversion of paroxysmal atrial fibrillation (PAF) to sinus rhythm (SR) is high and not affected by low dose amiodarone (Am) treatment. We evaluated high-dose Am in the treatment of PAF.

Methods: 120 patients (pts) with PAF (<48 h) were randomized to receive for 24 hours: (1) Group A (n. 60), Placebo; (2) Group B (n. 60), continuous IV Am 120 mg/hour (total 3 gr). Group A pts not converting to SR within 24 hr were crossed over to Am therapy. All pts received digoxin.

Results: Baseline ventricular rate (MVR) was 123 ± 21 and ± 23 beats/min in groups A and B. In group A, 39 pts (65%) converted to SR vs 55 (92%) in group B ($p = 0.001$). Thirty-four of 39 pts (87%) converting spontaneously (in group A) have converted within 10 hours. Seventeen pts (81%) in group A not converting on placebo have converted after being crossed over to high dose Am treatment.



Finally 9 pts (in both groups) did not convert on high dose Am, 6 converted after electrical cardioversion, but 8 pts (89%) were in chronic AF after 1 month. In pts still in AF after 8 hours of treatment, the MVR decreased to 117 ± 24 beats/min in group A vs 81 ± 19 beats/min in group B ($p = 0.001$). No adverse events requiring treatment occurred in group B pts.

Conclusion: IV high-dose Am treatment (120 mg/hr) is safe and facilitates conversion of PAF to SR. Spontaneous conversion commonly occurs within 10 hours, therefore, high-dose Am may be reserved for pts requiring rate control or not converting within 10 hours. Pts resistant to high-dose Am are at high risk of developing chronic AF.

P661 Sinus node chronotropy following isoproterenol challenge in patients with chronic atrial fibrillation after cardioversion

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Animal studies have shown that sinus node chronotropy is attenuated after atrial fibrillation induced with rapid atrial pacing. Limited studies are available in humans. The purpose of our study was to examine the sinus node chronotropy following isoproterenol challenge in patients with chronic atrial fibrillation after cardioversion (CV) and correlate it to the recurrence of atrial fibrillation.

Methods: Twenty-eight patients (pts) with chronic atrial fibrillation (mean duration 2 ± 1 months, range 1–3 months) were successfully cardioverted to sinus rhythm with external defibrillation. All were free of any medical treatment except anticoagulants and ACE inhibitors. They had been evaluated by echocardiography before CV. Ten minutes after CV, isorpoterenol was infused in all pts (10 γ for one minute). Heart rate was recorded at baseline, at the end of isoproterenol infusion and 10 minutes later. Pts were discharged with oral therapy (sotalol) and followed-up at six months for atrial fibrillation recurrence. ANOVA was used for analysis.

Results: Twelve pts remained in sinus rhythm (group I) and the rest 16 recurred (group II). No statistical difference was noted between the two groups regarding the age of the patients (52 ± 5 vs 49 ± 7 years) the atrial fibrillation duration (1.9 ± 1 vs 2 ± 2 months) as well as the left atrial dimensions (45 ± 3 vs 46 ± 2 mm).

Time	Group I	Group II	p value
Baseline	69 ± 8 bpm	61 ± 20 bpm	0.01
End of infusion	105 ± 7 bpm	83 ± 35 bpm	0.001
10 min	76 ± 11 bpm	65 ± 21 bpm	0.017

Conclusions: Heart rate is higher in pts who remain in sinus rhythm six months following electrical cardioversion not only ten minutes after the procedure but also after isoproterenol challenge. Atrial fibrillation recurrence might be related to sinus node dysfunction as well.

LOW-ENERGY INTERNAL CARDIOVERSION OF ATRIAL FIBRILLATION

P662 Low-energy internal cardioversion of persistent atrial fibrillation

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Background: Low energy internal cardioversion has recently been developed and proposed in patients (pts) with persistent atrial fibrillation.

Methods: Thirty-three pts (mean age 68 yrs, range 50–75, 24 M, 9 F) affected by chronic atrial fibrillation dating from 40 to 250 days, were included in the study.

The selection criteria for the enrollment were the following: a) persistent atrial fibrillation for at least 1 month; b) effective anticoagulation for at least 3 weeks, c) previous unsuccessfull attempts of cardioversion (drugs or DC shock).

Initially, three intracavitary temporary leads were used: two 6 F catheters with a large surface coil (>500 sqmm, InControl Inc.) for shock delivery and one 5 F bipolar or quadripolar lead for ventricular synchronization. More recently, a single lead double coil catheter was used for defibrillation.

The configuration catheter was Right Atrium (RA) and Left Pulmonary Artery (22 pts) (LPA) or coronary sinus (9 pts) (CS). In 2 pts a tripolar configuration was necessary (RA, CS, LPA). All the pts received a mild sedation with Diazepam. Shocks were delivered from a defibrillator system analyzer (DSA 2101 InControl Inc.), at 250 V (4J), 300 V (6J), 350 V (7.5J) and 400 V (10J). All the shocks were properly synchronized and no ventricular arrhythmia was induced.

Results: Sinus rhythm was restored with a mean energy of 6.5 J (mean impedance 58 ohm) using RA + LPA configuration catheters, and 3.1 J (mean impedance 50 ohm) using RA + CS configuration. Internal cardioversion was successful in 31/33 pts, restoring sinus rhythm in 93.94%. No pts referred severe discomfort or pain from the procedure: the sensation produced by the internal shock was defined as a moderate precordial punch.

Conclusions: Low energy internal cardioversion is a safe, simple and highly effective procedure in restoring sinus rhythm.

P663 Clinical results with a new device for internal cardioversion of atrial fibrillation and dual-chamber pacing

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Background: Based on the experience that internal cardioversion (IntCV) of atrial fibrillation (AF) is effective with electrodes in the right atrium and pulmonary artery, a new balloon guided catheter and external defibrillation device with optional dual chamber pacing was evaluated.

Methods: IntCV of AF was performed in 81 patients (pts) (age: 58 ± 12 years, duration: 11 ± 14 months, postcardiothoracic surgery: 16 pts). A single lead balloon guided 7.5 french catheter for intCV (EP MedSystem) was introduced via the brachial (76 pts) or femoral vein (5 pts). The distal shock array was placed in the left pulmonary artery, the proximal shock array had firm contact to basal atrial tissue. Each array consits of five 5 mm ring electrodes with a total surface of 2.5 cm^2. Via a distal lumen haemodynamic measurements can be performed. R-wave triggered biphasic shocks of 50% tilt were delivered by a new external defibrillator (Alert, EP MedSystem) device that incorporates combined 12 lead surface ECG, intraatrial and ventricular EGM online recording and monitoring. Optional atrial stimulation (AAI, AOO) for overdrive suppression of atrial premature beats after intCV for prevention of early recurrence of AF could be performed. For safety backup pacing in case of post shock bradycardia ventricular stimulation (VVI, VOO) was available.

Results: In 76 of 81 pts (94%) sinus rhythm (NSR) was restored with a mean energy of 6.7 ± 4.8 Joules. In 14 pts with early recurrence of AF (within 30 s) after initially successful intCV atrial pacing (2–5 minutes) for overdrive suppression of atrial premature beats was performed after the following successful shock application. All of those pts remained in NSR. The fluoroscopy time was 1.8 ± 1.6 minutes.

Conclusion: IntCV of AF by the means of this new device proofed to be save, effective and easily performable. Our data indicate that post shock atrial pacing for overdrive supppression of atrial premature beats might be helpful for prevention of early recurrence of AF. With the additional option of ventricular stimulation and heamodynamic monitoring also post cardiac surgery pts might benefit of the from this system.

P664 Low-energy endocavitary electrical cardioversion: characteristics of patients undergoing sure relapse

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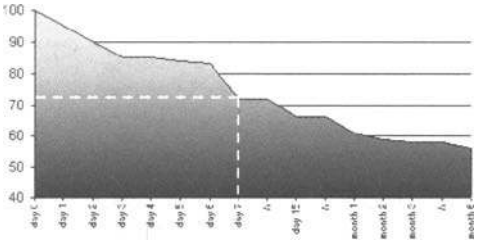
Identification of pts with atrial fibrillation (AF) relapse (AFR) after low energy electrical cardioversion (LEEC) is important to choose therapy.

Methods: 100 pts (mean age 64 ± 12 yrs) who underwent LEEC for chronic AF were studied: 38 (65 ± 10 yrs) had AFR within 7 days, 13 (63 ± 13 yrs) had AFR between 7 days and 6 months and 49 (65 ± 14 yrs) did not have AFR. The 3 groups were age-matched. Evaluated parameters: age, associated cardiopathy, left atrial dimension (LAd, 44 ± 5 mm), arrhythmia duration (AD, 4 ± 11 months), months since the first AF episode (1^{th}AFT: 29 ± 44 months), left ventricular EF (0.53 ± 0.12), and antiarrhythmic theraphy (AT: amiodaron, propafenone, Ca-antagonists, digitalis, flecainide). The time behaviour of AFRs is shown in the figure.



Results: Kaplan-Meyer analysis: 1. all pts with Lad > 52 mm or age > 76 yrs or AD > 8 months or 1^{st}AFT > 100 months had AFR; 2. AFR was always within 7 days when LAd > 49 mm or AD > 8 months or 1^{th}AFT > 40 months.Valvular heart disease showed a greater incidence of AFR (p = 0.015). AT did not significantly change the incidence of AFR.

Conclusions: Results of this study help both to identify pts with AFR and to predict the time to AFR after LEEC. This is important to decide whether to perform LEEC and what therapy to choose after LEEC.

P665 Ineffective shocks results on local atrial fibrillation intervals and different types of sinus rhythm restoration during low-energy internal cardioversion

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Background. The effect on unsuccessful shocks (US) on local atrial fibrillation (AF) as well as the modality of termination of AF has not been carefully evaluated in humans.

Methods. In 29 patients undergoing low energy internal cardioversion of persistent AF an octopolar lead was positioned in the right lateral atrial wall. The mean local fibrillation intervals (FF) were recorded in basal condition (3 sec), before (3 sec), during and after each shock (first 3 sec). The interval between the last atrial electrogram and the shock (AS) was evaluated in the unsuccessful and successful shocks (SS). Beginning from 100 V a 50 V step-up protocol was used until sinus rhythm (SR) restoration. The modalities of AF termination after shock delivering were classified in the following types. Type A: no atrial electrogram (AE) before the sinus beat (SB); Type B1: only 1 recorded AE before the sinus beat; type B2: 2–5 recorded AE before the SB; type B3: more than 5 AE before the sinus beat.

Results. A total of 104 endocavitary shocks were analysed. A significant difference between pre-shock and 0–3 post-shock FF intervals was found at the 50% and 75% of the defibrillation threshold energy (162.7 ± 33.7 ms vs 176.8 ± 7.1 ms and 183.8 ± 20.1 ms vs 194.9 ± 32.5 ms respectively, $p < 0.05$ in both). The mean AS was 63.3 ± 40.9 ms in the SS and 96.9 ± 47.7 ms in the US shocks ($p < 0.001$). Type A termination was observed in 12 (43%) pts, type B1 in 7 (22%), type B2 in 7 (22%) and type B3 in 3 (13%). Pts with type A and B1 termination compared to pts with type B2 and B3 termination showed a less complex local AF (Type 1 AF in 80% and in 12%, respectively, $p < 0.005$) and a significantly shorter AS interval (64.6 ± 48 ms vs 103.7 ± 38 ms, respectively, $p < 0.05$).

Conclusions. 1) FF interval prolongation lasts up to 3 seconds and predicts the efficacy of the following shocks. 2) This suggests the possibility to restore SR delivering a second low energy shock within 3 seconds after the first. 3) The chance of AF termination is greater when the AS interval is short, implying the importance of synchronisation of the shock with at least a portion of the atrial tissue. 4) The modality of AF termination seems related to the complexity of the AF preceding the shock and 5) to the duration of the AS interval.

P666 Efficacy and pain perception using a low peak voltage biphasic waveform for internal atrial cardioversion

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Background: To evaluate the influence of peak voltage of different waveforms (WF) used for internal cardioversion (IC) of atrial fibrillation (AF) on defibrillating efficacy and pain perception (PP) we compared a low peak voltage 500 μF, 40% tilt biphasic WF (LV-WF) to a 60 μF, 80% tilt standard peak voltage biphasic WF (SV-WF).

Methods: In 19 patients (pts) with paroxysmal AF the atrial defibrillation threshold (ADFT) for both WF was determined under sedation in a paired randomized order using a step-up protocol. A single lead with one coil in the coronary sinus and the other in the right atrium position was used. After ADFT testing, sedation of the pts was reversed. One shock (S) at ADFT with each WF was given in random order to the conscious pts. When the ADFT was >3 J, PP was determined at 3 J. Pts compared their PP in response to the 2 different WF.

Results: In 1/19 pts AF could not be terminated. In 15/18 pts IC could be achieved at delivered energies < 4 J. The mean values of the delivered energies revealed a reduction from 3.5 ± 3.9 J for the SV-WF to 2.1 ± 2.4 J for the LV-WF ($p < 0.01$). Peak voltage level at ADFT was lower for LV-WF than for SV-WF (100 ± 53 V vs. 290 ± 149 V, $p < 0.01$). Mean duration of the LV-WF at ADFT was longer than the value for SV-WF (16.6 ± 1.2 ms vs. 6.4 ± 0.4 ms, $p < 0.01$). ADFTs were above the pain threshold in 17/18 pts. One pt perceived no pain at all. In another pt the PP testing was terminated because of intolerable pain at 0.5 1 with the LV-WF. Ten out of the remaining 16 pts perceived the LV-WF as more painful. In 8 of these 10 pts the LV-WF was tested after the SV-WF has been applied. Six pts out of 16 perceived the SV-WF as more painful. In all these 6 pts the SV-WF was tested in the 2nd place. The 2nd S was perceived as more painful in 88% of pts independent of the WF used.

Conclusion: ADFT can be significantly reduced at lower peak voltages and longer shock duration by using a 500 μF, 40% tilt biphasic WF instead of a 60 μF, 80% tilt biphasic WF. However, this did not affect PP. PP increases with the number of applied shocks.

P667 Low-energy intracardiac cardioversion of chronic atrial fibrillation by single femoral approach

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The low energy intracardiac cardioversion of atrial fibrillation is usually performed positioning an electrode in right ventricle, a second one in right appendage (RA), and a third one in the coronary sinus (CS) or in the left branch of pulmonary artery (LPA). The RA-CS configuration is normally preferred, but it is frequently time-consuming requiring a second venous access (subclavian or internal jugular) with additional risk of complications. The aim of this study was to assess the effectiveness of a systematic single femoral venous access, with unselected RA-CS or RA-LPA configuration.

Methods. We studied 40 patients (24 males, 16 females, mean age 64 years) with chronic atrial fibrillation. All patients were treated with a mild sedation (diazepam). These information were collected: 1) acute efficacy; 2) mean energy and impedence required; 3) mean number of shocks needed; 4) mean time required to perform the procedure; 5) level of discomfort related to the intrathoracic shock, 6) incidence of complications.

Results. Twenty patients had RA-CS and 20 RA-LPA electrode configuration for defibrillation. In all patients sinus rhythm was acutely restored. No significant differences were found concerning mean energy and impedance required to obtain cardioversion in RA-CS and RA-LPA groups (10.1 ± 3.0J vs 10.6 ± 3.9 J J and 50.9 ± 10.1 Ohms vs 57.2 ± 10.2 Ohms, respectively, p = ns). Mean number of shocks required was 2.35 ± 1.35 in RA-CS group and 2.30 ± 1.30 in RA-LPA group (p = ns). Mean time required to complete the whole procedure was 42 ± 11 minutes for RA-CS group and 38 ± 8 minutes for RA-LPA group (p = ns). The chest discomfort was minimal or mild in 80% and moderate in 20% without differences in the two groups. No major complications was observed (only one case had a femoral arterovenous fistula, surgically treated).

Conclusion. Low energy intracardiac cardioversion of atrial fibrillation by single femoral approach is safe and effective. The RA-LPA electrode configuration allows restoration of sinus rhythm with the same efficacy as the RA-CS configuration. The systematic single femoral approach with unselected RA-CS or RA-LPA configuration is well-tolerated and it allows to obtain a very short procedure time.

P668 Immediate recurrence of atrial fibrillation following internal DC cardioversion predicts subsequent late recurrence

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Background: Internal DC cardioversion (ICV) for atrial fibrillation (AF) is highly effective at restoring sinus rhythm (SR), however the recurrence rate is high. Previous reports have suggested that immediate recurrence of atrial fibrillation (IRAF -recurrence of AF within 1 minute of restoring SR) does not predict subsequent late recurrence of AF.

Methods: Fifty-one consecutive patients (40 male, mean age 59 years), undergoing ICV for chronic persistent AF (mean duration 33 months [3–384]) were studied. Patients had all cardioactive medication stopped 3 days before the procedure (except for 2 patients on amiodarone), and cardioactive medication was not recommenced for the duration of the study. Patients were closely monitored for recurrence of AF by Holter monitor and daily trans-telephonic monitoring.

Results: Forty-seven patients had successful ICV and 15 of these patients experienced IRAF (mean of 2 episodes per patient). Patients with IRAF were no different in clinical characteristics to those without IRAF (mean age 58 v 61 years, mean duration AF 29 v 25 months, mean LA size 4.11 v 4.06 cm, all $p > 0.25$). IRAF occurred a mean of 21.6 seconds (range 1–72) following cardioversion. IRAF episodes were treated by further shocks alone (n = 11), flecainide (n = 3) and pacing (n = 1). Of the 15 patients with IRAF 7 left the lab in SR. Subsequent late recurrence of AF occurred in all 7 (100%) of patients with IRAF and in 23 of 37 (62%) of patients without IRAF (p = 0.029).

Conclusions: IRAF is an important predictor of late recurrence of AF. Patients with IRAF are at increased risk of late recurrence of AF and prophylactic antiarrhythmic strategies should be considered in these patients.

P669 A new steerable electrode for internal cardioversion of atrial fibrillation with a solely transfemoral approach

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The use of regular electrodes for internal cardioversion of atrial fibrillation is performed by placement of one cardioversion electrode (CE) in the coronary sinus (CS) via the subclavian or internal jugular vein. A solely transfemoral approach to IC is desirable for both chronic AF (cAF) or intermittent AF (iAF) occurring during ablation procedures. The feasibility of a solely transfemoral IC was systematically studied in 30 consecutive patients (Pt) (cAF:15 Pt, iAF:15 Pt, atrial size: 43 ± 6 mm) with the use of a newly designed steerable CE for placement in the CS in combination with a regular CE for placement in the lateral right atrium (RA). A special sheath for CE introduction in the CS was used in case of unsuccessful placement.

Results: In 27 of 30 Pt (90%) the placement of the steerable CE in the CS was feasible, in 3 Pt (10%) CS placement was successfully performed making use of the introduction sheath. A distal CS position was achieved in 21 Pt (70%), a proximal CS position in 9 Pt (30%). The IC to sinus rhythm was possible in all Pt with 12 ± 10 Joules (397 ± 127 Volt, 60 ± 9 Ohm) after 2 ± 1 shock deliveries. The energy needed was not significantly different comparing Pt with cAF and iAF and Pt with proximal and distal position of the steerable CS electrode ($p > 0.05$). Fluoroscopy time was 10 ± 5 min, procedure duration 30 ± 15 min. In 9 Pt (30%) 3 ± 2 AF recurrence were documented in minute 1–3 after IC. In all Pt with iAF ablation was successfully performed after IC. No IC-related complications were seen.

Conclusion: (1) Internal cardioversion of atrial fibrillation with a solely transfemoral approach is feasible and safe making use of a newly designed steerable cardioversion electrode. (2) The transfemoral internal cardioversion is proven to be particularly useful in patients with the onset of atrial fibrillation during ablation procedures.

ATRIAL AND VENTRICULAR DEFIBRILLATION

P670 High failure rate among the first Endotak C-leads in patients with implantable defibrillators

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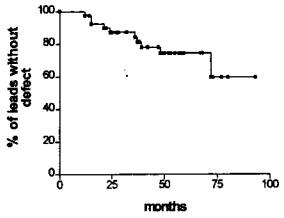
The Endotak-C lead series was the first lead introduced for transvenous implantation of ICD-systems. The Endotak-C lead is a tripolar lead with a silicone insulation (IN) which used thicker lead body diameters and thinner isolators at the terminals of the anode and cathode proximal to yokes compared with the newer Endotak lead generations. Therefore the goal of this study was to assess the long term performance of this lead system. We included in this analysis 41 patients (pat.) (age: 62 ± 10 years) with ICD and Endotak C leads of the 0060 anf 0070 series. All pat. received an abdominal implant and the leads were inserted in 42% via the left V. cephalica.

Results: The mean follow up (FU) time of all leads was 49 ± 19 months (m) (range: 12–93 m). 10 lead IN failures were detected after a mean FU of 30 ± 19 m. In 8 pat. the sensing electrode near to the generator was affected, 1 IN was broken in between the shock coils and in 1 pat. an IN break of the proximal shock electrode was detected during ICD replacement. 8 pat. received multiple inadequate shock deliveries, in 6 pat. the stored ECG of the device and in 2 pat. impedance-measurements led to the diagnosis of lead failures. The incidence of lead failure was age-dependent but not related to implantation techniques or pat. characteristics.



Conclusion:. Potentially life threatening lead failures occurred due to IN breaks in 24% of the pat. After 5–6 years an incidence of 24% of lead failures which lead to surgical revisions has to be expected. Whether the decreased lead body diameters and increased diameters of IN at the lead terminals in the newer Endotak lead-generation is associated with a better long term performance has yet to be determined. Detailed follow-up visits and regular applications of test shocks are mandatory to detect insulation failures in this type of old lead systems.

P671 Reduction of the defibrillation threshold by half using a novel transvenous technique of epicardial electrode placement

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This study aimed to emulate epicardial patch placement using a transvenous approach to placing multiple electrodes on the epicardial surface of the heart in the middle cardiac vein (MCV). Detailed anatomical evaluation of the MCV was performed to elicit its similarities with human anatomy.

Method & Results: In 8 anaesthetised pigs (35–71 kg) an Angeflex™ electrode was advanced via the jugular vein to the right ventricular apex (RV), with the proximal electrode positioned in the superior vena cava (SVC). Three electrodes (length: 2 × 25 mm + 1 × 50 mm) were then placed in branches of the MCV using a novel delivery system incorporating a modified 8F angioplasty guide catheter. Each electrode was deployed via a sheath/stylet that was withdrawn after electrode placement. An active-can electrode (43 cc) was implanted in the left pectoral region. Ventricular fibrillation was induced with 60 Hz AC and rectangular biphasic defibrillation shocks were delivered by an external defibrillator. The DFT was measured using a 4-reversal binary search with 4 different electrode combinations being randomised. The data were analysed using repeated measures ANOVA. Detailed post-mortem anatomical analysis of the MCV was performed using angiography, latex casting and dissection. This demonstrated that the MCV drained into the coronary sinus at a location close to its orifice (2.7 ± 2.2 mm), bifurcating into two main branches that drained the right and left ventricles, the left branch being the dominant vessel in the majority of cases.

Electrode Configuration	RV→Can	MCV + RV →Can	MCV→ Can	RV→ SVC + Can
DFT ± SD (J)	27.3 ± 9.6	11.9 ± 2.9	15.2 ± 4.3	21.8 ± 9.3
P Value (vs RV→Can)		<0.001	<0.001	<0.05
P Value (vs RV→SVC + Can)	<0.05	<0.01	<0.05	

Conclusion: Placement of specialised electrodes within the coronary venous system provides more efficacious defibrillation than conventional electrodes, used either alone or in combination with traditional lead systems.

P672 European long-term experience with a dual-chamber defibrillator

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For ICDs, sensitivity is the most important criterion, with the risk of lowering the specificity. Dual chamber (DC) ICDs have a better discrimination between VT and supraventricular tachycardia (SVT) and allow the programming of a lower cut-off rate (COR) without increasing the risk of inadequate therapies.

Methods: We report the first pooled data of 4 clinical studies concerning Defender I & II (Ela Medical, France) ICDs. In total 187 patients (pts) (170 M, LVEF = 38 ± 14%, 62 ± 12 years) were analysed. These pts were implanted for malignant ventricular arrhythmias (42 VF, 112 VT, 25 VT/VF, 5 na). The indication for 67 was sudden cardiac death, for 54 syncopal VT and 66 other. All but 7 pts had cardiopathy. 57 pts had AV block, 30 sinus dysfunction (SND), 24 AV block + SND and 55 pts a previous history of atrial arrhythmias.

Results: The mean follow-up was 13 ± 8 months. 827 spontaneous events were recorded in Tachy zone (with PARAD Algorithm). Slow VT are characterised by a rate ≤ 153 bpm. These slow VTs are not detected with single chamber (SC) ICDs since they are generally programmed with COR ≥ 160 bpm. The overall sensitivity and specificity were 99% and 93% respectively. 4 false negative (FN) occurred in 4 pts, 2 were due to VA crosstalk and spontaneous terminated in less than 50 seconds, the 2 others did not meet the acceleration criteria (1 initiated on a rapid sinus tachycardia (ST) and 1 was below the COR). 31 false positive (FP) were also documented in 11 pts due to ST post shock therapy (1), loss of atrial sensing during exercise ST (2), ventricular bigeminy with stable RR intervals (1), atrial tachycardia after a PVC (1), atrial fibrillation (25) and atrial flutter (1). Only 11 FP were treated by shock in 6 pts. The sensitivity and specificity were 98.4% and 96.5% for spontaneous events detected at rates < 153 bpm and 99.5% and 80.0% for those detected at rates ≥ 153 bpm. The latter parameter would have been 96.8% if PARAD+ (the new detection algorithm) had been used and therefore only 2 fast AF would have been inappropriately detected. Success rate on documented ventricular arrhythmias was 85.6% for ATP. All the ventricular arrhythmias treated by shocks were successfully reverted.

Conclusions: Due to the limitation of SC ICDs, we are used to consider the sensitivity only for fast VTs. Our experience demonstrates that DC ICDs have a high sensitivity, regardless of the VT rate and preserves an overall specificity greater than 92%.

P673 Evaluation of coronary vein availability for placement of pacing and/or defibrillating lead system on the left ventricle

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Background: The use of a lead inserted tranvenously into a coronary vein residing on the left ventricle has been proposed for CHF pacing therapies. We evaluated the coronary venous system in twenty-eight patients (Pts) receiving an ICD system.

Methods: A balloon occlusion catheter was inserted into the patient's coronary sinus (CS). After balloon inflation contrast media was hand-injected. X-ray images were analyzed to assess the presence, position and course of coronary veins.

Results: The location, size, visibility and course of four major coronary veins identified varied considerably from patient to patient. A prominent anterior interventricular vein (V. interventricularis anterior) was visible in 25/26 (96%) Pts and typically traversed at least half way down the interventricular groove before dividing into numerous smaller branches. A prominent posterior vein (V. posterior ventriculi sinistra) was visible in 18/26 (69%) Pts. Its ostium was seen anywhere from next to the CS ostium to well out onto the left free wall. It typically branched 3–4 cm down the ventricular wall and did not always extend toward the apex. An additional small left marginal (lateral) vein was clearly visible in 30% of x-ray images. A larger diameter middle cardiac vein (V. cordis media) was identified in 90% of venograms due to filling with contrast media via collateral flow. This vein proceeded in a straight path to the apex down the posterior interventricular grove.

Conclusion: This is the first extensive, systematic study of the coronary vein system structure in a patient population that potentially could benefit from using a pacing and/or defibrillating lead residing on the left ventricle. Despite the considerable variability in the presence and location of the coronary veins, an acceptable vessel for lead introduction was always seen. Use of the coronary vein system for CHF pacing and/or defibrillation systems should be feasible.

P674 Method for increased energy field distribution during defibrillation evaluated by catheter mapping

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Purpose: A further reduction in the size of implantable cardic defibrillators can be achieved by decreasing the total energy requirements needed for termination of ventricular fibrillation (VF). Assuming that a minimum energy density is necessary for successful defibrillation, efforts should be made to equalize field distribution across the heart.

Methods: A 3.5 cm standard right ventricular (RV) defibrillation coil was placed in the RV of eight mongrel dogs. Shocks were applied between the coil and a subcutaneous can that was either fully conductive or conductive only along the outer edge (edgeband). An additional subcutaneous ring electrode was placed over the apex of the left ventricle; the ring electrode was connected to the can in parallel for active mode and disconnected for passive. Six treatments were tested: standard can to RV coil; standard can to RV with active and passive ring electrode; edgeband can to RV coil; and edgeband can to RV with active and passive coil. Shocks of increasing voltage from 100 to 600 V were applied during NSR and induced VF for each treatment. Measurements were made at the apex of the left ventricle (LV), the mid-coronary sinus (CS) and the right ventricular outflow tract (RVOT) and recorded via a custom-designed three-dimensional electrical field sensor (EFS) system (Sulzer Intermedics, USA).

Results: Using the EFS system, an electric field of 9.0 ± 11.6 V/cm/100 V was found at the LV apex when using a standard titanium Res-Q can and RV defibrillation coil. The addition of an active subcutaneous ring electrode increased the LV electric field to 13.1 ± 12.8 V/cm/100 V ($p < 0.0001$). Furthermore, by combining the edgeband defibrillator can with the active subcutaneous ring electrode, the electric field of the LV apex was elevated to 14.1 ± 14.2 V/cm/100 V ($p < 0.0001$). The use of the edgeband can alone and in conjuction with the passive ring electrode showed no significant increase in field strength. No significant increases or decreases were noted in the mid-CS or the RVOT during the experiment.

Conclusion: During RV-can defibrillation, there is an inhomogenous electrical field distribution, which can result in a low electric field in the LV apex. By combining the edgeband can and an active subcutaneous ring electrode, a significant increase in the field density of the LV can be brought about without an increase in shock voltage or loss of field strength elsewhere.

P675 Atrial pacing during atrial fibrillation may influence the defibrillation thresholds

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Synchronization of atrial activation during atrial fibrillation may be related to a lower defibrillation threshold (DFT). We evaluated the effect of a single site right atrial pacing on atrial DFT in patients (pts) with idiopathic paroxysmal atrial fibrillation (PAF)

Methods: Two series of randomized step up internal cardioversion tests, with increasing energy levels from 0.2 to 10 joules, were performed in 10 pts with recurrent episodes of PAF (7 male, 57 ± 12 yrs, LVEF 61 ± 5%). We used a single 6F lead defibrillation system with two defibrillation coils and a proximal sensing ring (ATAK) positioned in high right atrium and coronary sinus; the capture was validated by MAP signal. After induction of sustained AF (>10 min), internal shocks were delivered, preceded or not by at least 20 sec overdrive local atrial pacing, according to a randomized protocol using external cardioverter defibrillator (ECD, 2815 model – CPI).

Results: A total amount of 133 shocks was delivered. There was no significant difference overall in DFT whether or not the overdrive atrial stimulations preceded the cardioversion (3.2 ± 1.8 J vs. 4.9 ± 2.6 J respectively, p = NS). No correlation was found between FF intervals preceding the successful shock and DFT. However analyzing the DFT according to the stability of capture during atrial pacing, a significant reduction was observed in pts with stable capture (SC) in comparison with those with unstable capture (UC) (SC 4 pts 5.2 ± 3.2J vs. 3.0 ± 2.3J, UC 5 pts 3.1 ± 1.7J vs. 3.4 ± 1.6J). In 70%(14/20 successful shocks) the shock discharge was observed to be synchronized to spontaneous or stimulated atrial activation.

Conclusions: In our study a stable atrial capture of pacing during atrial fibrillation is followed by a lower DFT. Whether this approach could lead to a DFT decrease of clinical relevance has to be confirmed.

P676 Comparison of a new 2-lead system with a 3-lead system for atrial defibrillation

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For safe and effective low energy defibrillation, an implantable atrial defibrillator (IAD) currently requires a 3-lead system: a right atrial (RA) and a coronary sinus (CS) defibrillation lead and a right ventricle (RV) bipolar lead for R-wave synchronization and post-shock pacing.

Methods: We studied a new 2-lead system consisting of a catheter with bipolar RV electrodes distal and a proximal RA shock electrode array and a CS decapolar defibrillation catheter in 16 pts (14 men, mean age 54 ± 9 year) who underwent cardioversion of atrial fibrillation (AF). For the 3-lead system, a third catheter was added in the RA. AF signal amplitude detection (RA-CS) and AF defibrillation thresholds (ADFT) were compared in each patient using the 2-lead and 3-lead system in a randomized order. ADFT were determined twice for each lead system using a 2 success, 40V step-up protocol.

Results: Successful defibrillation was obtained in all pts with a mean ADFT of 370 ± 112 V(9.3 ± 5.2J) in the 2-lead system and 316 ± 100 V (6.8 ± 4.2J) in the 3-lead system. ADFT in the 2-lead system was significantly higher caompared to the 3-lead system (voltage: $p < 0.05$, energy: <0.05). In contrast, there was an increase in impedance for the 3-lead system (77 ± 16 vs 68 ± 13 ms, $p < 0.05$). The mean RA-CS signal amplitudes were 1.70 ± 0.80 mv during sinus and 0.86 ± 0.17 mV during AF using the 2-lead system and 2.54 ± 1.07 mV during sinus rhythm and 1.59 ± 0.53 mV during AF using the 3-lead system ($p < 0.05$).

Conclusions: The use of a 2-lead system in this configuration is not superior to a 3-lead system regarding AF signal amplitude detection and AF defibrillation threshold. Further study is needed using actual leads in place of the catheters used in this study.

P677 Atrial lead stability and sensing during detection of spontaneous tachyarrhythmias in a dual-chamber ICD

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Introduction: Atrial sensing in the Gem DR dual chamber ICD uses auto-adjusting sensitivity with no atrial blanking after ventricular sensed events and 30 ms atrial blanking after ventricular paced events. While this allows maximal sensing of atrial events during atrial tachyarrhythmias, oversensing (OS) of far-field R-waves (FFRW) may occur. The effects of FFRW OS on ICD function are minimized by using pacemaker refractory periods and a FFRW rejection algorithm. The purpose of this study was to evaluate clinically significant atrial undersensing (US) and FFRW OS and to determine the effect of atrial lead placement.

Methods: Patients (pts) implanted with the Gem DR and a bipolar atrial lead (tip-ring spacing = 10 mm) were studied. Spontaneous SVT and VT/VF episodes (n = 1105, 91 pts) stored in the Gem DR were reviewed. The atrial leads were positioned in the right atrial appendage (RAA, n = 51), high right atrium (HRA, n = 21), lateral wall (LW, n = 16) or atrial septum (SEP, n = 3). Episodes were classified into 3 categories: FFRW OS (≥1 beat), atrial US during AF (≥3 beats), and atrial US during non-AF (≥1 beat).

Results: The % of pts with atrial OS and/or US is listed by atrial lead position. Atrial OS was observed in 23% of pts, and resulted in inappropriate VT/VF detection in 5% of pts. Atrial lead position had a significant effect on FFRW OS ($p < 0.05$), with the LW having the lowest incidence (0/16). Atrial US was observed in 13% of pts during AF and in 7% of pts during non-AF rhythm, and resulted in inappropriate detection in 3% of pts. All reported inappropriate VT/VF detections occurred during SVTs that were rapidly conducted into the VT detection zone and were a direct result of atrial US or atrial OS. Atrial lead dislodgements were observed in 5 patients (2 HRA, 1 LW and 2 RAA).

Atrial Sensing	RAA (51)	HRA (21)	LW (16)	SEP (3)	Total (91)
OS, FFRW	14 (27%)	5 (24%)	**0 (0%)**	2 (67%)	21 (23%)
US, AF	5 (10%)	2 (10%)	4 (25%)	1 (33%)	12 (13%)
US, non-AF	2 (4%)	2 (10%)	1 (6%)	1 (33%)	6 (7%)

Conclusion: Bipolar atrial leads placed on the right atrial LW significantly reduce the amount of FFRW OS without causing significant atrial US.

P678 Detection and treatment of slow ventricular tachycardias: a new concept for dual chamber defibrillators

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Defender dual chamber implantable defibrillator (ICD), with algorithms based on atrial and ventricular detection (PARAD, Ela Medical, France), allows the programming of a lower cut-off rate (COR) to better diagnose slow ventricular tachycardias (VT), therefore increasing the specificity without modifying the sensitivity.

Methods: The IDEF05 study is an ongoing prospective randomised clinical trial performed to evaluate the result of programming COR at 128 or 153 bpm in patients implanted with Defender II (Ela Medical, France). 63 patients (pts) (59 M, LVEF = 40 ± 17%, 63 ± 12 years) were included in IDEF05 and implanted for clinical malignant ventricular arrhythmias (17 VF, 39 VT, 7 VT/VF). 24 pts had AV block or bundle block branch, 7 sinus node dysfunction (SND), 8 AV block + SND and 12 pts a previous history of atrial arrhythmias. In this study we defined slow VT as VT with a rate ≤ 153 bpm.

Results: During a mean follow-up period of 30 weeks ± 14, 244 spontaneous events were recorded, 224 of them in VT zone.

Spontaneous events	Sensitivity %	Specificity %	No. of spont. events
≤153 bpm	97.7 (42/43)	98.5 (133/135)	178
>153 bpm	100 (49/49)	94.1 (16/17)	66

In this series, 1 non sustained slow VT (rate: 128 bpm) was not diagnosed due to VA crosstalk (because of an atrial lead with space between tip and ring > 23 mm). One post shock sinus tachycardia was treated by the device (false positive), as well as one atrial tachycardia treated in VF zone and one episode of ventricular bigeminy. Success rate on documented ventricular arrhythmias was 92.5% for ATP and 100% for shocks.

Conclusions: The first results of this study show that the Defender II can diagnose slow VTs with a high sensitivity and a high specificity. Depending on the slow VTs' tolerance and patient's clinical profile, this new algorithm offers the possibility to detect and treat this type of tachycardia.

P679 Patient alert: clinical experience with a new patient monitoring system in a dual-chamber defibrillator

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The Patient Alert (PA) feature of the Medtronic Models 7271Gem DR and 7227 Gem ICD notifies the pt that a condition exists in the ICD that may require investigation by the physician. It does so, when turned ON, by emitting an audible sound at the programmed time once a condition(s) is met. Two different alert signals can sound depending upon the condition and programming.

A total of 497 pts were implanted with the Gem DR ICD as part of the worldwide Gem DR study. Of these, 485 (98%) pts had the PA turned on at pre-hospital discharge. PA was later programmed off in 14 (3%) pts due to notification of an alert condition that was not clinically meaningful. At 2 months post-implant, clinicians conducted a telephone interview to ascertain if the PA tone could be heard by the pt as well as the clinician over the telephone, and whether the type of tone could be identified by the pt and clinician. Of the 296 telephone contacts that were completed, there were 291 [98.3%, 95% C.I. (96.1–99.5)] cases where the tone was audible to both the pt and clinician and 286 [96.6%, 95% C.I.(93.8–98.4)] cases where the different tones were identifiable by the pt and clinician. During a mean follow-up of 2.8 months, there were 3 instances where the PA tone was primiraly responsible for identification of a lead dislodgement. In one each, the following was seen: a ventricular lead dislodgement identified by PA for ventricular pacing lead impedance > 2000 ohms, a SVC lead dislodgement identified by PA for the delivery of multiple shocks for the same episode (episode of VF that was successfully terminated but only after delivery of 3 maximum energy shocks), an atrial lead dislodgement identified by PA for atrial pacing lead impedance out of range.

Conclusions: The PA is a useful tool for identification of device functionality between in-office visits. Long term follow-up will further demonstrate the utility of the PA feature.

P680 Evaluation in the electrophysiology laboratory of the performance of a pattern-based dual-chamber (DDD) ICD algorithm

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The DDD-ICDs are expected to provide improved detection of supraventricular tachycardias (SVT), but assessment of this benefit may require a long clinical follow-up. We tested the algorithm of one of the newest DDD-ICD on SVTs induced during electrophysiology studies (EPS) and report its efficacy.

Methods: in 46 patients (pts) [24 men, mean age ± SD 46 ± 18 years] undergoing an EPS for SVT [31 pts], ventricular tachycardia (VT) [6 pts] and sincope/palpitations [9 pts], the atrial (A) and ventricular (V) sensing channels of a Medtronic 7271 GEM DR ICD were connected via custom made adaptors to standard EP catheters in the right A and V. All ICD therapies were disabled. SVT detection criteria were all on; VT stability off. Detection (lower rate 500–600 ms) was tested during spontaneous SVTs or induced with premature stimuli and/or isoprenaline. V pacing (VP) at 300–400 ms was performed in 24 cases during atrial fibrillation (AF) or atrial flutter (AFl), to simulate the onset of VT during an ongoing SVT.

Results: 70 SVTs were observed: all the 24 sinus tachycardias, 11 AFl and 13 AF were correctly detected. Overdetection occurred in 5/11 atrial tachycardias, due to a long AV interval, causing detection of VT with long 1:1 VA conduction. VT was detected in 4/9 AVNRT and 2/2 AVRT. Both VT and SVT were correctly detected in all 24 cases of V pacing during SVT. Excluding AVNRT and AVRT, clinically not relevant in ICD pts, the overall accuracy was 91%, with 54/59 SVTs correctly detected.

Conclusions: All SVTs usually responsible for inappropriate ICD therapies were correctly detected by the algorithm tested. Overdetection of SVT with a long AV interval may be possible and requires simple algorithm software adjustments.

P681 Potential pitfalls of a new dual-chamber detection algorithm: implications for patient selection and device programming

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Dual-chamber implantable cardioverter-defibrillators include the atrial sensing information into the detection algorithm to discriminate supraventricular from ventricular tachyarrhythmias. However, to dateit has not yet been studied, if ventriculo-atrial sensing can cause arrhythmia misinterpretation in dual-chamber ICDs. A new PR-recognition based algorithm, dividing the RR-intervals into zones of antegrade and retrograde conduction, may harbour the risk of misclassification in the clinical setting of atrial tachycardias with long PR or ventricular tachycardias with long RP intervals. This prospective study was conducted to assess the incidence of inappropriate device detections in order to guide patient selection and device programming.

Patients and Methods: 34 patients (pts) with a Medtronic Jewel AF 7250 were included in the study. A total of 399 supraventricular (SVT) (225) and ventricular (174) tachyarrhythmias. (VT) were used for analysis. Arrhythmia classification was based on atrioventricular stored electrograms and stored RR and PP-intervals.

Results: A total of 12/399 (3%) episodes (E) were falsely classified by the device due to failure of the PR-pattern recognition detection algorithm. 11 sinus tachycardias (ST) with a long PR-interval were misclassified in 2 pts as VT due to the allocation of the atrial signal to the zone of retrograde conduction. One of the two pts had an AV-block I°. The other pt had normal AV-conduction at rest and experienced several shocks during a ST with a PR/RR cycle length ratio < 50% i.e. the limit for antegrade conduction zone in the device algorithm.

Conclusions: 1. The incidence of algorithm failure of the new PR-pattern recognition algorithm in the clinical setting for 1:1 tachycardia is low with 3%. **2.** However, pts with AV-block I° or long PR during sinus tachycardia and overlap of sinus rate and VT rate may receive inappropriate therapies. Thus, AV-nodal conduction should be assessed by exercise test also in pts without AV-block I°.

P682 Influence of anaesthetic agents on the endocardial ventricular defibrillation threshold

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Anesthetic agents are known to interfere with cardiac cellular electrophysiology. We studied the influence on the ventricular defibrillation threshold (DFT) of drugs used for anesthesia or sedation in clinical practice.

Methods: The DFT was assessed in 20 pigs (26.0 ± 1.6 kg) using a right ventricular endocardial defibrillation lead (Endotak-CPI) and a subcutaneous patch-electrode. Ventricular fibrillation (VF) was induced by 50 Hz AC, and the DFT was evaluated using the "3 reversal up and down" method. Acido-basic equilibrium and hemodynamic parameters were maintained constant throughout the procedure. Each animal received Halothane (H) and Propofol (P) in a random order. DFT was evaluated with the first drug and reevaluated with the second drug after complete wash-out. After elimination of the second drug, the DFT was measured under simple sedation by Flunitrazepam (F) as a control situation. This situation was always tested last because of the long elimination half-life of F.

Results: The animals received a mean of 43.9 ± 7.2 shocks per animal. DFT was higher with H than with P or F (12.94 ± 3.04 J versus 12.08 ± 3.09 J and 11.88 ± 3.17 J respectively, $p < 0.05$ both); it was not statistically different with F than with P.

Conclusion: Endocardial ventricular DFT is higher with Halothane than with Propofol or Flunitrazepam. Halothane might be less appropriate for anesthesia when the DFT is evaluated.

P683 VDD for dual chamber ICDs: a new single lead electrode

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Background: Dual chamber ICD systems use two separate leads for sensing and pacing in the atrium and the ventricle. Complications due to the atrial (A) lead have been reported several times. So we designed and evaluated a new single lead dual chamber VDD-lead for dual chamber ICDs.

Methods: In a German multicenter study we tested a prototype VDD-lead, a single-coil defibrillation electrode with two additional fractally coated rings for bipolar sensing in the atrium. In 28 pts. A. arrhythmias were induced using a bipolar stimulation catheter or an A. screw tip electrode. A. and ventricular (V.) signals were recorded during sinus rhythm (SR), A. flutter (AFLU), A fibrillation (AF) and V tachycardia (VT) or ventricular fibrillation (VF). Terminations of V. arrhythmias were performed by internal DC-shock. The position of the A. sensing rings was in close contact to the lateral A. wall.

Results: In 26 of of 28 pts. (92.8%) the implantation of the electrode in the apex of the right ventricle and the atrial sensing rings at the lateral right-atrial wall was successful. Mean A. pacing threshold was 2.4V/0.5 ms, mean A. impedance was 216 ± 27.7 Ohms. For A. sensing see Tab.1. The mean V. sensing was 13.3 ± 7.1 mV, mean V. impedance was 559 ± 86.3 Ohms. DFT was <20 J. Under the induced arrhythmias the A sensing by the VDD-sensing rings was reliable (Tab. 1).

Table 1. Atrial Sensing of the VDD electrode and reliability of detection by Phylax 06

	SR/SD (mV)	AFlu/SD (mV)	AF/SD (mV)	VF/SD (mV)
Atr. VDD signals	2.6/1.6	1.47/0.59	0.94/0.38	1.42/0.95
Reliability of atrial detection by Phylax	99.7%	86.2%	57.5%	90%

Conclusions: The new designed single lead dual chamber electrode with fractally coated atrial sensing rings provides stable detection of atrial and ventricular signals independent of the induced arrhythmias in the acute clinical experiment. To evaluate the long-term stability of the new electrode further investigations with a chronical implanted VDD-electrode are necessary.

P684 A single centre experience of implantable atrial defibrillators

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Between October 1997 and February 1999 we have implanted atrial defibrillators (Metrix 3020, InControl) in 8 pts (7 male, mean age 57 years). Indications for implant were frequent, symptomatic paroxysms of atrial fibrillation (AF) resistant to drug therapy or persistent AF requiring regular DC cardioversion. Pts chose defibrillator implant rather than AVN ablation and pacemaker implant. Mean follow-up is 8.4 (1–16) months. 2 pts had lead repositioning for high defibrillation thresholds.

7 pts have had documented AF since implant (median 2 episodes/month, range 0–6/month). Not all episodes have been symptomatic (required for pt activation mode). Sinus tachycardia was misinterpreted as AF in one pt (25/27 episodes) but the device algorithms would not allow shock synchronisation. 6/8 pts have undergone shock therapy (median 3 shocks per month, range 1–8) which successfully cardioverted AF in 70% of episodes (47% of shocks delivered). A single shock was required in 36% of cases, multiple shocks (± additional drug therapy) in 64%. 2 pts have suffered early recurrence of AF after every shock (i.e. within 60 seconds). In 2 pts the device was unable to administer shock therapy as the ventricular rate was too rapid. Additional drug therapy was required to slow the heart rate. No pt has shown a reduction in frequency of AF episodes since implant. No pt has inappropriately self-administered shock therapy. No complications have occurred from shock therapy. 2 pts who have had successful cardioversion of AF have had symptomatic paroxysmal atrial flutter (not previously documented).

Although these devices accurately identified AF, frequent shock therapy resulted in sustained sinus rhythm in only a minority of pts. Further follow-up will evaluate the long-term efficacy of these devices in the treatment and prevention of AF.

P685 Multicenter experience with a new dual-chamber defibrillator

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The high incidence of inappropriate therapy due to supraventricular tachycardias (SVTs) is a major challenge and has been reported to affect up to 25% of patients with implantable cardioverter-defibrillators (ICDs). In a multicenter clinical study, the sensitivity and specificity of the dual-chamber ICD (Defender, ELA Medical, France) was evaluated in 128 patients (pts). The new algorithm (PARAD) is based on the following criteria: rate, RR interval stability, atrioventricular (AV) relation analysis and atrial or ventricular acceleration in case of 1:1 AV relation.

Results: During a follow-up of 16 ± 9 months (range 1–41 months), a total of 1048 spontaneous episodes were recorded in 87 pts and classified by the device as ventricular fibrillation (VF, n = 63), ventricular tachycardia (VT, n = 512), SVT (n = 465), or undetermined (n = 8). Stored data was reviewed by independent investigators. In 15 pts, 45 episodes of atrial fibrillation with a stable ventricular rate and 2 episodes of sinus tachycardia due to loss of atrial sensing during exercise were inappropriately detected as VT. In 6 pts, 4 VTs were detected just below the programmed VT cut-off rate and 3 episodes of irregular VT were classified as SVTs. All of the irregular VTs were <12 s in duration. In 4 pts, 6 VT episodes did not meet the ventricular acceleration criterion. This resulted in a specificity of 87% and in an overall sensitivity for all detected VTs/VFs of 98%. Success rates were 81% for antitachycardia pacing and 92% or 95% for the first shock therapy for the VT or VF episodes, respectively. 13 deaths were reported: 3 arrhythmic, 8 non-arrhythmic, and 2 non cardiac deaths.

Conclusions: Dual-chamber ICDs provide equivalent efficacy and safety rates compared to single-chamber ICDs. With the new PARAD algorithm based on analysis of atrial and ventricular signals, dis-crimination of ventricular from supraventricular tachycardia is achieved with a specificity of 87% and with a sensitivity of 98% for all ventricular tachyarrhythmias.

P686 Long-term efficacy of ablation procedures in ICD patients with multiple inappropriate shocks

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Multiple consecutive shocks due to drug-refractory rapid atrial fibrillation (rAF) and atrial flutter type I (AFL) remain an unsolved problem in defibrillator therapy. This is the first systematic, prospective study of the efficacy of radiofrequency (RF) modification/ablation of the AV node in 12 consecutive patients (pts) with rAF and RF isthmus block in 6 pts with AFL (CAD: 65%, EF: 35 ± 10%, NYHA III-IV: 100%) causing 34 ± 17 (14–104) shocks (15 ± 10 shocks/6 months) during a follow-up of 45 ± 25 months.

Results: Modification of the AV node was successfully performed in 10 of 12 pts (83%) with rAF after 4.5 ± 3.3 RF applications and a significant mean/maximum ventricular rate reduction of 30/32% in holter recording, respectively. In the remaining 2 pts (17%) AV node ablation was performed in a second procedure. A complete isthmus block was achieved in 5 of 6 pts (83%) and a unidirectional block in 1 pt (17%) with AFL after 8.7 ± 5.5 RF applications. During a follow-up of 15 ± 6 months none of the 18 pts had recurrences of inappropriate shocks for the index supraventricular arrhythmia ($p < 0.01$ versus before ablation procedure). NYHA classification and ejection fraction were unchanged in the pts with AV node modification/ablation after 3 months ($p > 0.05$, respectively).

Conclusion: 1. RF catheter modification/ablation of the AV node for rAF and RF isthmus block for AFL type I are demonstrated to be highly effective in ICD pts with drug refractory multiple inappropriate shocks. 2. In pts with rAF RF ablation of the AV node should only be performed after RF modification without sufficient drop in heart rate. 3. Left ventricular function and NYHA classification are not effected after AV node modification/ablation in ICD pts with severe chronic heart failure.

P687 Effects of antiarrhythmic drugs on defibrillation threshold applying biphasic shock in humans

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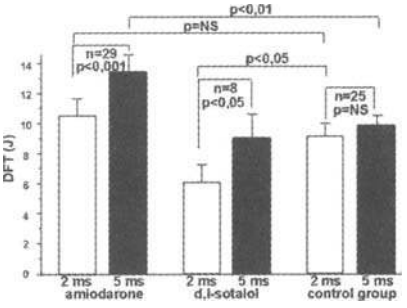
Background: The biphasic waveform and antiarrhythmic drugs are known to influence defibrillation efficacy. However, the optimal biphasic waveform for 2nd phase duration has not been clarified yet in man.

Methods: In a multicenter, randomised and prospective study, the defibrillation efficacy of 2 msec vs. 5 msec 2nd phase duration of biphasic pulses using two 100 μF capacitors was compared in 62 patients (age: 54 ± 13 years, male: 74%, CAD: 60%, DCM: 19%, EF: 43 ± 17%, amiodarone: 47%, d,l sotalol 13%) with a unipolar pectoral transvenous defibrillation system (RV-E vs. can; fractally coated SPS-lead vs. Phylax 06 or XM active housing, BIOTRONIK). The 1st phase parameters for both biphasic waveforms were as follows: charging voltage 100%, switching voltage 40%. Defibrillation threshold (DFT) was determined in a random order with either 2 msec or 5 msec second phase tested first during ICD implantation.

Results: significant difference was found in stored energy at DFT between 2 msec and 5 msec 2nd phase duration pulse form (9.5 ± 0.6 vs. 11.3 ± 0.7 p < 0.01). In subgroup analysis in patients treated with class III drugs, such as amiodarone or d,l sotalol, there was a markedly significant difference between DFTs with shocks of longer or shorter 2nd phases, but in the control group there was no difference (figure).



Conclusions: chronic amiodarone treatment increases DFT using biphasic shock only with the longer second phase duration. In patients treated with class III drugs DFT is significantly lower with shorter second phase duration.

P688 Single center experience with a dual-chamber detection algorithm

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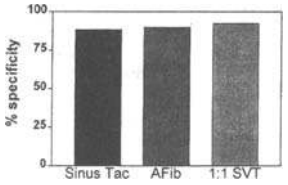
Non specificity of detection is one of the major shortcomings of therapy with an implantable defibrillator (ICD). Theoretically the disadvantages of single chamber detection can be overcome if additional atrial information is added to a detection algorithm. 53 consecutive patients (60 ± 14 years, 57% coronary artery disease, left ventricular ejection fraction 37 ± 14%) received the Medtronic 7271 GEM DR, an ICD with dual chamber detection. ICD's were programmed to a tachycardia detection interval of 500 ms and an supraventricular tachyarrhythmias (SVT) limit of 240 ms: During a median follow up of 207 days a total of 600 episodes with a stored electrogram occurred. 113 episodes of ventricular tachycardia or ventricular fibrillation, all classified by the device as ventricular tachyarrhythmia. In the SVT zone 484 SVT's were recorded, 429 classified as SVT by the device (specificity 88.6%). 89.8% (n = 49) of atrial fibrillation (AFib) episodes in 6 patients were identified by the device as AFib. Mean atrial rate during AFib was 356 ± 93/min, mean ventricular rate was 185 ± 38/min. In 361 out of 409 episodes (88.3%) of sinus tachycardia therapy was withhold (14 patients). In 5 patients 26 episodes of atrial tachycardia occurred, all but 2 classified as SVT (92.3%).



Conclusion: Sensitivity for VT detection was 100%. With the use of the detection algorithm in the GEM DR 88.6% of SVT's were classified as SVT. Sinus tachycardia with long PR-interval was frequently miss classified as VT with retrograde conduction.

P689 Detection of myocardial ischaemia is possible using implantable defibrillators

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Implantable defibrillators (ICDs) provide a unique opportunity to register continuous intra-thoracic ECGs (IT-ECG). For IT-ECG the defibrillation-coil in the right ventricle and the superior vena cava, and the can of the ICD are used for bipolar leads. With these triangular electrodes an IT-ECG similar to the standard ECG (SECG) leads I, II, III, aVR, aVL, aVF can be recorded.

Patients and Methods: In a prospective PTCA-study we first investigated the presence of ischemic ST-segment changes in comparison to 12-lead SECG. In 22pts we recorded IT-ECGs and SECG in 27 PTCAs, an IT-ECG was shown to be more senstive to ischemic ST-changes than SECG during PTCA. In a subsequent study in 5 pts with residual ischemia SECG and IT-ECG were analyzed during and after 10 episodes of ischemia induced by 16.0 sec (± 4.6) of ventricular fibrillation (VF) while testing the defibrillation threshold during ICD-implantation. ECGs were recorded using a high resolution digitizer.

Results: After VF and ICD-shock, ST-deviations (STD) were present in all IT-ECG leads and were more pronounced than in SECG: post-Shock STD for all leads of IT-ECG was (max/mean/std.dev): 1.2/0.3/0.33 mV and in SECG 0.4/0.04/0.08 mV. After 2 min STD > 0.1 mV was observed in one or more leads in 1 of 10 episodes in SECG but in 10 of 10 IT-ECGs.

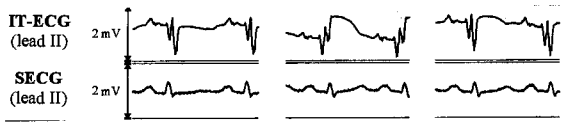

Figure 1 demonstrates lead II on the SECG and IT-ECG before, immediately after and 4 min after ICD shock for VF.

Conclusion: IT-ECG can be recorded with standard electrodes and only minor changes in defibrillator design. IT-ECG is superior to SECG in assessing ST-segment changes independent from the underlying cause and may provide a reliable method to monitor myocardial ischemia.

P690 Reduction in defibrillation threshold using an auxiliary shock delivered in the middle cardiac vein: a comparison of configurations incorporating the superior vena cava and an active pectoral can

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A low amplitude auxiliary shock (AS) from an electrode sutured to the left ventricle at thoracotomy has previously been shown to reduce defibrillation threshold (DFT) if delivered immediately prior to a conventional biphasic shock delivered between electrodes in the right ventricle (RV) and superior vena cava (SVC). This study investigates the effect of delivering an AS from a lead system deployed transvenously in the middle cardiac vein (MCV).

Method and Results: An Angeflex® electrode was positioned in the RV in 8 anaesthetised pigs (35–43 kg) with its proximal electrode in the SVC. A 50 × 1.8 mm electrode was inserted in the MCV through a modified 8Fr angioplasty guide catheter. A monophasic AS of 150 V leading edge was delivered from a 95 μF capacitor. A Sentinel® (95 μF capacitor, phase 1: 44% tilt, 1.6 ms extension and phase 2: 2.5 ms fixed duration) primary biphasic shock (PS) was delivered from RV → Can/SVC ± AS delivered from MCV → Can/SVC with three differing pulse widths (3, 5, 7 ms). The six configurations were randomised and DFTs (PS + AS) assessed using a modified 4-reversal binary search. Ventricular fibrillation was induced with 60 Hz AC followed 10s later by the test shock. The DFTs were compared using repeated measures analysis of variance (ANOVA).

PS	RV→Can				RV→SVC	
AS	MCV→Can				MCV→SVC	
	No AS	3 ms	5 ms	7 ms	No AS	5 ms
Mean DFT (J)	13.8	11.0*	11.5*	10.6*	14.3	11.9**
S.D. (J)	7.4	5.4	6.0	5.3	4.5	4.4

* = $p < 0.05$ (compared to No AS, RV→Can) ** = $p > 0.05$ (compared to No AS, RV→SVC)

Conclusion: Delivering an AS from a transvenous lead system deployed in the MCV reduces the DFT by 23% compared to a conventional RV→Can shock alone. Delivering an AS produced a non-significant reduction in DFT.

P691 The reliability of the electrogram width criterion in implanted cardioverter defibrillators depends on changes of the body position

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Background: In some implanted cardioverter defibrillators (ICD) the electrogram (EGM) width criterion is a feature discriminating supraventricular from ventricular tachyarrhythmias. We report a case whose change of body position led to a widening of the EGM analysed by the ICD. The patient's sinus-tachycardia was detected as ventricular tachycardia, leading to antitachycardia pacing and finally inducing ventricular fibrillation. As a consequence, we studied prospectively the reliability of the EGM width criterion depending from changes of the body position.

Methods: In 15 patients with ICDs (PCD 7223, Medtronic) and narrow QRS in the surface ECG, the EGM width criterion was programmed following the recommendations of the manufacturer analysing 50 consecutive complexes in the EGM sources HVA/HVB, HVA/P+, and P−/HVB, respectively, in supine position. The correct classification of the measured EGM in narrow and wide complexes was assessed using the surface ECG. The results were controlled in sitting position.

Results: In 10 of 15 patients (67%) in the supine position correctly as narrow classified EGMs were misclassified as wide in the sitting position. In none of the three EGM sources the dependence on body position was significantly different (misclassification rates in 30%, 50%, and 50% of patients in HVA/HVB, HVA/P+, and P−/HVB, respectively). No correct classification was achieved neither by programming the EGM width criterion first in the sitting position with control in the supine position, nor by repeating the complete protocol with the next higher slew treshold.

Conclusions: The EGM width criterion strongly depends on body position. To avoid potentially lethal complications, programming of the EGM feature requires an accurate examination with the patient's body in different positions.

P692 Far-field R-wave oversensing in a new dual-chamber-defibrillator: incidence and influence on device detection performance

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R-wave far-field oversensing could be observed in dual-chamber pacemaker systems. Little is known on the incidence of far-field R-wave sensing in modern dual-chamber implantable defibrillators (ICD). Multiple counting of R-waves in ICD-patients can in contrary to pacemaker patients induce atrial therapies and in the worst case inhibit ventricular therapies by mimicking a supraventricular rhythm with fast rapid conduction. Aim of this prospective study was, to assess the incidence of R-wave far-field oversensing and its influence on device detection.

Patients and Methods: 27 patients were implanted a Jewel 7250 AMD (Medtronic Inc.). All patients received a common right ventricular lead in the right ventricular apex and an *atrial* pace/sense or pace/sense/shock lead.

Results: The atrial lead was located in the right atrial appendage (RAA) in 19 patients, right lateral free wall (RFW) in 4 patients and the high right atrium (HRA) in 4 patients. R-wave oversensing occurred in 3/19 patients with the lead in the RAA, one patient in RFW and one patient in the HRA. In all but one patient, who experienced an inappropriate atrial shock therapy for R-wave oversensing due to multiple counting in the atrial channel, oversensing could be eliminated by decreasing atrial sensitivity from 0.3 to 0.45 or 0.6 mV. In the patient with the inappropriate shock oversensing was not further seen at 0.9 mV sensitivity.

Conclusions: 1. R-wave far-field oversensing occurs frequently in 5/27 patients. 2. It appears independently from the location of the atrial lead. 3. It is recommended to test all patients accurately for R-wave far-field oversensing, because it has potential proarrhythmic effect and may inhibit ventricular tachycardia detection in the worst case scenario. 4. Of note, if detected, R wave oversensing can be abolished in all patients by decreasing atrial sensitivity.

P693 Morphology discriminator algorithm for improved tachycardia discrimination in implantable cardioverter-defibrillators

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Background: The Morphology Discriminator (MD) feature is a recently introduced, dynamic electrogram template matching algorithm in implantable cardioverter-defibrillators (ICD) that aims to improve the discrimination of supraventricular tachycardia (SVT) from ventricular tachycardia (VT). We aimed to evaluate the performance of this algorithm during spontaneous tachyarrhythmias and exercise-induced sinus tachycardia.

Method: 16 pts (14 M; 55 ± 6 yrs) with Ventritex Contour MD/Angstrom MD devices were studied. Prior to discharge, morphology templates were acquired during sinus rhythm and activated if similarity scores were consistently greater than 90%, indicating a good match to the baseline. Matching threshold was set to 60%. Stability of the acquired template and performance of the algorithm during spontaneous tachyarrhythmias were evaluated during follow-up. A chronotropic assessment treadmill test was also performed along with telemetric monitoring of matching scores.

Results: Variations in electrogram morphology necessitated new template acquisition in 5 pts (31%) at first follow-up visit (6–8 weeks post-implant). 14 spontaneous SVT episodes in 8 pts and 4 spontaneous VT episodes in 3 patients were appropriately discriminated by the MD feature during follow-up. A common observation was post-shock changes in electrogram morphology that resulted in transient mismatch with the template. Exercise testing showed appropriate discrimination of sinus tachycardia in 12/13 pts (92%). Minimum observed matching scores were 90% in 2 pts, 85% in 2 pts, 75% in 4 pts, 70% in 2 pts, 65% in 2 pts and <60% in 1 pt.

Conclusion: The recently introduced MD feature in ICDs improves discrimination of SVT from VT. Programming the matching threshold to 60% may avoid inappropriate VT confirmation during sinus tachycardia in most pts. Variations of electrogram morphology over time may be a concern, especially during the maturation of the electrode.

P694 Implantable cardioverter/defibrillators: lead-related complications in 340 patients over a period of 7 years

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Aim of this study was to evaluate the rate of lead-related complications (LRC) in 340 consecutive patients (pts) with an implantable cardioverter/defibrillator (ICD).

Methods: From 2/91 to 5/98 340 pts had an ICD implanted. Mean age was 64 ± 9 years, ejection fraction 38 ± 14%, 82% of pts were male, 60% had coronary artery disease, 31% dilative cardiomyopathy, 9% others. Indication for an ICD was in 57% of pts ventricular tachycardia and in 43% ventricular fibrillation. 93% of pts received a single-chamber ICD and 7% a dual-chamber ICD. In 8% of pts an additional patch or array electrode was implanted. In 27% implantation site was abdominal, in 73% pectoral.

Results: During 7 years overall 38 LRC occurred (9.7%), after a median of 2 months after implantation. Diagnosis was made by routine chest x-ray in about 55% of LRC, by clinical presentation (inadequate therapy, pain) in 24% and by electrical parameters in 21%. In pts with abdominal implantation site LRC occurred in 20% in contrast to 6% in pts with pectoral implantation site ($p < 0.0001$). Regarding pts with pectoral implantation site LRC were observed in 12% of pts with a dual-chamber ICD vs 4% with a single-chamber ICD ($p = 0.05$) due to dislocation of atrial electrodes with dual-chamber ICD. There were no differences in clinical parameters between pts with pectoral vs abdominal and between single vs dual-chamber ICD.

Conclusions: 1. In ICD pts with abdominal implantation site LRC were three times as frequent as in pts with pectoral implantation site. 2. Regarding pts with pectoral implantation site LRC occurred three times as frequent as in pts with dual-chamber than in pts with single-chamber ICD.

P695 Optimized programming in patients with implantable cardioverter-defibrillator and atrial fibrillation

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Differentiation of supra- (SVT) versus ventricular (VT) tachycardias is a problem to avoid inadequate therapies in patients (Pts) with cardioverter-defibrillator (ICD). Therefore, detection criteria such as onset (0), stability (ST) and QRS-width may be used to differentiate. The sustained rate duration (SRD) initiates the programmed therapy at a present tachycardia in spite of ST or 0, that are not fulfilled after a programmed time and represents a safety criterion. The aim of the study was to evaluate if the SRD is useful in Pts with atrial fibrillation (AF) and to assess an optimal progamming.

Results: In 292 Pts with ICD of the third generation, 44 Pts (15%) had AF (36 Pts CAD, 8 Pts DCM, LVEF 36 ± 18%); 18 Pts had known tachyarrhythmic episodes (TAE) in range of the programmed VT-zone (>160 bpm); in 15 Pts a new TAE was observed; and 11 Pts had normofrequent AF. After a mean follow up of 12 ± 11 months, 172 tachycardias were observed in 34 of these 44 Pts (77%). The tachycardias could be classified as SVTs by stored electrograms of the device (in all cases stored electrograms of the known VT were available). ST (22–26 msec) was fulfilled in 16 pts (36%) and they were treated inadequate with antitachycardia pacing (ATP) in 7 Pts (16%) and with ATP and consecutive shocks (CS) in 9 (20%) Pts. In 18 Pts of the 44 Pts (41%) ST was not fulfilled at a present ongoing TAE (39 episodes) and the SRD-criterion initiated the therapy: these Pts were treated inadequately with ATP in 7 (16%) Pts and with ATP and CS in 11 pts (25%). The mean programmed SRD was 25 sec in all Pts. After the first inadequate therapy (IAT) SRD was prolonged to a mean value of 85 sec and after recurrence of a IAT at TAE up to a mean of 195 sec (150–300 msec).

Conclusion: In our ICD-collective of 292 Pts AF occurs in 15% (44 pts). In these 44 Pts, TAE were observed and treated inadequately in 77%, and released by SRD in 41%. The primary programming of SRD should be long (>90 sec) in Pts with known TAE as wells as in Pts with normofrequent AF who can hemodynamically tolerate the cycle length of the programmed zone with SRD as additional feature.

P696 Heart rate variability in patients with thalassemia major: association with clinical and echocardiographic features

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Cardiac arrhythmias and heart failure are the main cause of death in patients with Thalassemia Major (TM). Impaired sympathovagal balance might contribute to the genesis of arrhythmic events in these patients. Heart rate variability (HRV) is an accepted tool for the assessment of cardiovascular autonomic tone. The aim of this study was to evaluate cardiac autonomic control in patients with TM and to assess indexes of HRV in relation to clinical and echocardiographic data of TM patients.

Methods: We studied 40 patients with TM, 20 men and 20 women, age ranging between 17–40 years (mean age 27 ± 6 years). All patients were in synus rhythm. Patients with clinical evidence of heart failure, suffering from diabetes melitus and on chronic therapy with beta blockers were excluded from this study. Ambulatory 24 hour ECG recordings were analyzed. After standard holter analysis the following time domain measures of HRV were obtained: Percentage of cycles differing from preceding one by >50 ms for entire 24-hour recording (pNN50), Standard deviation of normal RR intervals (SDNN), Root mean square of successive differences of R-R intervals (RMSSD). In this study pNN50 and PMSSD time domain measures considered to represent the parasympathetic modulation of HRV. Forty healthy volunteers, 20 men and 20 women, (mean age 26 ± 5 years) not taking any medication, were used as control group.

Results: Values of pNN50, SDNN and RMSSD were lower in patients with TM than in control group. pNN50 was 8.0 ± 7.0% in patients with TM and 18.2 ± 9.7% in normal subjects ($p < 0.001$) SDNN was 116.0 ± 28.7 ms in patients with TM and 154.9 ± 40.9 ms in the control group ($p < 0.001$). RMSSD was found 28.4 ± 10.8 ms in TM compare to 42.8 ± 13.3 ms in normal subjects ($p < 0.001$). The same significantly statistical diferences were found between the two groups according to sex. The relationship between the above dependent variables of time domain measures of HRV and the independent variables of clinical and echo measurements (Compliance to chelation therapy, endiastolic diameter of left ventricle, L.V. Mass on M-Mode Echo) using multiple regression and correlation analysis, showed that pNN50 and RMSSD, which represent the vagal control, were found directly related to the compliance to chelation therapy ($p < 0.005$) and inversely related to LVMass ($p < 0.05$).

Conclusions: Measures of vagal modulation of HRV were lower in TM patients than in control subjects indicating cardiac autonomic dysfunction and decreased parasympathetic activity in patients with TM. We hypothesize that this deminished parasympathetic activity may be responsible (with other factors) for the electrical instability and the pathogenesis of arrhythmias in patients with TM and may be an important index for risk stratification of these patients.

P697 Prevalence of baroreflex heart rate reaction for the detection of autonomic nervous system impairement at insuline resistance syndrome

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We aimed to compare the sensitivity of baroreceptor (BR) cardiac reflex and heart rate (HR) variability analysis for an early detection of autonomic nervous system impairement in non-insulin dependent diabetus mellitus (NIDM).

Methods: on 15 pts with NIDM (men, 63 ± 1.8 yr aged, HbA_{1C} 10.1 ± 0.9%, ranged from 8.7 to 11.2%, with time of manifestation syndrome 9 ± 1.5 yrs) and 19 controls (C, gender and age matched), beat-to-beat HR, finger mean arterial pressure (MAP) were monitored before and during BR reflex activation by neck suction (−60 mmHg, for 5 s) and 512 R-R (ECG) interval files in supine and upright postures were stored, analysing mean R-R interval, its standard deviation (SD), total power spectrum, power of the low (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.4 Hz) bands and LF:HF ratio. All medications with the exception of hypoglycemic agents were discontinuated 2 weeks before the study. Values are expressed as means ± standard error.

Results: for sitting NIDM pts, the HR (80 ± 2 vs 70 ± 3 bpm; $P < 0.05$) and finger MAP (113 ± 2.7 vs 90 ± 1.4 mmHg; $P < 0.05$) were increased, but BR reflex bradycardic reaction (1.8 ± 0.3 vs. 10 ± 0.6 bpm, $P < 0.02$) was reduced comparing to C. In supine position, mean R-R interval (772 ± 25 vs. 1017 ± 28 ms; $P < 0.001$) and its standard deviation (27 ± 2.5 vs. 54 ± 5.3 ms; $p < 0.001$) as well as R-R interval decrease in upright position (108 ± 12 vs 254 ± 21 ms; $P < 0.001$) were less in NIDM pts. than in C, but LF, HF and LF:HF ratio (1.07 ± 0.2 vs. 1.33 ± 0.21) values and LF:HF ratio increase failure in upright position ($\chi^2 = 3.2$), didn't reveal to be significant.

Conclusions: For NIDM patients, BR reflex bradycardic reaction is superior to HR variability analysis to ascertain an early impairment of cardiovascular neuropathy.

P698 Haemodynamical specfics in essiential hypertensive patients with various degree of left ventricular hypertrophy

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Aim: To assess the haemodynamic indicies in essential hyper ten sive (EHTN) pts in dependence of left ventriculer mass (LVM)

Methods: Echo cardiography (Echo) Radionuclide ventriculography (RVG)

Eighty four (84) EHTN Pts with II stage (WHO) and 20 healthy persons as control group, all with average age of 44.3 ± 0.8 years, were examined

Results: LVH was diagnosed when left ventricular mass index (LVMI) was greater them 131 gm/m^2 in males and greater them 108 gm/m^2 in females. Pts were divided into three groups according of the LVM Indicies of structural and functional status of myocardium in EHTN pts with various degree of LVH

Groups	LVMI	ΔP	BPs	BPd	SVR 5 dyn.cm.m^2
Healthy persons (n = 20)	85 ± 3	0.38	56.4 ± 4.0	78 ± 2	1145 ± 56
Pts with normal LVM. (n = 36)	106 ± 2	0.40	71.6 ± 3.9	102 ± 2	1980 ± 105
Pts with Mild LVH (n = 37)	149 ± 3	0.43	85.6 ± 8.9	105 ± 3	2165 ± 126
pts with Severe LVH (n = 11)	189 ± 19	0.45	88.1 ± 8.4	113 ± 9	2394 ± 133

LVMI correlated with systolic and diastolic blood pressure (BPs BPd) relative well thickness (ΔP) was directly proportional to BP. End systolic tension (EST) was directly proportional to LVH. ΔP was directly proportional to systemic vascular resistance (SVR)

Conclusion: the haemodynamic determinants of left ventricular hyper trophy are blood pressure and systemic vascular resistance and systolic tension.

DUAL-CHAMBER IMPLANTABLE DEFIBRILLATORS

699 Worldwide clinical experience with a dual-chamber implantable cardioverter defibrillator in patients with atrial fibrillation and flutter

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Atrial tachycardia (AT) and fibrillation (AF) as well as ventricular tachycardia (VT) and fibrillation (VF) can be discriminated by the Medtronic 7250 Jewel® AF dual chamber ICD based on the rate and regularity of the atrial rhythm. Programmable atrial therapies include antitachycardia pacing (ATP), 50 Hz burst pacing, and shocks.

Methods: In a multi-center study, we analyzed detection and therapy of spontaneous arrhythmias in patients with symptomatic AT/AF and no prior VT/VF.

Results: There were 51 patients (37 US and 14 Europe), left-ventricular ejection fraction: 55% ± 16%, left atrial dimension: 43 mm ± 9 mm. 35% of the patients were in NYHA Class II or III. During follow-up (averae 3.2 ± 2.5 months) a total of 156 spontaneous AT and 206 AF episodes were detected in 13 and 28 patients, respectively. The table shows the efficacy of the last programmed therapy for treated episodes:

Therapy	AT	AF
ATP	33/37 (89%)	Not applicable
50 Hz Burst	22/95 (23%)	22/55 (40%)
Atrial Shock	24/24 (100%)	139/151 (92%)

Of 151 spontaneous AF episodes treated with shocks, 43/44 were successfully treated by 9 patients themselves using the patient activator (Model 9464). One patient with structural heart disease had 2 double-tachycardia episodes (VF + AF) that were treated successfully by two 27 J shocks. One of 2 patients, who were not known to have a prior history of VT and/or VF, did receive successful therapy for a spontaneous VF episode. There were 28 clinical adverse events of which 5 required surgery.

Conclusion: 1) Painless therapies successfully terminated 41% of AT episodes. 2) AF shock efficacy is 92%. 3) Observed adverse clinical events are comparable to those observed with dual chamber ICD patients. 4) The availability of ventricular therapy in patients with AF who have structural heart disease may be a significant advantage of the Jewel® AF.

700 Dual-chamber pacing and sensing with a single lead: first results with a new single pass defibrillation lead

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Background: Dual chamber defibrillators are increasingly used to avoid inappropriate shocks. However, placing of an atrial pacing and sensing lead is associated with a higher morbidity and complication rate. The purpose of this study was to investigate a new single pass right ventricular defibrillation lead designed for bipolar atrial and ventricular sensing and pacing.

Methods: In 8 pts (all CAD, 66 ± 8 years; NYHA 2.1 ± 0.4; EF 44 ± 17%), the new single pass, right ventricular defibrillation lead with integrated bipolar ventricular and true bipolar right atrial pacing and sensing was tested (Medtronic, model 14108). Pacing and sensing in the right atrium occurred between an atrial ring and an electrode on a tine 15.5 cm proximal to the right ventricular tip. In order to enhance the contact between these electrodes and the atrial wall, the lead had a 90° curve just distal to the atrial electrodes.

Results: Implantation of the new lead was successful in all pts, the operation time was 76 ± 30 minutes, the fluoroscopy time 4.2 ± 2.3 minutes. The defibrillation threshold was 9.0 ± 3.2 Joule. The intraoperative atrial sensing measured 1.6 ± 0.6 mV, the atrial threshold product was 0.20 ± 0.15 (median 0.15) V*ms. At pre-hospital-discharge (PHD), 1-month follow-up (1-FU), and 3-month follow-up (3-FU) the atrial sensing was as high as 1.5 ± 0.6 mV, 2.0 ± 0.6 mV, and 2.5 ± 0.9 mV (p = ns, p = ns, p = 0.05 to implant), the median of the atrial threshold product was 0.66 V*ms, 0.60 V*ms, and 0.45 V*ms. At PHD, 1-FU, and 3-FU, no significant differences of atrial sensing or atrial threshold product were measured during resting supine, lying on the left side, right side, sitting, standing, or at deep inspiration, respectively. All spontaneous, (13× SVT, 11× MVT) and inducted (2× MVT, 9× pVT, 4× VF) episodes of tachycardia were detected and terminated correctly.

Conclusions: Atrial and ventricular sensing and pacing with a single lead is feasible and likely to shorten operation time and possibly to decrease morbidity and complication rate associated with an atrial lead.

701 Analysis of dual-chamber cardioverter-defibrillators electrograms for discrimination of ventricular from supraventricular tachycardia: implication for ICD-specificity and programming

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Background: Inappropriate therapy (shock and antitachycardia pacing) remains a major problem in patients with implantable cardioverter defibrillators (ICDs), and the ability to differentiate ventricular (VT) from supraventricular (SVT) tachycardia is a major objective of discrimination algorithms.

Methods: On the basis of AV relationship, this study aimed to evaluate the clinical performance of the CPI dual-chamber ICDs algorithms for discrimination of VT from SVT or sinus tachycardia (ST). The analysis of 175 spontaneous episodes of tachycardia from electrograms (EGMs) source was performed in 10 patients with Ventak AV ICDs (Model 1810, 1820 and 1821). ICDs were interrogated every 3 months or when patients received shocks. A double-blind review of EGMs for arrhythmia diagnosis and appropriateness of therapy was performed by two senior physicians and by a third one in case of conflict. Algorithms for discrimination of VT from SVT or ST were onset, stability and V rate > A rate. Sustained rate duration (SRD) criterion was also programmed.

Results: After review of the 175 stored EGMs, the final diagnosis were VT = 98, SVT = 29, ST = 42 and artifacts connector related = 6. Among the 98 VT episodes, V rate was > to A rate in 91 cases and therapy was always appropriate. V rate was equal to A rate in 7 cases: retrograde 1/1 conduction was found in 6 cases, and bitachycardia in 1 case. Therapy was delivered to 3 of these 7 cases, and inhibited in the 4 others (instability = 3, instability and progressive onset = 1) until spontaneous termination of VT before SRD. SVT episodes were atrial flutter (n = 8) and atrial tachycardia (n = 21). Inappropriate therapy occurred in 11 (38%) of SVT episodes, and therapy was adequately withheld in the 18 others. Inappropriate VT detection of true SVT was primarily due to SVT with 1/1 AV conduction. No inappropriate therapy was delivered among the ST episodes owing to progressive onset. Finally, detection algorithms appropriately classified 94/98 (96%) true VT episodes as VT and 60/71 (84.5%) true SVT episodes as SVT. Sensitivity of the Ventak AV algorithms was 100% (owing to the SRD criterion) and specificity was 89%.

Conclusions: The programming of detection criteria based on onset, stability, V rate > A rate and SRD allows a 100% sensitivity in Ventak AV ICDs. However, discrimination between VT and 1/1 SVT remains difficult, and additional algorithms may be useful for significant reduction of inappropriate therapy.

702 Does a dual-chamber detection algorithm really improve discrimination between supraventricular and ventricular tachycardias in implantable cardioverter-defibrillators recipients?

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Background. Single-chamber Implantable Cardioverter-Defibrillators (ICDs) face up to 30% of inappropriate shock delivery. New single chamber criteria based on the onset and stability of tachycardia and on the width of ventricular electrogram can improve specificity of tachycardia detection, but on the other side can reduce sensitivity and need careful follow-up and tailored programming. Dual chamber pacing combined with ICD therapy has recently become available in clinical practice.

Aim of our study was to evaluate the overall performance of a new dual chamber detection algorithm (PR Logic) which has been introduced in the DDDR-ICD Gem DR 7271 and in the Dual-ICD Jewel AF 7250 (Medtronic, Inc., Minneapolis, MN). The device first utilizes the single chamber rate-only VT/VF detection algorithm, and then applies the PR Logic rules which withhold detection if one of three specific SVT rules are met: atrial fibrillation or flutter (AF), sinus tachycardia (ST) or other 1:1 SVT.

Patient population. 38 patients, 31 male and 7 female, mean age 67 + 9 years, have been implanted with a dual chamber ICD, 27 with the model 7250 and 11 with the model 7271. Ischaemic cardiomyopathy was present in 77% of patients, dilated cardiomyopathy in 23%. VF was the primary indication for ICD implantation in 31% of patients, sustained recurrent and poorly tolerated VT in 67% and recurrent AF in 2%. 13 patients experienced AF before implantation. Follow-up lasted 1–20 months.

Results: 56 episodes of VF were appropriately detected and successfully treated. 495 episodes of VT were detected. 490/495 (99%) were correctly detected and treated with a success rate of 96%. 5/495 (1%) were inappropriately detected as VT while they were SVT episodes. Inappropriate detection episodes included: ST with long PR interval and P wave falling in the retrograde conduction zone, 1:1 SVT with P wave in the retrograde zone and AF with ventricular rate higher than the SVT limit (rejection rules excluded). 404 Atrial Tachycardia episodes and 107 AF episodes were appropriately detected. The detection Positive Predictive Value was 93%.

Conclusions. The dual chamber detection algorithm PR Logic performed very well in our experience. Strong points of the system seem to be: improved specificity without decreased sensitivity; easy programming independent from the individual arrhythmic profile of the patient.

703 Efficacy of anti-tachy-pacing and low energy cardioversion in terminating spontaneous atrial tachyarrhythmias in patients with dual implantable defibrillator

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About 30% of patients with low left ventricular ejection fraction (LVEF) implanted with ICD suffer from recurrent atrial tachyarrhythmias. Recently, a dual implantable defibrillator (Medtronic model 7250) has been introduced for clinical implantation. The device combines DDD pacing with atrial and ventricular arrhythmia automatic detection and treatment. Available atrial therapies for Atrial Tachycardia (AT) include Ramp, Burst+, 50-Hz Burst and Low-Energy Cardioversion. Atrial therapies for Atrial Fibrillation (AF) include 50-Hz Burst and Low-Energy Cardioversion. Aim of our study was to evaluate the efficacy of the dual defibrillator in detecting and treating atrial tachyarrhythmias. Patient population included 22 patients, 18 M, 4 F, mean age 67 ± 9 years. 15 pts had ischaemic dilated cardiomyopathy (DCM), 6 idiopathic DCM and 1 no structural heart disease. Mean LVEF was 38 ± 17%. Indication to ICD implantation was ventricular tachycardia in 16 pts and ventricular fibrillation in 6. 11 had AT/AF before implantation. A two lead configuration (right atrium and double coil right ventricle) has been utilized. The follow-up ranged between 1 and 19 months.

Results: 589 atrial episodes were detected, 450 classified as AT (76%) and 139 as AF (24%). AT/AF detection sensitivity was near 100% with no known missed spontaneous symptomatic episodes The detection Positive Predictive Value was 93%. 62 atrial episodes (10%) were automatically treated. The success rates in the AT zone were: ATP therapy (Burst+ and/or Ramp) 77% (10/13 episodes), 50-Hz Atrial Burst 79% (15/19). In the AF zone 14/15 episodes (93%) were successfully terminated by 50-Hz Burst and 10/15 (67%) by atrial shock. The mean energy delivered was 13.8 ± 8.3 J, with a mean impedance of 42 ± 9 Ω.

Conclusions: Atrial ATP Therapies and Low-Energy Cardioversion available in the dual defibrillator represent an effective option to treat atrial arrhythmias in patients candidated to ICD implantation. Optimization of ATP therapy programming and lead configuration are needed to increase success rate, to reduce atrial defibrillation threshold and to improve patient tolerance.

704 Reconstructed "farfield" ECG leads in the ICD versus standard surface ECG: a new option to monitor myocardial ischaemia

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ICDs with the capability of analysing multiple intrathoracic "farfield" ECGs with respect to acute ischemic episodes (IE) will soon be available. These systems will use the ST-segment for analysis of IE. Aim of our study was to investigate the diagnostic accuracy of detecting IE in 6 ECG leads available in the ICD in comparison to the surface ECG by brief periods of PTCA-induced myocardial ischemia.

Methods: We prospectively assessed ST-segment deviations at 27 sites (22 pts.) during PTCA using ECG leads available in an implantable ICD (electrodes: RV apex, VCS, cutaneous patch at typical location of ICD generator over left pectoral muscle (LPM): 3 bipolar leads = BI–III; 3 tripolar leads = TI–III) and compared these findings with surface ECG. ST-segment deviations due to occlusion and reperfusion of a coronary artery were measured during PTCA.

Results: Mean ST-segment deviations in mV after certain times of balloon insufflation are given in the following table:

Lead	PTCA:	30 s	60 s	max..	5 min post
Surface I	0.01 ± 0.03	0.01 ± 0.02	0.03 ± 0.06	0.00 ± 0.01	
II		0.02 ± 0.03	0.05 ± 0.06	0.05 ± 0.07	0.01 ± 0.03
III		0.03 ± 0.04	0.04 ± 0.06	0.05 ± 0.06	0.01 ± 0.03
V4		0.18 ± 0.27	0.22 ± 0.38	0.26 ± 0.38	0.07 ± 0.10
V5		0.13 ± 0.18	0.17 ± 0.24	0.21 ± 0.24	0.09 ± 0.07
V6		0.11 ± 0.11	0.16 ± 0.18	0.19 ± 0.18	0.06 ± 0.06
BI (VCS vs. LPM)	0.12 ± 0.21	0.42 ± 0.27	0.50 ± 0.31	0.08 ± 0.04	
BII (LPM vs. RVA)	0.31 ± 0.31	0.46 ± 0.53	0.51 ± 0.54	0.16 ± 0.20	
BIII (VCS vs. RVA)	0.28 ± 0.33	0.40 ± 0.43	0.43 ± 0.44	0.13 ± 0.15	
TI (RVA + LMP vs. VCS)	0.20 ± 0.19	0.25 ± 0.30	0.30 ± 0.29	0.08 ± 0.09	
TII (RVA + VCS vs. LPM)	0.14 ± 0.11	0.18 ± 0.15	0.20 ± 0.15	0.09 ± 0.12	
TIII (VCS + LMP vs. RVA)	0.28 ± 0.30	0.35 ± 0.34	0.39 ± 0.36	0.11 ± 0.12	

At 30 sec of PTCA the bipolar leads (BI 40%, BII 78%, BIII 67%) and the tripolar leads (TI 67%, TII 67%, TIII 78%) were superior to surface ECG (V4 37%, V5 37%, V6 41%) to detect ischemic ST-changes.

Conclusion: Detection of IE by ECG leads available in the ICD is feasible. Early assessment and diagnostic accuracy are superior to the surface ECG.

MECHANISMS AND MAPPING OF VENTRICULAR TACHYCARDIA

705 Use of the electroanatomical Carto™ mapping to design an individual strategy for catheter ablation of ischaemic monomorphic ventricular tachycardias

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Catheter ablation of monomorphic ischemic ventricular tachycardia (VT) is limited in regard to mapping and ablation success. The aim of the present study was to investigate the safety and efficacy of VT catheter ablation using an electroanatomical (EA) mapping approach (CARTO™). Between 6/97 and 10/98, 13 post-MI pts (67 ± 6 yrs) were referred for RF ablation of VT (12 already under AA drugs and 8 ICD therapy). The clinical VT (cycle length, 420 ms; range, 300–540 ms) was inducible in all pts. In all pts, EA map of the left ventricle (LV) was attempted during sinus rhythm (map 1) and during VT (map 2); map 1 was completed in 11 pts (2 pts were in incessant VT) and map 2 in 6 pts (4 pts had VT mechanical block and 3 were hemodynamically unstable during VT). RF pulses delivered at scar sites of slow conduction within the reentrant circuit abolished VT in 7 pts (acute success) during 1 (1–2) procedure; an irrigation catheter was used in 2 such cases to consolidate the transient effect obtained with conventional techniques. In the remaining 6 pts, superimposition of map 1 and 2 was used to sever the scar area with a linear lesion; a second linear lesion was made to connect the scar boundary to the closest anatomical barrier. Procedure duration was 531 ± 119 min. At discharge, AA drugs were discontinued in 6 of 7 pts with acute success and were continued in remaining pts. One pt died 28 days after the procedure due to progressive heart failure. During a FU of 8.5 (1–15) mos, 1 pt had VT recurrence.

Conclusion: In pts with post-MI VT, use of EA mapping allowed: 1) identification of scar sites with slow conduction within the reentrant circuit with high accuracy; 2) to produce linear ablation models severing the scar surface as well as ventricular isthmuses between the scar area boundary and closest anatomical barriers. Combination of these techniques was used to design an individualized strategy for RF ablation of post-MI VT which allowed to extend the indications to new pts categories and was associated with a 92% success rate over an intermediate FU.

706 Mapping and ablation of re-entrant ventricular tachycardia using a three-dimensional non-fluoroscopic system

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We report our experience and results with mapping and ablation of reentrant ventricular tachycardia (VT) using a three dimensional non-fluoroscopic mapping system. A total of 19 patients with either ischemic ventricular tachycardia (16 pts) or right ventricular dysplasia (RVD)(3 pts) underwent ablation for the occurrence of multiple defibrillator shocks. In the 3 patients with RVD, a total of 12 different VTs were mapped and ablated. In the remaining 16 patients with ischemic heart disease, a total of 30 VTs were induced and mapped. In all VTs the site of earliest activation was identified with the three dimensional activation map. Pacing at the earliest site showed concealed entrainment in 25 of the 42 tachycardias (59%). In the remaining VTs, concealed entrainment was demonstrated in an area close to the earliest site on the three dimensional activation map. After termination of VT was obtained during radiofrequency energy delivery ablation was extended radially in the same region. This approach was facilitated by the real time visualization of the catheter location and tagging of each ablation site on the 3-D map. In 5 patients ablation had to be completed using a 8 mm tip catheter. At the end of the procedure no monomorphic VT was inducible. In 4 patients ventricular flutter was induced with an aggressive pacing protocol during isoproterenol infustion. At follow-up, 1 patient with RVD experienced 1 episode of VT successfully terminated by pacing through the ICD. Two patients with ischemic heart disease experienced recurrence of VT. Both patients underwent successful re-ablation and had no recurrence. In conclusion, this 3 dimensional non-fluoroscopic mapping system has the potential to facilitate identification of successful ablation sites for reentrant ventricular tachycardia and to allow a more accurate and adequate ablation of the tissues surrounding the earliest site of activation which could result in a lower long term recurrence rate.

707 Non-contact mapping-guided radiofrequency ablation of ventricular tachycardia in patients with frequent defibrillator therapy

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Patients (pts) with implantable defibrillators (ICD) and frequent episodes of ventricular tachycardia (VT) or slow VT, receive unacceptably frequent and/or inappropriate device therapies. 10 patients with recurrent VT and ICD had RF ablation guided by a non-contact mapping system, because of slow VT in 1 and frequent device therapy in 9. Mean age was 58 ± 12 years, all were male. 6 had coronary artery disease and the remaining 4 had dilated cardiomyopathy. Mean LV diastolic dimension was 6.4 ± 0.45 cm and follow-up was 12.4 ± 13.7 months.

Results: 40 VT morphologies were mapped. The non-contact mapping system identified 40 exit sites, 9 complete and 17 partial diastolic pathways (mean 43 ± 37.8% of diastolic interval). 19 VT were ablated with a mean of 11.7 ± 12.1 RF applications given per patient. Over a mean follow-up of 12.4 ± 13.7 months, ICD shocks were reduced after ablation from 9.4 ± 7 to 0.22 ± 0.52 discharges per month ($p < 0.01$) and anti-tachycardia pacing was reduced from 42.5 ± 96 to 2.5 ± 6.2 episodes per month ($p < 0.03$). Total device therapy was reduced from 62 ± 126 to 2.76 ± 6.7 episodes ($p < 0.02$). During follow-up there has been 4 deaths, 3 from non-arrhythmic events with no therapies recorded by their device post mortem, the remaining patient died of incessant VF. Complications: 2 patients developed false femoral aneurysms requiring surgical repair and 1 patient sustained a minor stroke during the study from which he made a full recovery.

Conclusion: In patients with drug refractory VT, ablation guided by non-contact mapping system is able to effectively reduce frequent ICD therapy.

708 Bystander activation of the His-Purkinje system during ventricular tachycardia after myocardial infarction

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Apart from bundle branch reentry we tested the incidence and consequences of a bystander activation of the His-Purkinje system during VT following myocardial infarction (MI). We considered this activation to occur when the following criteria were met: (1) variation in the activation pattern of a monomorphic VT due to secondary optional breakthroughs (BKT) (2) spatial coincidence of these secondary BKTs with BKTs in sinus rhythm (3) remoteness of these BKTs from the scar. The study was conducted prospectively during isochronal mapping of 99 VTs obtained at surgery in 32 MI pts, with a 128-electrode system, using an epicardial sock and a left ventricular endocardial balloon.

Results: At least one VT following these criteria was mapped in 5 pts (16%), 2 with an inferior and 3 with an anterior MI, 2 of them having a bundle branch block in sinus rhythm. These tachycardias represented 5% of the total VT number, 4 of them were clinical. These VTs originated from the septum or from the left free wall in 2 and 3 cases respectively. Changes in the activation sequence involved the right bundle branch in 2 VTs, the left posterior fascicle in 2 VTs, both in the remaining VT. The VT cycle length was unaffected in 2 cases and either slower or faster in the 3 other cases. Changes in ECG morphology were analyzed at surgery in the frontal plane only, the QRS axis rotation ranged from 15 to 150° (mean 55°). Therapy (resection or cryoablation) was not targeted to the elements of the His-Purkinje system.

In conclusion, A bystander activation of the His-Purkinje system may occasionally be observed during postMI VT inducing dramatic changes in the surface ECG. This phenomenon has important implications in the interpretation of intraoperative or catheter-based activation maps.

709 Short-long-short sequences are important arrhythmia mechanisms in over 1000 analysed spontaneous ventricular arrhythmias

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In this study the importance of short-long-short sequences as a trigger mechanism of spontaneous ventricular tachycardias (VTs) was analysed. The short-long-short sequence was defined for RR intervals with changes of ≫30% directly preceding the arrhythmia. In 250 patients with survived sudden cardiac death and implantable cardioverter-defibrillators (ICD) spontaneous arrhythmias were analysed for the preceding rhythm stored in the recorded ECG strip of the implanted device. Patients with atrial fibrillation and pacemaker dependent rhythm were excluded.

Results: During a follow-up of 31 ± 12 months 1004 spontaneous VTs in 102 patients were analysed. A short-long-short interval with ≫30% changes of RR intervals was obtained in 337 (33.6%) of 1004 spontaneous VTs and in 66 (65%) of 102 patients with spontaneous arrhythmia recurrences. The prolonged (long) RR interval was terminated in 60% by a sinus beat in 41 patients with coronary artery disease compared to 33% in 18 patients with cardiomyopathy. A pacer-induced ventricular complex was seen at the end of the prolonged RR interval in 57% of patients with cardiomyopathy but only in 30% of patients with coronary artery disease.

Conclusion: Short-long-short sequences are an important trigger mechanism in 33% of spontaneous VT and were seen in 65% of the patients with recurrent arrhythmias.

710 Wavefront velocity and turning characteristics of the diastolic pathway during human ventricular tachycardia

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Conduction properties of the diastolic pathway (DP) in human ventricular tachycardia (VT) are poorly characterised. We used a non-contact mapping system, which simultaneously reconstruct over 3,300 unipolar electrograms on a virtual endocardium to determine wavefront velocities within the DP and at entry and exit sites. Endocardial distances were calculated from Cartesian co-ordinates and angles of turn by 3 dimensional vector geometry. 7 patients (61.7 ± 5.3 years) with poor left ventricular function (EF 36 ± 5.3%) undergoing VT ablation were studied. 6 had ischaemic heart disease and 1 had dilated cardiomyopathy. 10 VTs with a cycle length of 354 ± 76 ms were mapped. All patients had ≥ 40% of the DP identified (mean 83%, range 40–100%). The 6 DP fully defined were 102 ± 40 mm long and occupied 71 ± 7.1% of VT cycle length. Overall, DP wavefront velocity was 0.81 ± 0.49 m/s. Angulations of the DP were defined as regions where trajectory of propagation changed by >7 degrees/mm. A total of 8 angulations were identified within the course of the DPs, which slowed the activation wavefront to 0.41 ± 0.1 m/s compared with a mean of 0.99 ± 0.26 m/s ($p < 0.0004$) in the immediate segments preceding and following angulation. 166 ± 41 degrees of angulation were seen during turning within the DP.

18 entry and 19 exit turns were mapped. Wavefront velocity changed from 1.25 ± 0.42 ms to 0.62 ± 0.26 ms ($P < 0.0001$) at entry site turning points (TP) and from 0.72 ± 0.28 m/s to 0.83 ± 0.25 m/s ($p = 0.11$) at exit TP. Entry TP is slower than exit TP velocity ($p < 0.008$). Wavefront turning at entry and exit were 115 ± 28 and 137 ± 69 degrees respectively.

Conclusion: Wavefront slowing occurs at entry and exit points of DP and also during turning within the DP.

HEART FAILURE: NON-INVASIVE MARKERS OF OUTCOME

711 Depressed frequency domain measures of heart rate variability as an independent predictor of sudden death in chronic heart failure

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Identification of patients with chronic heart failure (CHF) at risk for sudden death remains difficult. Time domain measures of heart rate variability were an independent predictor of all-cause mortality but failed to predict sudden death in CHF. We sought to assess the prognostic value for sudden death of frequency domain measures of heart rate variability in CHF.

Methods: we prospectively enrolled 190 patients with CHF in sinus rhythm, mean age 61 ± 12 years, 109 (57.4%) in NYHA class II and 81 (42.6%) in class III or IV, mean cardiothoracic ratio 57.6 ± 6.4% and mean left ventricular ejection fraction 28.2 ± 8.8%, 85 (44.7%) with ischemic and 105 (63.3%) with idiopathic dilated cardiomyopathy. Time and frequency domain measures of heart rate variability were obtained from 24-h Holter ECG recordings, spectral measures were averaged for calculation of daytime (10 am to 7 pm) and nighttime (11 pm to 6 am) values.

Results: during follow-up (22 ± 18 months), 55 patients died, 21 of them died suddenly and 2 presented a syncopal spontaneous sustained ventricular tachycardia. In univariate analysis, predictors for sudden death were: ischemic heart disease, cardiothoracic ratio ≥ 60%, left ventricular ejection fraction < 30%, standard deviation of the averages of RR intervals in all 5 min segments (SDANN) < 55 ms, root-mean square of difference of successive RR intervals (RMSSD) < 14 ms, daytime total frequency power < 2.4 ln (ms^2/Hz) and daytime low frequency power < 3.3. ln (ms^2/Hz). In multivariate analysis, independent predictors for sudden death were: ischemic heart disease (RR = 4.1, 95% CI 1.6–10.5) and daytime low frequency power < 3.3 ln (ms^2/Hz) (RR = 2.8, 95% CI 1.2–8.6).

In conclusion: spectral analysis of heart rate variability identifies an increased risk for sudden death in patients with CHF.

712 QT-dispersion in patients with end stage heart failure prior to cardiac transplantation correlates with dispersion in refractoriness in the explanted perfused heart

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Introduction: Patients with increased QT-dispersion are at increased risk for sudden death. QT-dispersion is thought to correlate with heterogeneity in repolarization, but direct evidence for this is lacking.

Methods: ECGs were obtained from 6 patients (4 ischemic heart disease, 1 hypertrophic cardiomyopathy, 1 dilated cardiomyopathy) with end stage heart failure on the day of cardiac transplantation. Explanted hearts were stored in cold Tyrode's solution, connected to a Langendorff apparatus and perfused with a blood-Tyrode mixture at 37°C. Refractory periods were determined with the extrastimulus technique at a cycle length of 600 msec with 2 msec accuracy at 8 to 16 epicardial sites across the heart (6 hearts). At the same sites monophasic action potentials (MAP) were recorded. MAPduration was measured at 80% repolarization. When measuring QT-dispersion (largest QT interval difference) the investigators were blinded to the identity of the patients. Bazett's correction was applied.

Results: QT_c-dispersion was measured based on an average of 10 leads per patient and ranged from 37 to 194. Dispersion of MAP duration ranged from 40 to 80 msec, in refractory period from 26 to 176. QT-dispersion correlated with refractoriness (r^2 0.87, $p < 0.01$) but not with MAP duration.

Conclusion: This study validates the use of QT-dispersion for the detection of heterogeneity in refractoriness.

713 Dispersion of QRS and QT in patients with advanced congestive heart failure: relation to cardiac and sudden death mortality

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This study examined the significance of QT and QRS dispersion (QTd, QRSd) in the prognosis of patients (pts) with advanced congestive heart failure and correlated these measurements with other known indices of left ventricular dysfunction that are predictors of increased mortality.

Methods: The study population consisted of 104 pts (mean age = 53 ± 13 yrs, mean left ventricular ejection fraction = 22 ± 10%), who were followed prospectively for 19.6 mo. QRSd and QTd were defined as the maximum difference in QRS and QT interval durations, respectively, measured among all leads of standard 12-lead electrocardiograms. The endpoints of the study were non sudden and sudden cardiac mortality.

Results: There were 13 non sudden and 10 sudden deaths. QTd and QRSd were significantly greater in non survivors (95 ± 48 ms and 54 ± 17 ms, respectively), than in survivors (78 ± 31 ms and 46 ± 16 ms, respectively, $p < 0.03$ and $p < 0.02$, respectively). Death rate in patients with QTd > 90 ms was 2.8-fold higher than those with QTd ≤ 90 ms (95% CI 1.2 to 6.4). Similarly, the death rate in patients with QRSd > 46 ms was 3.9-fold higher than in those with QRSd ≤ 46 ms (95% CI 1.6 to 9.5). The actuarial survival between 14 pts who had QRSd > 46 ms and QTd > 90 ms and 90 pts who had QRSd ≤ 46 ms and QTd ≤ 90 ms was 50% and 82% ($p = 0.0008$), respectively, at 36 mo. In a multivariate analysis, functional class ($p = 0.0007$), QRS dispersion ($p = 0.001$) and QT dispersion ($p = 0.01$) were the only predictors of cardiac mortality. Bundle branch block or intraventricular conduction defects ($p = 0.02$) and QRS dispersion ($p = 0.04$) were the only predictors of sudden death mortality.

In conclusion, these findings suggest that variability in QT and QRS durations on 12-lead electrocardiograms are useful predictors of mortality in patients with advanced congestive heart failure.

714 Comparison of the effect of coronary angioplasty on signal-averaged electrocardiogram in patients with normal and depressed left ventricular function

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Whether successful myocardial revascularisation can alter arrhythmia substrate is still a subject of controversy. **The aim** of the study was to evaluate the effect of coronary angioplasty (PTCA) on parameters of signal averaged electrocardiogram (SAEG) in patients with normal and depressed LV function.

Methods: 55 consecutive pts undergoing successful coronary angioplasty (43 men, 12 women, mean age 54 ± 9.9 yrs) were included. Before the procedure there were 25 pts with normal LV ejection fraction (LVEF > 59%) and 30 pts with depressed LVEF (mean 46.2 ± 10.3%). Before PTCA and 19.6 ± 4.3 days after the procedure parameters of signal averaged ecg (filtered QRS duration-fQRS, low amplitude signal duration of the terminal part of QRS-LAS and terminal root mean square voltage-RMS40) were assessed.

Results: Late ventricular potentials (LP) according to Simpson's criteria were present in 10 pts (50%) with normal and in 14 (47%) pts with depressed LVEF. After PTCA there was a significant improvement in SAEG parameters (f-QRS and LAS) in pts with normal LVEF. Despite highly significant increase after angioplasty of LVEF (to 51.4 ± 10.9%; p < 0.00001) in pts with depressed LV function there was no change in SAEG parameters.

	Normal LVEF			Depressed LVEF		
	f-QRS	LAS	RMS-40	f-QRS	LAS	RMS-40
Before PTCA	107.6±24.7	46.9±26.2	25.7±21.6	106.9±21.9	40.0±17.3	25.3±20.8
After PTCA	93.6±9.4	33.6±7.1	30.6±17.1	102.0±17.4	37.9±13.5	25.2±19.9
p	<0.05	<0.05	NS	NS	NS	NS

After PTCA LP were present in 14 (47%) pts with depressed LV function (there was a disappearance of LP in 7 pts but also appearance of new LP in another 7 pts). In pts with normal LV function LP disappeared after PTCA in 50% of pts.

Conclusion: Successful relief of ischaemia with coronary angioplasty may improve delayed ventricular activation and modify arrhythmogenic substrate only in pts with normal LV function.

715 Magnetocardiographic late fields and electrocardiographic late potentials in post-myocardial infarction patients with ventricular tachycardia and cardiac dysfunction

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High-resolution magnetocardiographic (MCG) late fields following QRS complex indicate high risk to ventricular arrhythmias after myocardial infarction (MI). We compared MCG to signal-averaged ECG (SAECG) in identifying which patients with significant post-infarction myocardial damage are prone to sustained ventricular tachycardia (VT).

Methods: Sixty-three patients with remote MI were studied, 30 without and 33 with documented VT. Left ventricular ejection fraction was 28 ± 6% in the VT and 29 ± 10% in the non-VT group. MCG with 7 axial channels and SAECG with three orthogonal bipolar leads were signal-averaged and 40 Hz high-pass filtered. The QRS duration (QRSd), low amplitude signal duration (LAS) and the root mean square amplitude of the QRS end (RMS) were analyzed.

Results: Optimal combinations of dichotomized parameter values (maximum sum of sensitivity and specificity) were calculated for MCG and the Simson criteria for SAECG (2/3 of the following: QRSd > 114 ms, LAS > 38 ms, RMS < 20 μV) to separate the VT and non-VT groups. The results are shown in table:

	Sensit.	Specif.
MCG: QRSd > 138 ms *or* RMS < 520 fT	73%	67%
SAECG: Simson criteria	58%	43%

This is the first study showing the discriminative power of high-resolution techniques in comparable post-MI patients with a large MI. Better performance of the MCG method may be due to its higher sensitivity to tangential myocardial currents present in damaged myocardium, whereas SAECG may lose discrimination if post-infarction lesion is extensive.

Conclusion: The new technique of high-resolution MCG is superior to SAECG in detecting propensity to malignant ventricular arrhythmias in patients with severe left ventricular dysfunction after MI.

716 Improvement of heart rate variability by exercise training in chronic heart failure is associated with a reduction of future cardiac events

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In patients (pts) with chronic heart failure (CHF), a low heart rate variability (HRV) is associated with a poor prognosis. Exercise training has been shown to increase HRV. This improvement may be related to an increased parasympathetic tone.

The aim of this study was to assess the relation between cardiac events and changes in HRV following exercise training in CHF pts. We included 51 CHF pts referred for a cardiac rehabilitation program (mean age: 53.3 ± 12.6 years, 47 men). All pts underwent a 24-hour Holter monitoring with temporal and spectral analysis of HRV before and after the cardiac rehabilitation program. Pts were submitted to a training program including calisthenics and bicycle training (21 ± 10 sessions).

Results: At a mean follow-up of 9.7 ± 5.3 months, 20 pts had cardiac events: rehospitalization (12 pts), heart transplant (4 pts) or death (4 pts). Exercise training improved exercise tolerance parameters: peak VO_2 + 2.2 ± 2.6 ml/kg/mn (+15%). Comparison of HRV parameters between pts with and without cardiac events are presented in the table:

	No cardiac event	Cardiac events	p
Age (yrs)	53.4 ± 11.9	53.3 ± 14.0	NS
Ejection fraction (%)	27.1 ± 7.5	23.5 ± 8.1	NS
Δ VO_2 (%)	+14.1 ± 14.7	+15.6 ± 16.9	NS
Δ Heart Rate (%)	−4.2 ± 6.6	−2.9 ± 2.3	NS
Δ SDNN (%)	+33.1 ± 37.9	+4.5 ± 34.9	<0.01
Δ LF/HF (%)	−26.7 ± 50.2	+23.3 ± 72.9	<0.01

In **conclusion,** pts with or without cardiac events had similar ejection fraction, and improvement in peak VO_2 and heart rate. However improvement in HRV was significantly higher in pts without cardiac events. These results suggest that changes in HRV may be of prognostic significance after cardiac rehabilitation.

RISK FACTORS: NEW AND OLD

727 Reduced risk of acute myocardial infarction at high serum levels of a mammalian lignan, enterolactone: a prospective population-based case-control study

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Background: The mammalian lignan, enterolactone, is produced from diet derived precursors by the intestinal microflora. Enterolactone has been postulated to have a role in the prevention of chronic diseases such as cancer. We investigated the association of serum enterolactone concentration with the risk of acute myocardial infarction (AMI) in a prospective nested case-control study in middle-aged men from eastern Finland.

Methods: Serum enterolactone measurements were carried out for 169 men who had an AMI during an average 7.7 years follow-up and for 167 control men. Both the cases and controls were from a cohort of 2005 men who had no clinical coronary heart disease (CHD) at baseline. The controls were matched for age, examination year and residence. AMIs were registered prospectively. Serum enterolactone measurements were done with time-resolved fluoroimmunoassay.

Results: The mean baseline serum enterolactone concentration was 21.5 percent lower among the cases than the controls (95 percent confidence interval, 4.0 to 44.3 percent; P = 0.02 for difference). The men in the highest enterolactone quarter (>30.1 nmol/l) had 62.5 percent (95 percent con-fidence interval, 29.8 to 80.0 percent; P = 0.002) reduced risk of AMI. After an adjustment for the eleven most predictive risk factors, men in the highest enterolactone quarter had 64.5 percent (95 percent con-fidence interval, 23.9 to 83.4 percent; P = 0.008) reduced risk of AMI compared to men in the lowest quarter.

Conclusion: Healthy men with high serum levels of enterolactone had a greatly reduced risk of AMI, supporting the hypothesis that plant-dominated fiber rich food lowers the risk of CHD.

728 Long-term prognosis of exercise-induced premature ventricular contraction: the Paris prospective study I

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The long term prognosis of the occurrence of premature ventricular contraction (PVC) during exercise test remains unknown in the population. Therefore we used the long follow up period of this cohort study to assess cardiovascular mortality in asymptomatic subjects with negative exercise test.

Methods: 7746 working men employed by the city of Paris aged 43–52 in 1967–72 underwent physical examination plus ECG, provided blood for laboratory tests and answered questionnaires. Men with cardiac failure, coronary or valvular heart disease, high blood pressure or abnormal resting ECG were excluded. 6032 men completed exercise test using standardized procedure (0–2 mn: 82 W, 2–8 mn: 164 W and 8–10 mn: 191 W).

Subjects with a positive exercise test (defined as a $\geq$1 mm horizontal or descending ST depression) or labile ST changes were excluded from analysis. Men were divided in 3 groups according to the percentage of PVC during 30 s: GR1 PVC = 0, GR2 PVC $\leq$ 10% and GR3 PVC > 10%. Men were followed for survival until January 94 and vital status was obtained for 96% of men.

Results: Of 5830 men who had a negative exercise test, 389 died from cardiovascular cause. There were 5203 men in GR1, 497 in GR2 and 130 in GR3. The rate of cardiovascular death was 6.5% (n = 336) in GR1, 6.4% (n = 32) in GR2 and 16.2% (n = 21) in GR3 (p = 0.001). The relative risk of cardiovascular death associated with the occurrence of PVC was 0.96 for GR1 (ns) and 2.70 for GR2 (p = 0.001). The occurrence of PVC ($\leq$10 or >10) before exercise (n = 75) or during recovery (n = 116) was not associated with an increased cardiovascular mortality.

Conclusion: There is an increased cardiovascular mortality associated with the occurrence of >10% PVC/30 s during exercise but not before exercise or during recovery in middle aged asymptomatic Frenchmen with negative exercise test.

729 QT interval and its prognostic value for death in Warsaw Pol-MONICA population

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QT interval in the resting electrocardiogram (ecg) is the sum of ventricular repolarization and depolarization time. It's prolongation is associated with bad prognosis for survival due to severe ventricular arrhythmia.

Aim: to evaluate the association between QT duration and total, cardiovascular (CVD) and ischaemic heart disease (IHD) mortality.

Methods: Warsaw Pol-MONICA population of 2646 men and women, aged 35–64, screened in 1984 was followed-up to 1996. All deaths were registered based on death certificate diagnosis. QT interval was measured manually in 3 consecutive QRST complexes in each ecg and corrected using Bazett's formula (QT corrected-QTc). For statistical analyses mean values of three QTc measurements were used. To assess the relationship between QTc and mortality Cox proportional hazard model was performed.

Results: Out of screened persons 459 died (309 men, 150 women), 226 of them due to CVD (162 men, 64 women) and 81 due to IHD (59 men and 22 women). Both men and women who died were significantly older at baseline and had significantly longer mean QTc compared to survivors (men: 457 ms vs 446 ms, p = 0.0001; women: 469 ms vs 459 ms, p = 0.0011). In men, after adjustment for age, mean QTc was significantly associated with total, CVD and IHD mortality. In women QTc was related to CVD and IHD mortality. The risk of death rose with increase in QTc duration. In men, with every increase in QTc by 20 ms the risk of all cause and CVD death rose by 14% (p – respectively 0.0001 and 0.02) and the risk of IHD death – by 17% (p = 0.02). In women, the risk of all cause death increased by 9% (NS), CVD death – by 28% (p = 0.004) and IHD death – by 43% (p = 0.009).

Conclusion: QTc interval was significantly related to all cause, cardiovascular and ischaemic heart disease mortality. The risk of death increased with longer QTc duration.

730 Unrecognized hypertension in diabetic patients with coronary disease: prevalence and prognostic significance

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Recent studies have shown a wide spreading of undiagnosed and accordingly untreated hypertension. However, scarce data are available regarding the prevalence and prognostic significance of the triple coexistence of undiagnosed hypertension, diabetes and ischemic heart disease. This study was aimed to evaluate the prevalence and prognostic significance of undiagnosed hypertension in cardiac diabetic patients defined previously as "normotensives" over a 5-year follow-up period.

Methods. The study sample comprised 11515 patients aged 45–74 with a previous myocardial infarction and/or anginal syndrome who were screened but not included in the Bezafibrate Infarction Prevention (BIP) study. Among them, 9033 were nondiabetics and 2482, diabetics. The diabetics were divided into 3 groups: 1) 1272 normotensives; 2) 152 patients without history of hypertension but with elevated blood pressure ("unrecognized hypertensives"); 3) 1058 hypertensives with established diagnosis.

Results. The prevalence of both diagnosed and unrecognized hypertension in diabetics pooled together rose from 49% to 69% when WHO and new JNC-VI criteria were compared. Crude all-cause mortality was lower in the nondiabetics than in diabetics (11.2% vs. 22.0%; p < 0.001). Among diabetics the lowest all-cause mortality was documented for the normotensives (19.3%), whereas the highest mortality was observed in unrecognized hypertensives (26.3%, p = 0.003). Both unrecognized and established hypertensives demonstrated a significant stroke-related mortality excess: about four-fold and three-fold increased of CVA death was observed, respectively (p = 0.002). On multivariate analysis both unrecognized and diagnosed hypertension were consistent predictors of increased all-cause mortality with a hazard ratio of 1.28 (95% CI 0.90–1.82) and 1.24 (95% CI 1.03–1.49), respectively.

Conclusions. We demonstrated a wide spreading of unrecognized hypertension in diabetic coronary patients; their 5-year mortality was significantly increased as compared with normotensives and tended to be even higher than in the diabetics previously identified as hypertensives.

731 Apoprotein E serum level and polymorphism in six European countries: the ApoEurope project

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As part of the ApoEurope project, the apolipoprotein E serum levels and polymorphism were determined in 6934 presumably healthy subjects aged 25 to 64 years recruited in six European countries: Finland, France, Greece, United Kingdom, Portugal and Spain. Age and sex influence apo E level with values significantly higher in men than in women aged 25 to 44 years. The effect of age was different by sex after the age of 50 years with a linear increase in women and a plateau in men. As expected the serum apo E concentration was the highest in epsilon2 carriers and the lowest in epsilon4 carriers in each country with a significantly higher frequency of epsilon4 allele in the Northern regions. The main finding of this study was a clear North-South increasing gradient in serum apo E concentration independently of age, sex and apo E genotype. Apo E levels increased from North to South by up to 20% for men and 32% for women in subjects aged less than 45 years having the epsilon3/epsilon3 genotype. In addition to genetic polymorphism, the geographical areas will be an important factor to take into account for studying serum apo E concentration in multicentric studies.

THROMBOTIC RISK AND CORONARY EVENTS

738 Social support as a risk factor for coronary heart disease and mortality in Warsaw Pol-MONICA population

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The aim of the study is to evaluate the association between social support level (SSL) and coronary heart disease (CHD) prevalence and subsequent total and cardiovascular mortality in Warsaw Pol-Monica population cohort.

Methods: In a random sample of 1474 men and 1498 women, aged 35–64, screened in 1988 and 1993 in the frame of Warsaw Pol-Monica Project the mortality was followed-up to 1995. All deaths were registered on the basis of death certificate diagnosis. SSL was evaluated by means of Berkman and Syme questionnaire and was categorized into 3 groups: low, moderate and high with the lowest level of SSL as a reference category. CHD was defined on the basis of Rose CVD questionnaire and/or ischaemic changes in ECG (by Minnesota code). For analysis of the association between SSL and CHD prevalence and between SSL and CHD mortality the Cox proportional hazard model was used.

Results: Out of 2972 persons, 500 had CHD symptoms (195 men and 305 women). Low SSL was observed in 23% of all men and in 35% women. Among men with CHD symptoms low SSL was observed in 30% in comparison to 21% in men without CHD (in women respectively – 40% vs 34%). We found the significant association between moderate SSL and CHD in men (OR = 0.66, p = 0.02) and almost significant association between moderate SSL and CHD in women (OR = 0.79, p = 0.09)). So there is a 34% lower chance to find a man with CHD symptoms among men with moderate SSL in comparison to men with low SSL (for women this chance is lower of about 21%). During follow-up – 129 persons died (85 men and 44 women) and 48 due to cardiovascular diseases (CVD) (35 men and 13 women). Among men who died low SSL was observed in 28% of them in comparison to 22% in men who survived (in women respectively 38% vs 35%). Among men who died from CVD cause low SSL was observed in 24% of them in comparison to 22% in those who survived (in women respectively 57% vs 35%). No significant association of SSL and mortality was proved although both in total as well as in CVD mortality the risk of death decreased with higher SSL. The relative risk of all cause death of man with moderate SSL was about 38% lower comparing to man with low SSL (RR = 0.62, p = 0.08).

Conclusion: Moderate SSL was significantly related to CHD symptoms in men. No significant association of SSL and mortality was found although the risk of all cause and CVD death decreased with higher SSL.

739 Acute psychological stress decreases plasma tissue plasminogen activator and tissue plasminogen activator/plasminogen activator inhibitor-1 complexes in cardiac patients

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BACKGROUND: Tissue plasminogen activator (tpa) promotes fibrinolysis and impaired fibrinolysis is associated with atherosclerosis and thrombosis. Plasminogen activator inhibitor-1 (PAI-1) inhibits t-PA expression. The present study examines the effects of acute laboratory stressors on tPA and tPA/PAI-1 complexes in a sample of clinically stable coronary artery bypass patients.

Methods: Eleven male patients were randomly assigned to either a stress or relaxation condition at time 1 and the alternative condition at time 2. The stress condition consisted of a series of standardised psychological stressors (the Stroop test PASAT, discussion of life events). In the relaxation condition participants listened to music or read. Blood samples were taken pre and post each session and tPA and tPA/PAI-1 levels were assessed by enzyme immunossay. Participants completed a battery of psychological questionnaires.

Results: Two-way repeated analysis of variance revealed a statistically significant decrease in tPA (P = 0.01) and t-PA-PAI-1 complexes (P = 0.04) during the mental stress condition. Furthermore, anger-in had a strong relationship to decreases in tPA/PAI-1 levels in the stress condition (R = 0.68, P = 0.04). In contrast, relaxation had no significant effect on tPA and tPA/PAI-1 levels.

Conclusion: Mental stress was associated with a statistically significant decrease in tPA and tPA/PAI-1 complexes. The strong correlation between anger-in and changes in tPA/PAI-1 level is consistent with research on repression and cardiovascular disease. These data suggest that decreased fibrinolysis may mediate the relationship between mental stress and atherosclerosis.

740 Baseline platelet aggregation and major receptor expression predict subsequent activity following thrombolysis for acute myocardial infarction

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The early identification of patients with heightened platelet activity for targeted antiplatelet regimens represents a critical clinical issue. It has been reported that platelets are not uniformly activated in patients presenting with acute myocardial infarction (AMI), but are most active at 24 hours after coronary thrombolysis. We correlated individual data on platelet aggregability and surface receptor expression at baseline and at 24 hours after coronary thrombolysis.

Methods: Platelets were investigated by aggregometry, (5 μM ADP, 10 μM ADP, thrombin, collagen, ristocetin), and flow cytometry (GP IIb/IIIa, P-selectin, PECAM-1, and vitronectin receptor) in 19 AMI patients treated with reteplase (n = 11), or alteplase (n = 8) enrolled in the GUSTO-III trial.

Results: Regression analysis reveals a significant positive correlation between baseline and at 24 hours after thrombolysis for 5 μM ADP (r^2 = 0.529), 10 μM ADP (r^2 = 0.445), thrombin (r^2 = 0.226), collagen (r^2 = 0.568), and ristocetin-induced aggregation (r^2 = 0.964). Platelet receptor expression was also highly linearly correlated for GPIIb/IIIa (r^2 = 0.337), P-selectin (r^2 = 0.817), PECAM-1 (r^2 = 0.586), and vitronectin expression (r^2 = 0.634).

In conclusion, the data strongly suggest that pre-reperfusion baseline platelet characteristics predict post-reperfusion activity, and may prospectively identify those patients who will exhibit heightened platelets after coronary thrombolysis. These patients can be detected early, and will probably benefit most from selective aggressive antiplatelet therapy.

741 Thrombotic factors and left ventricular ejection fraction in postinfarction patients

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Postinfarction patients with depressed left ventricular function have an increased risk of recurrent coronary events. The aim of this study was to determine the association between thrombogenic profile, potentially predisposing to recurrent coronary events, and left ventricular function, measured by ejection fraction in stable postinfarction patients.

Methods: Study population consisted of 769 patients who had blood drawn 2 months after myocardial infarction to evaluate levels of the following thrombotic factors:

fibrinogen, D-dimer, factor VII and VIIa, plasminogen activator inhibitor (PAI-1), soluble fibrin, and von Willebrand factor (vWF). Only patients who did not take warfarin at the time of blood drawing were included in the analysis. A long-term follow-up was acquired to determine the occurrence of coronary events (defined as nonfatal myocardial infarction or cardiac death).

Results: Table below shows median levels of thrombotic factors and number (%) of cardiac events that occurred during a mean 26-month follow-up in the studied postinfarction patients stratified by ejection fraction.

Thrombotic Factors by Ejection Fraction

	EF>50% n = 329	EF = 41–50% n = 254	EF = 31–40% n = 126	EF≤30% n = 60	p value
Fibrinogen	330	337	326	355	0.069
D-dimer	359	363	473	544	<0.001
F VII	112	108	105	111	0.777
F VIIa	2.5	2.7	2.3	3.0	0.189
PAI-1	19	19	22	26	0.200
Soluble Fibrin	3.3	3.6	5.1	7.5	<0.001
vWF	124	126	135	153	<0.001
Cardiac Events	17 (5%)	20 (8%)	14 (11%)	13 (22%)	<0.001

Median values for tested factors are shown. P values were calculated with the Kruskal Wallis test.

Conclusions: The levels of thrombotic factors, especially D-dimer, soluble fibrin, and VWF, demonstrate a significant and stepwise association with the extent of left ventricular dysfunction in postinfarction patients. This observation indicates that postinfarction patients with decreased ejection fraction may benefit from an antithrombotic therapy.

742 Prospective evaluation of gender differences in thrombotic risk reduction during lipid lowering therapy with pravastatin

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Background: Clinical trials of cholesterol (c) have included mostly men (M). The benefit rendered during statin therapy may be in part due to improved thrombotic profile. The association of coronary heart disease risk to HDL-C, LDL-C, lipid therapy and thrombosis in women (W) is unclear.

Methods: We prospectively studied markers of systemic thrombogenicity at 0, 3 and 6 months (mo) of therapy with pravastatin and AHA step I diet in 28 M and 29 W (93% postmenopausal) with untreated, fasting LDL-C > 145 mg/dl and triglycerides < 275 mg/dl. Thrombosis under dynamic flow conditions was also evaluated in a validated experimental perfusion chamber system.

Results: At baseline, M vs W differed in age (62 ± 2 vs 69 ± 2 y, $p < 0.05$) and HDL-C (39 ± 2 vs 55 ± 2 mg/dl, $p < 0.05$); p = NS for body mass index, CHD, risk factors, aspirin use, Lp(a), and homocysteine. Baseline thrombus area (TA) and hemostatic markers were similar in M vs W, except prothrombin fragment $F_{1.2}$ (1.4 ± 0.3 vs 2.4 ± 0.3 nmol/L, $p < 0.05$); $F_{1.2}$ at 6 mo was 1.5 ± 0.2 vs 1.6 ± 0.2 nmol/L, p = NS. Within 1 mo, LDL-C was reduced equally in M and W by 30% (188 ± 123 mg/dl). Trends at 3 mo and significant changes at 6 mo occurred in both M and W in tPA, PAI-1, and TA (table). Nonsignificant changes occurred in factor VIIa, fibrinopeptide A, and d-dimer in both M and W.

	tPA ng/ml	PAI-1 ng/ml	$F_{1.2}$ nmol/L	TA $\mu m^2 \times 10^3$
Men	−1.4 ± 0.4*	−11.5 ± 2.3*	0.0 ± 0.3	−2.9 ± 0.9*
Women	−1.5 ± 0.4*	−7.0 ± 2.2*	−0.8 ± 0.3*	−4.0 ± 1.3*

*change from baseline to 6-months $p < 0.05$

Conclusions: Despite higher HDL-C, W had higher baseline thrombin generation than M. Pravastatin abolished that difference and improved fibrinolytic markers related to endothelial function to similar levels in both M and W thereby decreasing blood thrombogenicity in both genders.

743 The influence of folate supplementation on coagulation factors in mild hyperhomocysteinaemia

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Introduction: Homocystein (tHcy) is a new risk factor of both atherosclerotic a trombotic vascular diseases. The core of Hcy metabolism is influenced by folates that enable to modify the tHcy levels. The aim was to evaluate in a pilot study the efficacy of folate supplementation on tHcy levels and several coagulation factors in the subject with mild hyperhomocysteinemia (MHHcy)

Methods: This pilot study included 18 subject without systematic pharmacotherapy (11 males, 7 females, mean age 58.8 y) with fasting tHcy ≥ 20 μmol/l. tHcy levels were estimated fasting and 6 hour after methinone load (100 mg/kg) using HPLC methods. The study included 1 month placebo intake, followed by 2 month treatment with 10 mg of folic acid daily. Biochemical and coagulation test were done in a routine laboratory using commercial kits. Statistical evaluation was done by Wilcoxon paired test.

Results: The table compares estimated variables at the end of placebo period and after 1 month therapy with folic acid supplement.

Variable	After 1 month placebo	After 2 month of folic acid treatment	p
Fasting tHcy [μmol/l]	30.2 (3.5)	13.3 (0.7)	<0.0001
Postload tHcy [μmol/l]	66.0 (8.93)	40.9 (5.05)	<0.001
Serum folates [μg/l]	5.63 (0.68)	18.4 (0.6)	<0.001
Serum B12 [ng/l]	322.1 (54.8)	380.5 (81.0)	ns
Fibrinogen [g/l]	3.29 (0.57)	2.30 (0.13)	<0.0001
Plasminogen [%]	92.9 (4.28)	109.1 (4.9)	<0.01
PAI-1 [A.U./ml]	16.7 (2.2)	16.9 (2.2)	ns

Conclusion: Two-month supplementation with folates in subject with mild hyperhomocysteinemia resulted in a significant tHcy and fibrinogen decrease and plasminogen increase.

Folates supplementation influenced favourably not only tHcy levels, but also the coagulation factors predisposing to thrombotic events.

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METHODOLOGY AND DIAGNOSIS IN CORONARY DISEASE

744 Reproducibility of exercise-induced ECG changes in patients with documented coronary artery disease

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Although exercise induced ECG changes are widely used as screening test for the assessment of coronary artery disease (CAD), little is known about its reproducibility.

Methods: 44 patients (42 males, 2 females, age 63 ± 8 years) with documented CAD underwent two symptom limited exercise tolerance test to a standard Bruce protocol performed within 9 ± 5 days. The following ECG parameters were assessed: time (sec) to 0.1 (n = 44) and 0.2 mV (n = 26) ST segment depression, maximal ST segment depression (ST depr; mV) and recovery (time to ST normalization, sec). Reproducibility was assessed both by regression analysis and using the Bland-Altman repeatability coefficient (rep. coeff.)

Results: Heart rate and mean arterial blood pressure were similar at rest and at peak exercise during both tests.

	First	Second	Rep. coeff.	r	p
ST depr (mV)	2.4 ± 0.9	2.3 ± 0.8	1.1	0.82	0.0001
0.1 mV (sec)	266 ± 115	294 ± 106	181	0.68	0.0001
0.2 mV (sec)	331 ± 109	353 ± 115	99	0.89	0.0001
recovery (sec)	337 ± 126	345 ± 142	165	0.81	0.0001

Conclusion: For patients with CAD maximal ST depression and recovery time were equally reproducible during symptom limited exercise tolerance testing. Correlation exists for both the time to 0.1 mV and 0.2 mV ST depression is but the latter is clearly more reproducible and, thus, more reliable. However, this criteria was only achieved in 60% of the patients.

745 Diagnostic value of exercise-induced ST-segment elevation in Q-wave leads in patients after myocardial infarction

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Exercise-induced ST segment elevation (STel.) in an infarct territory with abnormal Q waves is a known marker for more severe left ventricular wall motion abnormalities and an adverse prognosis. However, it is reported, that STel. during exercise in infarct leads may indicate residual viability in the infarct region.

The aim of the study was to test, if exercise induced STel. is related to LV dysfunction or to persistent viability in patients (pts) with previous myocardial infarction (MI). We investigated the relation between STel. on infarct-related leads during exercise with: (a) the severity of the regional LV dysfunction, (b) myocardial viability (evaluated by low dose dobutamine stress echo- LDSE).

145 consecutive pts (119 men, 26 women, age 58 ± 11 yrs) 2–3 weeks after Q wave MI (anterior: 67, inferior: 78) but without STel. at rest EKG, were enrolled in the study. All pts underwent a target heart rate or symptom limited exercise testing (ET) with Bruce protocol. ST segment was quantified using an automated software (Marquette Inc). Exercise induced STel. > 1 mm above the baseline ST segment level (80 ms after J point) in more than 1 ECG lead with Q wave was considered significant. Pts were divided in 2 groups according to ET results: G1 – 25 pts (after anterior MI: 17, inferior: 8) with significant stress induced STel. and G2- 120 pts without STel. during ET.

All pts underwent rest ECHO and LDSE within 7 days after ET. LV function was estimated using ejection fraction (EF). More severe LV dysfunction was observed in pts from G1(EF 31 ± 8.16% vs. EF 45 ± 10.3% in G2).

Myocardial viability (defined as an improvement of regional systolic wall thickening in the regions with resting regional wall motion abnormalities during LDSE −5 to 15 (g/kg/min.) was recognised in 8 pts (32%) in G1 and 31 pts (25.8%) in G2. There was no relation between exercise induced STel. and myocardial viability (Chi-squared test: 0.809; NS).

Conclusion: 1. Exercise-induced STel. in most cases is associated with left ventricular dysfunction. Pts with exercise-induced STel. have a lower EF than those without and greater severity of resting wall motion abnormalities.

2. Our results suggest that exercise induced STel. is not related to residual myocardial viability.

746 The relative prognostic importance of clinical, exercise electrocardiography and stress echocardiography data in patients with known or suspected coronary artery disease

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In this study we sought to investigate the relative value of clinical, exercise electrocardiography (ExECG) and stress echo (SE) findings in risk stratification of patients (pts) referred for proven or suspected coronary artery disease (CAD). The study group was 696 pts (400 men; 59 ± 10 yy) who underwent both bycicle ExECG (incremental workloads of 25 W every 2') and SE with either dipyridamole (n = 454) (up to 0.84 mg/kg over 10' + atropine up to 1 mg) or dobutamine (n = 242) (up to 40 mgr/kg/min+atropine up to 1 mg). ExECG was positive (ST-segment shift ≥0.1 mV at 80 msec after the J point) in 260 pts; SE was positive (new or worsening of preexisting wall motion abnormality) in 173 pts. During the follow-up (43 ± 26 months), 36 hard cardiac events (12 deaths, 24 infarctions) and 93 revascularizations occurred. With an interactive stepwise procedure, ipercholesterolemia (OR = 3.0; 95% CI = 1.5–5.9; p = 0.0012), prior infarction (OR = 2.8; 95% CI = 1.4–5.4; p = 0.0022), age > 70 years (OR = 2.3; 95% CI = 1.0–4.9; p = 0.0388) and family history of CAD (OR = 1.7; 95% CI = 0.9–3.4; p = 0.0978) were clinical predictors of hard events; the global chi-square was 31.6. After the addition of ExECG data, ipercholesterolemia (OR = 3.0; 95% CI = 1.5–5.8; p = 0.0015), prior infarction (OR = 2.8; 95% CI = 1.4–5.4; p = 0.0020) and ExECG positive result (OR = 2.3; 95% CI = 1.2–4.6; p = 0.0139) showed prognostic power; at this second step the global chi-square increased to 38.4. At the third step, with the addition of SE findings, ipercholesterolemia (OR = 2.7; 95% CI = 1.4–5.2; p = 0.0036), prior infarction (OR = 2.4; 95% CI = 1.2–4.7; p = 0.0145) and SE positive result (OR = 2.5; 95% CI = 1.1–5.4; p = 0.0205) had independent prognostic value; the global chi-square was 43.5. The 4-year infarction-free survival rate was 97% for pts with negative and 83% for pts with positive SE (p = 0.0000); it was 97% for pts with negative and 89% for pts with positive ExECG (p = 0.0023).

In conclusion, in pts with known or suspected CAD, SE data provide incremental prognostic power when compared with clinical and ExECG ones. However, a simple negative ExECG is able to identify a vey low-risk population in whom additional imaging testing seem not to be warranted.

747 QRS width changes during exercise as an index of ischaemia: high-resolution computer analysis in patients with false positive ST response

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False-positive ST response limits the diagnostic value of exercise ECG test. We have demonstrated with use of high-resolution computer analysis of multiple ECG leads that QRS width prolongs during exercise in patients with inducible ischemia and ST depression. Since QRS width changes seem independent of repolarization abnormality (i.e., ST change), patients with false-positive ST responses might be correctly diagnosed with QRS width changes.

Methods: Continuous 12-leads exercise ECG data sampled at 500 Hz during conventional treadmill test were analyzed in 22 false-positive (FP, 8 women, 9 with hypertension) and 25 true-positive (TP) ST depression responses. The diagnosis of coronary artery disease (CAD) was determined by angiography and/or exercise scintigraphy. The onset of the QRS was defined by the earliest deflection and the end was defined as the latest deflection among 12 leads with use of algebraic sum of the absolute voltage from 12 leads and that of the absolute value of the first derivative (dV/dt) from 12 leads. We compared QRS complexes from the averaged data of 5 complexes before and 1-min after exercise. We also examined 24 age-matched healthy subjects.

Results: QRS width did not significantly alter after exercise in either healthy controls (+0.5 ± 1.4 ms) or FP subjects (+1.2 ± 1.7 ms), while patients with TP showed a significant QRS prolongation (+4.0 ± 2.9 ms, p < 0.0001). When we tried to identify the ischemia by QRS prolongation ≥ 2 ms (Mean ± SD of controls), 14 of 22 patients (63%) with FP were correctly diagnosed as normal (negative), and 22 of 25 patients with TP (88%) were identified correctly (positive).

Conclusions: QRS width after exercise did not significantly change in subjects with false positive ST response as well as in healthy contrlos. QRS width analysis is a useful tool to discriminate false-positive from true-poistive ST responses.

748 Non-invasive metabolic evidence of myocardial ischaemia in patients with early non-obstructive atherosclerosis and coronary risk factors

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It is still unclear whether a reduced endothelial-modulated vasodilator function may really induce myocardial ischemia on the cellular metabolic level due to nonobstructive coronary atherosclerosis (CA) on the basis of risk factors. Since free fatty acid transport into myocardial tissue was demonstrated to be an endothelium carrier-mediated process and decreased fatty acid influx is a marker of myocardial ischemia, we investigated consecutive patients with angina, risk factors but without obstructive CA assessing noninvasively myocardial fatty acid influx rates (vi).

Methods: All fasting patients underwent dual isotope studies after symptom-limited exercise and at rest. Dual isotope technique with 37 MBq Tl-201 as perfusion tracer and 74 MBq 15-(p-123-I-Iodophenyl)-pentadecanoic acid (IPPA) as metabolic tracer for fatty acid turnover were applied simultaneously at peak exercise and 4 hours after exercise at rest. The ratio between metabolic and perfusion uptake was defined as a measure of regional fatty acid extraction rates. From this, vi was calculated. The results were compared to that obtained in 10 healthy age- and sex-mathed controls without risk factors. Baseline data: 13 patients (8 men, 5 women), mean age: 55 ± 11 years, EF: 73 ± 8%, LV-mass: 91 ± 19 g/m^2, PLVED: 14 ± 7 mmHg, risk factors: mild-to-moderate hypertension and/or hypercholesterolemia (LDL > 150 mg/dl), near normal or mildly affected coronary arteries (minimal stenosis < 30%).

Results: (mean ± SD) Regional fatty acid influx rates at exercise was significantly reduced in patients with early CA: vi: 0.136 ± 0.03 vs 0.225 ± 0.04 μmol/g·min in controls (p < 0.01). Involved myocardial regions were predominantly septal (63%), posterolateral (40%) and anteroapical (38%), inferoposterior to a minor degree (32%). In addition, all patients had both inhomogeneous perfusion and IPPA distribution with regional defects.

Conclusions: As far as to our best knowledge, this study demonstrates for the first time noninvasively stress-induced myocardial ischemia with consequent alteration of fatty acid metabolism in patients with nonobstructive CA and associated coronary risk factors. This dual isotope technique might be a promising approach to assess vasodilator function and myocardial metabolism under risk factor interventions to prevent progression or induce functional improvement in early stages of CA.

749 Magnitude of ST-segment elevation during exercise correlates to the severity of myocardial sympathetic nerve denervation after Q-wave myocardial infarction

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Exercise-induced ST segment elevation after Q-wave myocardial infarction (MI) is recognized as a marker of larger wall motion abnormalities of the left ventricle, but the exact mechanism for ST elevation is uncertain. To test the hypothesis that the magnitude of such ST elevation would be dependent on the severity of myocardial sympathetic nerve denervation, we examined the relation between exercise-induced ST elevation and single photon emission computerized tomographic images with I-123 metaiodobenzylguanidine (MIBG) and thallium-201 (Tl) in 25 patients with first documented anterior MI one month after onset. Each tomographic image at four hours after administration was divided into 26 segments and visually analyzed using a 0 to 3 scale to provide a defect score. The degree of mismatch between MIBG and Tl images was evaluated by expressing the differences between the defect scores (delta defect score). ST segment changes during supine bicycle exercise was gauged. All 25 patients showed more extensive defects of MIBG than those of Tl (defect score; 45.0 ± 9.8 vs 29.7 ± 7.3, P < 0.01). The sum of exercise-induced ST changes in leads V2, V3, and V4 (delta ST) positively correlated to MIBG (R = 0.58, P < 0.01) but not to Tl defect scores (R = 0.24, NS). In addition, delta ST correlated to delta defect scores (R = 0.62, P < 0.01), indicating that the magnitude of ST elevation was more pronounced as the degree of mismatch between MIBG and Tl imaging became larger.

Conclusion: The magnitude of exercise-induced ST elevation gives an estimate for the severity of sympathetic nerve denervation as assessed by MIBG imaging after Q-wave MI. The positive correlation between the ST elevation and the degree of mismatch between MIBG and Tl imaging suggests that ST elevation could be arisen from regional disparities of the sensitivity to beta-adrenergic stimulation between the infarcted and denervated noninfarcted myocardium.

NITRIC OXIDE IN MYOCARDIAL ISCHAEMIA AND REPERFUSION

753 Sarcoplasmic calcium release contributes substantially to the positive chronotropic effect of nitric oxide donors

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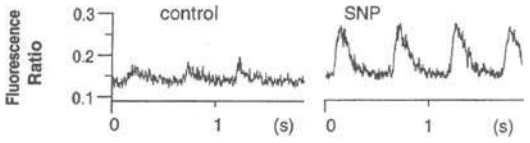
Nitric oxide (NO) exerts a positive chronotropic effect in vitro by stimulating the pacemaker current I_f without affecting I_{CaL}. If activity is modulated by $[Ca^{2+}]_i$ and recent evidence indicates that NO can activate ryanodine receptors in cardiac sarcoplasmic (SR) vesicles.

The aim of this study was to test whether exogenous NO stimulates pacemaker activity by promoting SR Ca^{2+} release.

Methods: In isolated guinea-pig atria, we examined the chronotropic response to increasing concentrations (from 0.1 μmol/L to 1 mmol/L) of the NO donors SIN-1 (+superoxide dismutase 100 U/mL, n = 6) or DEA/NO (n = 8), *(i)* alone, or *(ii)* after pre-treatment (40 min) with 2 μmol/L ryanodine (n = 7) to block the SR Ca^{2+} release or 60 μmol/L cyclopiazonic acid (2 h) to deplete SR Ca^{2+} stores (n = 9). In addition, we evaluated the intracellular Ca^{2+} transient (fluorescence with 5 μmol Indo-1 AM) in guinea pig isolated sinoatrial node cells (n = 6) before and after application of sodium nitroprusside (SNP, 5 μmol/L.

Results: SIN-1 or DEA/NO alone progressively increased heart rate (HR) with a peak effect of +51 ± 5 bpm and +41 ± 5 bpm at 0.1 mmol/L ($p < 0.05$). Ryanodine reduced HR from 169 ± 7 to 125 ± 7 bpm (mean ± SEM, $p < 0.05$), whereas CPA caused a transient increase in HR (from 163 ± 6 to 196 ± 9 bpm) followed by a reduction to 133 ± 6 bpm ($p < 0.05$). After pre-treatment with ryanodine or CPA, the peak increase in HR was only +19 ± 4 bpm with SIN-1 and +16 ± 3 bpm with DEA/NO ($p < 0.05$). In isolated sinoatrial node cells, SNP significantly augmented diastolic Ca^{2+} (+13 ± 9%), peak Ca^{2+} (+33 ± 21%), and the amplitude of the Ca^{2+} transient (+102 ± 49%) (figure), and increased the spontaneous beating rate by 34 ± 12% ($p < 0.05$).



In conclusion, exogenous NO stimulates SR Ca^{2+} release in sinoatrial node cells. This novel pathway contributes substantially to the positive chronotropic effect of NO donors.

754 Nitric oxide modulates mitochondrial function in neonatal cardiocytes by reversible inhibition of respiration

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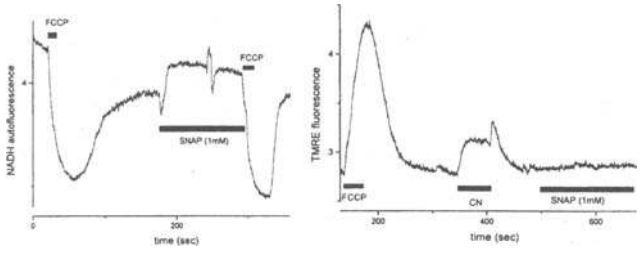
Mitochondrial dysfunction is a critical component of ischaemia-reperfusion injury which is associated with ATP depletion, dissipation of the mitochondrial membrane potential and induction of the mitochondrial permeability transition. Nitric oxide (NO) can cause both irreversible and reversible inhibition of respiratory chain complexes but the latter may represent an important physiological mechanism for the regulation of mitochondrial function and the protective adaptation to hypoxia.

Methods: Fluorescence microscopy was performed on cultured rat neonatal cardiocytes. We studied the effect of the NO donor s-nitroso-N-acetyl-L-penicillamine (SNAP) on redox state, using NADH autofluorescence, and mitochondrial membrane potential, using teramethyl ethyl ester (TMRE 10 μg/ml). Maximum and minimum signals were achieved using the uncoupler FCCP and Cyanide.



Results: SNAP 100 μM–1 mM produced a sustained increase in NADH autofluorescence suggesting inhibition of mitochondrial respiration which was not associated with dissipation of the membrane potential. These responses were reversed by FCCP.

Conclusion: We have demonstrated reversible inhibition of mitochondrial respiration by NO in neonatal cardiocytes in culture. This may represent an important physiological mechanism by which NO modulates mitochondrial function in the myocardium.

755 The control of cardiac function and nitric oxide production by the extract of Ginkgo biloba in ischaemic/reperfused rat hearts

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The aim of the present study was to evaluate the effect of Ginkgo biloba extract (EGb 761) on the production of nitric oxide (NO) in relation to the recovery of postischemic cardiac function in isolated working rat hearts.

Methods: Rats were orally treated with various doses (25, 50, 75 and 100 mg/kg/day) of EGb 761 for 10 days. Hearts were isolated and subjected to 30 min ischemia followed by 120 min of reperfusion. NO was directly measured by electron spin resonance spectroscopy (ESR). The expression of inducible nitric oxide synthase (iNOS) mRNA was detected by reverse transcription-polymerase chain reaction (RT-PCR) in the ischemic-reperfused myocardium.

Results: EGb 761 inhibited NO production and improved the recovery of postischemic cardiac function in ischemic/reperfused hearts. Thus, rats (n = 6 in each group) treated with 25, 50, 75, and 100 mg/kg/day of EGb 761 and hearts subjected to ischemia/reperfusion, aortic flow was increased from its postischemic drug-free control value of 8.0 ± 4 ml/min to 8.6 ± 0.4 ml/min (NS), 17.3 ± 0.9 ml/min ($p < 0.05$), 21.5 ± 1.1 ml/min ($p < 0.05$), and 23.6 ± 1.2 ml/min ($p < 0.05$), respectively. The same improvement of postischemic recovery in coronary flow, left ventricular developed pressure and its first derivative was also observed. In the initial phase of reperfusion, NO production was reduced by 90% in the 75 mg/kg/day of EGb 761 treated group in comparison with the drug-free ischemic/reperfused group. iNOS mRNA measured by RT-PCR was also reduced by 41% and 58% in the groups treated with 75 mg/kg/day and 100 mg/kg/day of EGb 761, respectively.

Conclusion: The results show that EGb 761 directly acts as an NO scavenger and concomitantly inhibits the expression of iNOS mRNA improving the recovery of postischemic cardiac function in isolated ischemic/reperfused rat hearts.

756 The endothelin A receptor antagonist LU 135252 protects against myocardial ischaemia and reperfusion injury via a nitric oxide-dependent mechanism

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The hypothesis of the present study was that the previously demonstrated protective effect of ET receptor antagonists against ischaemia and reperfusion injury is due to enhanced nitric oxide (NO) production. We therefore evaluated the cardioprotective effect of the ETa receptor antagonist LU 135252 (LU) in the absence and presence of the NO synthase inhibitor L-NA.

Methods: Anaesthetised pigs were subjected to 45 (protocol I) or 30 (protocol II) min ligation of the left anterior descending coronary artery followed by 4 hours of reperfusion. In protocol I, four groups were given vehicle (n = 6), LU (5 mg/kg i.v.) 10 min before ischaemia (n = 6), the NO synthase inhibitor L-NA (10 mg/kg i.v.) 30 min before ischaemia (n = 5) or L-NA in combination with LU (L-NA+LU) 30 and 10 min before ischaemia (n = 6). In protocol II, two groups were given vehicle or L-NA as above.

Results: In protocol I, mean arterial pressure and rate pressure product were higher in both groups treated with L-NA compared to the LU and vehicle groups. The infarct size was 74 ± 7% of the area at risk in the vehicle group and 95 ± 2% in the L-NA group. LU reduced the infarct size to 43 ± 7% ($p < 0.05$ vs. vehicle). When L-NA was administered prior to LU, the the infarct limiting effect of LU was completely abolished (infarct size 76 ± 6%; $p < 0.05$ vs. LU). In protocol II, infarct size produced by 30 min ischaemia in the vehicle group (62 ± 14) was not increased by L-NA.

Conclusion: Inhibition of NO synthase abolishes the cardioprotective effect of the selective ETa receptor antagonist LU, suggesting that the effect is mediated by release of NO.

757 Essential role of endogenous nitric oxide for perfusion-contraction matching in short-term hibernating myocardium

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In isolated rabbit hearts the activity of NO-synthase III increases during low-flow ischemia. Whether the subsequent increase in the interstitial NO concentration impacts on myocardial function in situ, however, is still a matter of debate. We therefore investigated the role of endogenous NO in short-term hibernating myocardium, i.e. a situation where contractile function is reduced in adaptation to reduced flow. In 16 enflurane-anesthetized pigs the LAD coronary artery was cannulated and perfused from an extracorporeal circuit. Anterior wall thickness was measured and a work index (WI, mm·mmHg, sonomicrometry and micromanometry) calculated. Transmural blood flow (TMF) was measured with radioactive microspheres. Six pigs (G1) were subjected to 90 min moderate ischemia and 120 min reperfusion. In 5 pigs, NO synthesis was blocked by 30 mg/kg L-NA i.v. before coronary inflow was reduced (G2). Since NO blockade significantly increased LV pressure from 97 ± 11 (SD) to 124 ± 28 mmHg, LV pressure was increased by aortic banding in 5 additional pigs (G3) to match the LV pressure observed in group 2. Following 90 min ischemia and 120 min reperfusion, the myocardium remained completely viable (TTC) in all pigs, indicating successful hibernation. With a comparable decrease in TMF, WI was lower in pigs with NO blockade than in pigs with or without LV pressure match.

	5 min ischemia		85 min ischemia	
	TMF	WI	TMF	WI
G1	50 ± 12	52 ± 12	49 ± 18	46 ± 21
G2	44 ± 13	11 ± 17*	45 ± 11	14 ± 16*
G3	57 ± 16	54 ± 10	57 ± 19	55 ± 16

Values are expressed as % control ± SD. All values are significantly different from control
*: $p < 0.05$ vs. groups 1 and 3; 2-way ANOVA

We conclude that NO is essential for perfusion-contraction matching in short-term hibernation.

NON-LIPID RELATED EFFECTS OF STATINS

759 Improvement of nitric oxide-dependent vasodilatation by HMG-CoA reductase inhibitors through suppression of endothelial superoxide anion formation

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Recent reports suggest that the increased production of reactive oxygen species in the vessel wall may lead to enhanced expression of atherosclerosis-associated gene products. The aim of this study was to show that besides the well documented reduction in serum LDL cholesterol, the anti-atherosclerotic effects of the HMG-CoA reductase inhibitors may be explained by a shift in the nitric oxide (NO)/superoxide anion (O_2^-) balance in the vessel wall towards an increased bioavailability of NO.

Methods: The effects of HCRI on phorbol ester-stimulated O_2^- formation by endothelium-intact segments of the rat thoracic aorta were measured by lucigenin-enhanced chemiluminescence and ferricytochrome c reduction. RT-PCR analysis and enzyme measurements were performed to elucidate the effect of HCRI on superoxide dismutase (SOD), NADPH oxidase and endothelial NO synthase (ecNOS). Vascular reactivity studies were performed in a superfusion bioassay system.

Results: Exposure of the segments to the HCRI (0.1–10 μmol/L) resulted in a time- and concentration-dependent decrease of both basal and stimulated O_2^- formation (maximum inhibition of 70% after 18 hours), the latter of which was predominantly endothelium-dependent. Mevalonic acid (400 μmol/L) reversed the inhibitory effect of the HCRI which was mimicked by Clostridium sordellii lethal toxin that inactivates p21 Rac, but not by Clostridium botulinum exoenzyme (C3) that inactivates p21 Rho. HCRI did not reveal any effect on SOD or NADPH oxidase (p91-phox subunit) expression, while that of ecNOS was enhanced twofold. Acute or long-term inhibition of ecNOS activity, however, did not affect O_2^- formation. Exposure of the segments to atorvastatin resulted in a significant improvement of endothelium-dependent NO-mediated relaxation, and this effect was abolished in the presence of SOD.

In conclusion, these findings suggest that apart from augmenting endothelial NO formation, HCRI prevent the isoprenylation of p21 Rac which is critical for NADPH oxidase activity and hence endothelial O_2^- formation. The resulting shift in the balance between NO and O_2^- in the endothelium, namely the decrease in O_2^- formation, improves endothelial function even in healthy blood vessels and therefore may provide a reasonable explanation for the beneficial effects of HCRI in patients with coronary heart disease besides or alternative to the reduction in serum LDL cholesterol.

760 Effects of HMG-CoA reductase inhibition on human saphenous vein endothelial and smooth muscle cells: molecular basis for local drug delivery system to prevent venous bypass graft disease

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Venous bypass graft failure is an important cause of morbidity and mortality in patients with coronary artery disease. Endothelial cell (EC) dysfunction and smooth muscle cell (SMC) proliferation is involved in venous bypass graft disease. Substances that improve EC function and inhibit SMC proliferation would therefore be of clinical relevance, if they could be delivered locally to the blood vessel wall and remain there for a prolonged periods of time. We studied the effect of a HMG-CoA reductase inhibitor cerivastatin on human saphenous vein EC and SMC and developed a local drug delivery system.

Methods and Results: EC and SMC were isolated from human saphenous veins. Endothelial nitric oxide synthase (eNOS) expression and NO production were analysed by immunoblotting and porphyrinic microsensor. SMC proliferation was analysed by ^{3}H-thymidine incorporation. Cerivastatin (1 nmol/L to 1 μmol/L) concentration-dependently upregulated eNOS protein level and increased NO release in EC in response to calcium ionophore (10 μM) and inhibited ^{3}H-thymidine incorporation ($n = 9$; $p < 0.001$) to platelet-derived growth factor (PDGF; 5 ng/ml) in SMC; the latter was associated with complete inhibition of Cdk2 activation, pRb hyperphosphorylation and partial prevention of p27Kip1 downregulation, while MAPK and p70S6K remained unaffected. Encapsulation of cerivastatin into biodegradable and biocompatible PLA/PLGA polymers produced a sustained long-term release of the active drug over 60 days.

Conclusion: In human saphenous veins cerivastatin improves human EC eNOS expression, NO release and inhibits SMC growth and cell cycle progression via a mechanism(s) other than inhibition of MAPK and p70S6K pathways. These effects on vascular EC and SMC could contribute to vascular protective effects of HMG-CoA reductase inhibitors. Microencapsulation of cerivastatin into biodegradable PLA/PLGA microspheres for local delivery could be used in patients for prevention of venous bypass graft disease

761 Statin therapy increases coronary vasodilator capacity in 30 patients with early stages of coronary atherosclerosis assessed non-invasively with positron emission tomography.

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Background: Aim of our study was to assess noninvasively coronary flow reserve (CFR) after short-term therapy (≈6 months) with simvastatin (20–40 mg) in 30 patients with angina and very early stages of coronary atherosclerosis and mild-to-moderate hypercholesterolemia on an average.

Methods: Regional and averaged myocardial blood flow was measured at rest (MBFR) and after dipyridamol-induced maximal vasodilation (MBFD) with 0.56 mg dipyridamole/kg using positron emission tomography (PET) and N-13-ammonia as flow tracer. Each patient, previously not receiving lipid-lowering drugs, served as his or her own control. Exclusion was smoking, diabetes, cardiomyopathy, leftventricular hypertrophy, uncontrolled hypertension and hormonal replacement. Coronary angiogram was normal overall in 13 and mildly affected in 17 patients (focal luminal irregularities and/or minimal stenosis ≤ 30%). Baseline data: 21 males; 9 females; mean age: 56.9 ± 7.7 years. Total cholesterol: 243 ± 43 mg/dl, LDL-cholesterol: 168 ± 34 mg/dl, HDL: 45 ± 16 mg/dl, averaged dipyridamole flow: 187 ± 40 ml/min·100 g; minimal coronary resistance (MCR = mean arterial pressure/MBF_D): 0.51 ± 0.1 mmHg/ml/min·100 g; CFR was reduced at baseline: 2.2 ± 0.6. MBFR: 89 ± 19 ml/min·100 g.

Results: After 6-month follow-up (mean ± SD): LDL: 96 ± 25 mg/dl ($p < 0.001$); HDL: 49 ± 11 mg/dl ($p < 0.02$); MBF_D: 235 ± 55 ml/min·100 g ($p < 0.01$); MCR: 0.4 ± 0.1 mmHg/ml/min·100 g ($p < 0.01$); CFR: 2.7 ± 0.6 ($p < 0.01$); MBF_R: 91 ± 18 ml/min·100 g (n.s). Concomitantly, a significant regression of effort angina or atypical angina ($p < 0.01$) was observed in the majority of patients.

Conclusions: Short-term statin therapy increases overall coronary vasodilator capacity in patients with early stages of coronary atherosclerosis in conjuction with a regression of anginal symptoms suggesting improved endothelial function.

762 Cholesterol lowering drugs reduce recurrences of ventricular arrhythmias after defibrillator implantation in patients with coronary artery disease

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Cholesterol-lowering drugs (CLD) reduce total and cardiac mortality in patients with coronary artery disease (CAD). We evaluated a possible effect of CLD on ventricular arrhythmias (VA) in a population of patients with CAD and life-threatening VA that required internal defibrillator (ICD) implantation.

Methods: We studied the recurrence of VA (VT or VF) requiring ICD therapy and the combined endpoint of cardiac death and hospitalization (hospitalization for angina, heart failure and electrical storm) in 78 consecutive patients (age 66 ± 9 years, 73 males, ejection fraction 33 ± 13%) with CAD and VA requiring ICD implantation. At discharge 27 (35%) patients were on CLD (16 statines, 11 fibrates) (group I) and 51 (65%) patients were not on CLD (group II)

Results: Baseline characteristics (including age, gender, ejection fraction, extent of coronary artery disease, presenting arrhythmia and medication at discharge) were comparable for both groups. After a mean follow-up of 476 ± 330 days, events in both groups were the following:

	Group I	Group II	p-value
ICD therapy for recurrences of VA	6 (22%)	29 (57%)	0.004
Total death	3 (11%)	9 (18%)	0.528
Cardiac death	2 (8%)	8 (16%)	0.479
Cardiac hospitalization	2 (8%)	15 (29%)	0.041
Cardiac death and hospitalization	4 (15%)	23 (45%)	0.015

Conclusions: CLD reduce recurrences of VA after ICD implantation in patients with CAD and life-threatening VA. Furthermore, the combined endpoint of cardiac death and hospitalization is significantly reduced in patients on CLD after ICD implantation.

763 Long-term effects of pravastatin on plasma concentration of C-reactive protein

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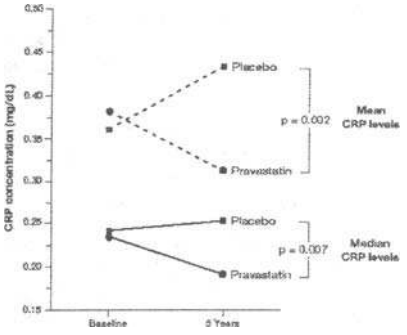
Elevated plasma concentrations of C-reactive protein (CRP) are associated with increased risk of myocardial infarction (MI) and stroke. In this study, we evaluated whether long-term therapy with pravastatin alters levels of this inflammatory parameter.

Methods: We employed a high-sensitivity assay to determine CRP levels among a randomly selected group of 472 participants in the CARE trial (pravastatin 40 mg orally qd, n = 258; placebo, n = 214) in whom both baseline and 5-year blood samples were available and who had remained free of recurrent vascular events during follow-up.

Results: Statistically significant differences were observed at 5 years between the pravastatin and placebo groups in terms of median CRP levels and absolute mean change in CRP.



These effects persisted in analyses stratified by age, body mass index, smoking status, blood pressure, and baseline lipid levels. There was no obvious relationship between the magnitude of change in CRP and lipid levels in both groups.

Conclusion: Pravastatin therapy significantly reduces CRP in post-MI patients. These data further support the potential for non-lipid lowering effects of this agent.

764 Statin therapy reduces adhesion molecule (VCAM-1) levels: evidence for an anti-atherosclerotic effect independent of LDL reduction

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Background: Cellular adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) mediate adhesion of leucocytes to the endothelium and play a key role in human atherosclerosis under the impact of risk factors. Previous data of our laboratory revealed a significant reduction after 6-month lipid lowering therapy with simvastatin. To assess the question of a possible independancy from concomitant LDL reduction VCAM-1 levels were measured ≈4 weeks after initiation of simvastatin therapy (20–40 mg) and after ≈5 months follow-up in 21 patients with mild-to-moderate hypercholesterolemia and reduced coronary flow reserve on positron emission tomography.

Methods: Soluble adhesion molecule VCAM-1 levels were measured by commercially available solid phase sandwich enzyme linked immuno sorbent assay (ELISA) in venous blood. 15 apparently healthy blood donors (10 males, 5 females) at equivalent age (51–60 years) served as a reference group: VCAM-1: 810 ± 243 ng/ml. Baseline data: 14 males, 7 females; mean age: 58 ± 8 years. LDL before lipid-lowering: 164 ± 32 mg/dl, after ≈4 weeks simvastatin therapy: 108 ± 41 mg/dl (−34%).

Results: (Mean ± SD) VCAM-1 levels decreased from 1108 ± 327 to 787 ± 313 ng/ml (p = 0.002) during ≈5 months (5.6 ± 2.1) simvastatin therapy. During the same period LDL only slightly decreased from 108 ± 41 mg/dl to 91 ± 30 mg/dl (p = n.s).

Conclusion: Statin therapy with simvastatin exerts, at least partly independent of LDL reduction, a favorable effect on atherosclerotic inflammation assessed in terms of decrease in VCAM-1. This non-lipid property may help to explain early cardiovascular event reduction in clinical trials of statin therapy.

NEUROHORMONAL CONTROL IN HUMANS

765 Physiological correlates of complexity of R-R interval dynamics

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Reduced complexity of R-R interval dynamics is related to aging and to various cardiovascular disorders, but the physiological background for complexity or predictability in heart rate (HR) behavior is not well know.

Methods: Approximate entropy (ApEn), a measure of complexity, along with traditional measures of HR variability were analyzed during physiological and pharmacological adrenergic stimulation: 1) noradrenaline (nor) 100 ng $kg^{-1}min^{-1}$, 2) combined noradrenaline and adrenaline (adr) (nor 100 + adr 16 ng $kg^{-1}min^{-1}$), were infused in 12 healthy volunteers (mean age 26 ± 5) who also underwent 3) passive head-up tilt test (60 degrees) and 4) dynamic treadmill exercise test with a steady-state work load of 4 km/h (Table 1).

Results: Noradrenaline resulted in an increase of mean blood pressure (from 94 ± 8 to 117 ± 13 mmHg, p < 0.001) and reduction in HR (from 61 ± 10 to 51 beats/min, p < 0.001) along with reduced ApEn and increased nuHF.

Table 1

	Base	Nor	Nor + Adr	Tilt	Exercise
ApEn	1.16 ± 0.15	0.98 ± 0.22**	1.04 ± 0.27	1.01 ± 0.18	1.28 ± 0.15*
HF (nu)	53 ± 20	71 ± 19**	58 ± 19	17 ± 12**	20 ± 13**
LF (nu)	47 ± 21	29 ± 18**	41 ± 19	85 ± 20**	80 ± 13**

*p < 0.05, **p < 0.001

Conclusion: Physiological and pharmacological adrenergic stimulation result in divergent effects on complexity of R-R intervals. Reduced complexity is most closely related to increased levels of noradrenaline, reflecting concomitant, accentuated sympathetic and vagal outflow to the sinus node.

766 Different effect of age on the autonomic modulation of sinus and AV nodes

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Parasympathetic modulation of the sinus node decreases with age. We investigated, whether autonomic modulation of the AV node also changed with age. Concomitant changes are not necessarily, because we have shown, that in healthy young man the autonomic nervous system can independently modulate sinus node and AV node.

Methods: A high-resolution (500 Hz) ECG was continuously recorded from about 10 pm to 6 am in 9 young (Group A, 25 ± 1 years) and 9 middle-aged (Group B, 52 ± 5 years) healthy subjects. The onset of P-waves and QRS-complexes was identified for all heart cycles by a computer algorithm with an accuracy of ±1 ms. Power spectra from the PP and PR intervals were integrated in the low frequency (LF) and the high frequency (HF) bands. The normalized HF power (nHF) of PP and PR intervals was used as an index of efferent vagal modulation and the LF/HF-ratio as an index of the sympathovagal balance of the sinus node (PP) and the AV node (PR).

Results:

	Sinus node (PP)		AV node (PR)	
	Group A	Group B	Group A	Group B
nHF	0.39 ± 0.14	0.20 ± 0.12*	0.38 ± 0.08	0.35 ± 0.15
LF/HF	1.84 ± 0.86	5.24 ± 2.86*	1.74 ± 0.64	2.30 ± 1.23
Sqr (TP) [ms]	145.2 ± 50.3	75.6 ± 22.9*	5.52 ± 1.16	5.24 ± 3.30

(mean ± SD; TP: total power; *p < 0.05 Group A vs. Group B)

In contrast to the known age-dependent decrease in the parasympathetic modulation of the sinus node, parasympathetic modulation and sympathovagal balance of the AV node was not significantly influenced by age.

Conclusion: Unlike autonomic modulation of the sinus node, autonomic modulation of the AV node was independent of age. Thus, changes in the autonomic modulation of the heart, that might be caused by different diseases, can be investigated irrespective of age on the AV node level but not on the sinus node level.

767 Baro receptor sensitivity and heart rate variability during acclimatization to high altitude

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Introduction: Hypobaric hypoxia may modify autonomic function. In the present study we assessed heart rate variability (HRV) and baroreflex sensitivity (BRS) during acclimatization to a simulated altitude of 4500 m (The Trysil Study).

Material and Methods: 8 healthy volunteers were examined during a one week stay in a hypobaric chamber built as a modern apartment. During the first 3 days there was a stepwise increase in simulated altitude up to 4500 m. The subjects then stayed at this altitude for 4 days before returning to sea level. HRV was assessed by 24 hour Holter recordings (Oxford). BRS was determined by the "transfer function" method, analyzing the relation between spontaneous fluctuations of 300 seconds of systolic blood pressure and heart rate (Finapres). A paired t-test was performed after log transformation of non normally distributed parameters.

Results: At a simulated altitude of 4500 m there was a significant decline in total power from 9200 ± 1779 ms.ms (Mean ± SEM) to 3135 ± 557 ms.ms ($p = 0.003$) compared to sea level. LF power decreased significantly (2423 ± 504 vs. 981 ± 204 ms.ms, $p = 0.007$) as did HF power (723 ± 193 vs. 252 ± 66 ms.ms, $p = 0.01$). BRS decreased significantly from 15.5 ± 2.0 ms/mmHg to 9.5 ± 2.6 ms/mmHg ($p = 0.004$).

Conclusion: We found evidence of blunted autonomic activity and reflexes during acclimatization to hypobaric hypoxia.

768 Plasma levels of volume regulating hormones in patients with obstructive sleep apnea syndrome treated with nasal continous positive airway pressure therapy

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In obstructive sleep apnea syndrome (OSAS) patients (pts.) develop short-term and long-term alterations (systemic and pulmonary hypertension, left and right heart failure) of the cardiovascular system. Increased venous return induced by pathologically high negative intrathoracic pressure during obstructive apnea leads to acute cardiac volume load. Secretion of natriuretic peptides from atria (Atrial natriuretic peptide; ANP) and ventricles (Brain natriuretic peptide; BNP) are stimulated by increased cardiac volume load. Aim of our study was to evaluate the course of volume regulating hormones in pts. with OSAS treated with nCPAP.

Methods: In 10 consecutive pts. (10 m; mean age 52 ± 11) we measured the circulating levels of atrial natriuretic peptide(NT-proANP) and brain natriuretic peptide (NT-proBNP) taken from an antecubital vein at 4 occasions: 8 pm (Rest), 5 am after diagnostic-night (Diag.), 5 am after therapy 1-night (Ther.1) and 5 am after therapy 2-night (Ther.2), respectively. During Ther.1 and Ther.2 pts. were treated with nasal continous positive airway pressure (nCPAP) therapy. Respiratory disturbance index (RDI) was determined during Diag., Ther.1 and Ther.2 by polysomnography.

Results: NT-proANP and NT-proBNP were significantly elevated after Diag. and dropped significantly after Ther.1 and Ther.2 parallel to a significant drop of RDI (Table 1).

Table 1

	Rest	Diag.	Ther. 1	Ther. 2
RDI [n/h]		61.09 ± 21.77	25.93 ± 19.14*	8.33 ± 8.44*
NT-proANP [nM]	0.24 ± 0.08	0.33 ± 0.07*	0.26 ± 0.07*	0.22 ± 0.05*
NT-proBNP [nM]	0.26 ± 0.09	0.41 ± 0.08*	0.24 ± 0.08*	0.20 ± 0.05*

Values are means ± SD; *p < 0.05; Rest vs Diag.; Diag. vs Ther.1; Diag. vs Ther.2

Conclusion: 1. Secretion of ANP and BNP increase during phases of apnea in pts. with OSAS. 2. Adequate treatment with nCPAP results in a normalization of ANP and BNP levels, respectively. 3. ANP- and BNP-concentrations could be a helpful marker to register successful treatment with nCPAP in pts. with OSAS.

769 Abnormal autonomic response to high-altitude exposure in acute mountain sickness

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Acute Mountain Sickness (AMS) is characterised by a variety of symptoms which frequently occur in lowlanders ascending to high altitude. AMS, usually self-limited, may progress to life-threatening cerebral edema. Although the exact mechanism is still unclear, it seems to be related to cerebral vasodilatation in response to hypobaric hypoxia, possibly mediated by the sympathetic nervous system.

Methods and results: To evaluate the role of the autonomic nervous system in the genesis of AMS, we studied baroreflex sensitivity (BRS) by means of a non-invasive technique (alpha-index) in 47 normal subjects (12 F, 16–57 yrs), a few hours after reaching high altitude (4559 m; HA). Medical history, physical examination, spirometry, arterial oxygen saturation, EKG, heart rate variability, and Lake Louise questionnaire were also performed. Nineteen subjects repeated the protocol at low altitude (200 m; LA). At HA, 17 subjects (36%) had AMS (Lake Louise score ≥ 3). No differences were found between subjects with and without AMS in terms of anthropometric and respiratory function data. In contrast, the subjects with AMS were older (40 ± 10 vs 34 ± 9 yrs, $p < 0.05$) and had a lower BRS (5.6 ± 3.1 vs 10.1 ± 7.3 ms/mmHg, $p < 0.05$). At LA the 8 subjects with AMS showed a tendency toward a lower BRS compared with the subjects who were asymptomatic at HA (9.7 ± 3.2 vs 12.4 ms/mmHg, ns).

Conclusions: These results show that AMS is associated with an abnormal autonomic reactivity to acute exposure to high altitude and suggest a possible role of the individual autonomic function in the genesis of symptoms at high altitude.

770 Assessment of autonomic control of the heart in patients with cardiac syndrome x

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Recent studies suggested a possible role of increased sympathetic activity in patients (pts) with cardiac syndrome X (SX) (angina, inducible myocardial ischemia and angiographically normal coronary arteries). In 18 pts (59 ± 3 years) with diagnosed SX we recorded standard ECG and finger arterial pressure (Finapres). 10 min records were taken in supine position (S) and after passive 60° tilting (T). Spectral analysis on time series of R-R period (RR) and systolic blood pressure (SAP) was performed by an autoregressive method, to quantify low (LF) and high (HF) frequency oscillations. Values are reported as means ± standard error. On 13 out of 18 pts a set of standardized vagal stimulation tests (VST), such as lay-to-standing, squatting, deep breathing, 40 mmHg Valsalva maneuver and cold face (pooled score). In 13 pts HF power of RR (67 ± 24 ms^2) in S was low and T induced a slight increase in the heart rate (814 ± 37.2 to 767 ± 27.8 ms), with an increase of LF power of SAP (from 4.8 ± 1.1 to 10.8 ± 1.9 $mmHg^2$), while the frequency domain values of RR did not change 9 of these pts performed the VST, and 8 showed vagal impairment. In the remaining 5 pts, heart rate (RR = 909 ± 65 ms) was lower and HF power of RR (231 ± 121 ms^2) was higher in S, and T induced the expected changes of RR. VST in 4 pts showed unaltered vagal responses. The results of spectral analysis suggest a vagal impairment in 13 pts, which is partially confirmed by VST. Thus, most of the pts with cardiac SX show a reduced vagal function not a sympathetic hypertone, as previously suggested. This finding may be important for the assessment of pathogenetic mechanisms of SX as well as for a novel treatment protocols.

MECHANISMS OF ATHEROSCLEROSIS

771 The GPI-anchor of T-cadherin is important for interaction with lipoproteins

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Differential lipoprotein-binding studies on intact smooth muscle cells (SMC) have indicated binding sites with novel characteristics which might represent candidate cellular lipoprotein-binding sites associated with intracellular signalling by lipoproteins. Two proteins, 105 kDa and 130 kDa, in lysates from SMC retain the property to bind lipoproteins after PAGE and blotting. Amino acid sequences of tryptic peptides of the purified proteins matched with human (pro) T-cadherin (T-cad), and with peptide-based anti T-cad antisera we could show that anti T-cad immunoreactivity colocalizes with LDL-binding. We expressed recombinant T-cad in stably transfected 293 cells to confirm identity of p105/p130 as T-cad. The transfectants express two anti-T-cad immunoreactive proteins of 105 and 130 kDa. The correct location of T-cad to the outer cell membrane of intact cells was demonstrated by FACS analysis and by its release upon incubation with PI-PLC. To date, binding studies on intact cells show only a moderate, albeit significant, increase in lipoprotein binding in T-cad expressing cells which is not accordance with their high expression of T-cad protein. The ligand binding characteristics of recombinant T-cad on blot are indistinguishable from SMC T-cad, since both bind native LDL, oxLDL, acLDL and also HDL_3 and delipidated HDL_3 with similar affinities. Unexpectedly, T-cad released by PI-PLC from transfectants and SMC is unable to bind lipoproteins on ligand blots. A T-cad variant which is expressed without the signal peptide for GPI anchor attachment and which is secreted into the culture medium as a soluble protein also lacks lipoprotein binding on blot. Taken together we conclude that the lipid anchor of T-cad is the important structural component for the binding of lipoproteins. Control experiments do not give any indication that lipoprotein binding is a property common to GPI-anchored proteins in general.

772 Overexpression of tissue inhibitor of metalloproteinase-3 inhibits neointima formation in porcine saphenous vein-to-carotid interposition grafts in vivo

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Drug or gene-based treatments to prevent neointima formation in coronary vein grafts remain elusive. Recent studies implicating metalloproteinases (MMPs) in vein graft neointima formation suggest inhibition of MMPs by tissue inhibitor of metalloproteinases (TIMPs) as possible therapy. Recently, we have demonstrated that TIMP-1, -2 and -3 equipotently inhibit smooth muscle cell migration while TIMP-3 uniquely promotes SMC apoptosis.

Methods: Adenoviruses expressing lacZ (RAdlacZ) or human TIMP-3 (RAdTIMP-3) were exposed to the lumenal surface of pig saphenous veins at 2.5 × 10^{10} plaque forming units (pfu)/ml for 30 minutes ex vivo prior to grafting into the carotid artery. Infection efficiency was evaluated by staining for β-galactosidase *en face* and in cross sections. MMP activity was evaluated by *in situ* zymography, proliferation by proliferating cell nuclear antigen (PCNA) staining and endothelial coverage by immunocytochemistry with DBA-lectin. Apoptosis was quantified by *in situ* end labelling (ISEL), terminal dUTP nick end labelling (TUNEL) and immunocytochemistry for the pro-apoptotic bcl-2 antagonist, bak. Neointimal and medial areas at 1 month were measured by planimetry.

Results: 40% of lumenally exposed cells expressed recombinant β-galactosidase 7 days post-implantation. RAdTIMP-3 induced high levels of TIMP-3 in the near lumenal extracellular matrix and powerfully inhibited MMP activity throughout the veins. SMC apoptosis was increased both in the neointima and media at day 7 but not at day 28. TIMP-3 overexpression reduced neointima formation at 28 days post-infection from 3.9 ± 0.5 mm2 for vehicle-treated and 4.8 ± 1.1 mm2 for RAdlacZ-treated to 2.0 ± 0.1 mm2 ($p < 0.05$ vs both controls, n = 6/group) without significantly affecting medial area, medial cell proliferation or endothelial coverage.

In conclusion: Our results clearly identify TIMP-3 gene therapy as a candidate for prevention of vein graft neointima formation.

773 Helicobacter pylori infection does not influence atherogenesis in vivo in mice

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Helicobacter pylori is now widely recognized as an important cause of gastric disease, and some reports have suggested a link to ischemic heart disease (IHD). Since the first report of a high incidence of H. pylori seropositivity in patients with coronary heart disease, numerous epidemiological studies have explored an association between H. pylori infection and IHD. The contradictory results of these studies have highlighted the debate between inflammation, infection and the development of IHD. Although H. pylori has not been detected within atherosclerotic lesions in situ, this infection might still promote vessel-wall cells activation and atherosclerotic lesions indirectly. To seek direct evidence for a role of H. pylori infection in atherogenesis, we examined the effect of this infection in atherosclerosis-prone mice.

Male wild-type C57/Bl6 mice and LDL-receptor deficient syngeneic mice (LDLR−/−) were randomly assigned to be infected with H. pylori strain SS1, a mouse-adapted cag+ strain or sham-infected (n = 8 per group). All animals were fed a high cholesterol diet (1.25%) lacking added cholate. After 6 or 12 weeks, mice were sacrificed and atherosclerotic lesion formation as well as lipid deposition measured using a quantitative computer-assisted image analysis, as described previously. H. pylori infection was confirmed by rapid urease test and by histology on gastric biopsies. Infected or uninfected mice had similar total cholesterol, triglycerides, circulating leukocytes, hematocrit or fibrinogen.

H. pylori infection did not influence aortic atherosclerotic lesions or aortic lipid deposition in this model of atherosclerosis. Aortic arch lesions were minimal in wild-type mice infected or not with H. pylori after 6 or 12 weeks of high cholesterol diet. In contrast, LDLR−/− mice showed extensive atherosclerotic lesions, as defined by aortic wall area and thickness ($p < 0.001$ for both parameters vs. wild-type values; Wilcoxon rank sum test), but H. pylori infection did not affect the severity of these lesions. Lipid deposition was minimal in infected (2.5 ± 1.0% of abdominal aortic surface area) and non-infected (2.3 ± 0.9) wild-type mice. In LDLR−/− mice, however, lipid deposition was 21 ± 3% ($p < 0.001$ vs. wild-type) in non-infected animals but was not modified by H. pylori infection (22 ± 4%).

To the best of our knowledge, this is the first experimental study investigating in vivo the influence of H. pylori infection on atherogenesis. Under the conditions of this experiment, H. pylori infection does not contribute to the development of atherosclerotic lesion formation.

774 Association between the lipoproteinlipase gene polymorphism, cholesterol levels and myocardial infarction

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Small studies have reported inconsistent data on the associations between the H2H2 lipoproteinlipase (LPL) genotype with dyslipidemia or premature coronary artery disease. This study involved 2585 individuals with complete pheno- and genotyping.

Methods: The association of LPL genotypes with cholesterol levels was assessed in survey participants from the general popultion of Augsburg, Germany (n = 1357. Genotype frequency in this healty population was compared to that in patients who had experienced a myocardial infarction (MI) under 60 years of age (population-based MI-register Augsburg), n = 613. In addition, to condensate genetic factors, 138 siblings of MI patients affected with MI and 477 siblings with no known coronary artery disease were genotyped.

Results: In the general population a significant association between the H2H2 genotype and unfavorable lipid levels was observed:

	H1H1	H1H2	H2H2	p-value H1H2 vs. H2H2
LDL-C (mg/dl)	143 ± 1	141 ± 2	147 ± 2	0.001
HDL-C (mg/dl)	55 ± 2	55 ± 1	53 ± 1	0.01
Total/HDL-C	4.6 ± 0.1	4.6 ± 0.1	4.9 ± 0.1	0.04

It persisted after adjustment for age, gender, body mass index, alcohol intake, smoking, hormone replacement, and lipid lowering therapy. However, neither men nor women displayed an association between the H2 allele frequency and MI: general population (men/women) 71.5/72.1%, MI register 71.6/70.6%, non-affected siblings 73.4/72.4%, affected siblings 73.3/72.4%. Similarly, genotype frequencies were not different between groups with and without MI.

This large study shows that the H2H2 genotype of the LPL gene polymorphism is associated with unfavorable lipid levels in the general population. However, these effects were not strong enough to reveal a significant association with MI in 751 patients with premature MI.

775 Role of oxidized low-density lipoprotein in the progression of coronary atherosclerosis in humans

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Previous pathological studies have shown that inflammatory processes are associated with progression of coronary atherosclerosis. In vitro studies have suggested that oxidized low density lipoprotein (OxLDL) plays a key role in the genesis of the inflammatory processes in atherosclerotic lesions. Recently, a new anti-OxLDL monoclonal antibody, DLH3, which recognizes oxidized phosphatidylcholine (OxPC), has been developed by one of us. This antibody is specific for OxLDL, and does not bind to either native, acetylated, or malondialdehyde-treated LDL. To verify the role of OxLDL in the progression of atherosclerosis in human coronary arteries, we have immunohistochemically studied the presence of OxPC, using this new antibody.

Methods: Eighty-six segments of coronary arteries were harvested at autopsy from patients over 50-year-old. Antibodies were used against smooth muscle cells (SMCs), macrophages (Mϕs), endothelial cells, T lymphocytes, apolipoprotein B and OxPC. For the identification of cell types which show staining positivity for OxPC, immunodouble (OxPC/SMC, OxPC/Mϕ) and immunotriple (SMC/Mϕ/OxPC) stainings were also performed.

Results: Fibrous plaques containing abundant SMCs without Mϕs showed no staining for OxPC. In contrast, fibrous plaques with foci of clustered foam cells (FCs) revealed distinct positivity for OxPC in these FCs. In atheromatous plaques, fibrous caps with inflammatory cells also showed OxPC positivity in FCs, however, a lipid core generally showed no staining for OxPC.

Conclusion: These results suggest that during human coronary atherogenesis, OxLDL plays a crucial role in the development of inflammatory processes and foam cell formation, which may be one of the mechanisms of plaque destabilization in human coronary atherosclerosis.

776 Total cholesterol/HDL ratio, but not LDL cholesterol, predicts the risk for future cardiovascular events: the Chin-Shan Community Cardiovascular Cohort Study – 8-year follow-up

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Despite clinical guidelines designed to decrease the risk for coronary heart disease (CHD) have focused on identifying persons with increased levels of low-density lipoprotein (LDL) cholesterol, controversy still exists about the relative ability of different measures of cholesterol to discriminate CHD risk. In this study, we evaluated this ability of 4 measures of cholesterol (total cholesterol, LDL cholesterol, total cholesterol/high-density lipoprotein (HDL) ratio, and LDL/HDL ratio) and the appropriateness of current LDL cholesterol-based assessment in comparison with approaches by other measures of cholesterol.

Methods: The incidence of CHD was assessed in 2,572 participants (aged ≥35 years old at baseline) from the Chin-Shan Community Cardiovascular Cohort Study, a prospective, population-based study begun in 1990, over an 8-year follow-up period. Serum lipid determinations at baseline were used in this study.

Results: During this time, 152 subjects developed CHD (5.9%). After adjustment for age and sex, only total cholesterol/HDL ratio (p = 0.005) and LDL/HDL ratio (p = 0.01), rather than total cholesterol (p = 0.36) and LDL cholesterol (p = 0.09), were associated with occurrence of new CHD events in proportional hazard models. The relation to total cholesterol/HDL ratio, but not LDL/HDL ratio, remained significant after adjustment for other risk factors (risk ratio, 1.15 for 1.0 increment in ratio; p = 0.01). Furthermore, the incidence of CHD in subjects with LDL cholesterol ≤ 160 mg/dl and total cholesterol/HDL ratio > 5 was significantly higher than the incidence in those with LDL cholesterol > 160 mg/dl and total cholesterol/HDL ratio ≤ 5 (44/456 (9.7%) vs 7/156 (4.5%); risk ratio, 2.4; p = 0.03).

Conclusion: Contrary to the clinical guidelines, the total cholesterol/HDL ratio, but not LDL cholesterol, is the only predictor of future CHD events. Current LDL cholesterol-based strategy for risk assessment may misclassify persons and reduce the cost-effectiveness of lipid-lowering therapy.

NEW METHODS OF CORONARY SURGICAL TREATMENT: PROBLEMS AND REMEDIES

781 Is minimally invasive coronary bypass surgery (MIDCAB) the favorite treatement for single high-grade LAD lesion? Experience with 520 MIDCAB patients

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Objectlve: Minimally invasive direct coronary artery bypass surgery (MIDCAB) is performed since November 1996 in an increasing number for patients with single high grade LAD lesion.

Methods:520 patients underwent MIDCAB surgery without cardiopulmonary bypass. Early post-Op angiography was performed before discharge in 353 patients. Mid-term follow-up angiography after 6 to 12 months is available in 214 patients so far.

Results: Preoperatively 5.6% of the patients had Type B-lesion of the proximal LAD, 50.8% Type C-lesion, 28.1% an occluded LAD and 17.0% an "in-stent" restenosis. In 501 patients a single ITA to LAD bypass was performed, and in 19 patients a double Y-graft, including the radial artery for revascularization of a major diagonal branch. Duration of the procedure was 93.2 ± 17.4 minutes. Operative mortality was 1/520 (0.2%). Early reintervention was necessary in 1.9% of the patients due to graft failure. On early angiography, patency was 98.1%, 3.4% of the patients showed severe stenosis of the anastomosis. On follow-up angiography 3.7% of the patients had moderate to severe anastomosis stenosis, 4 grafts were occluded. Follow-up patency was 95.6%. The total rate of reinterventions was 5.4% during follow-up, 6 patients underwent redo-CABG, and 6 patients successful PTCA of the stenosis. Three patients died during follow-up, thus follow-up survival was 99.1%.

Conclusion: MIDCAB-surgery is a safe and effective treatment for high grade single LAD lesion. In competition with PTCA the minimally invasive surgical treatment provides significant less restenosis and less need for reinterventions. Therefor, MIDCAB is the favorite therapy in patients having high grade Type C-lesion of the LAD with an expected restenosis rate of >20% for PTCA. Furthermore, MIDCAB should be the treatment of choise in patients with "in-stent" restenosis.

782 Does persistence of internal thoracic artery side branches after off-pump CABG affect myocardial perfusion? A preliminary SPECT study

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We sought to assess the effects on myocardial perfusion of the persistence of proximal side branches arising from the internal thoracic artery (ITA), usually unresected during minithoracotomy (MINI) exposure for off-pump myocardial revascularization.

Methods: Twenty-five patients underwent CABG without extracorporeal circulation. Ten patients (group 1) received ITA on the LAD after conventional midsternotomy and total isolation of the arterial conduit, whereas 15 patients (group 2) underwent MINI CABG on the LAD with partially harvested ITA. No differences existed between groups in terms of age, severity of CAD, or function of left ventricle (LV). After surgery, all patients were evaluated by Tc-99m SESTAMIBI SPECT at rest, during exercise, or after dypiridamole infusion. Extent (% of LV surface) and severity (arbitrary units) of reversible defects at SPECT scan in LAD territory (revascularized vessel) were quantified in comparison to gender matched polar map, subtracting the rest value to the stress one.

Results: No significant differences either in the severity or in the extent of myocardial perfusion were found between groups at rest. Although not statistically significant, a reversible perfusion defect >20% of LV surface occurred more frequently in group 2 patients (23% of G2 vs 12% of G1 after dypiridamole, and 33% of G2 vs 11% of G1 after exercise testing, respectively). Taking into account patients with a reversible perfusion defect < 20% of LV surface, a significant difference between groups was observed after dypiridamole (179 in G1 vs 499 in G2, respectively, $p < 0.05$), but not after exercise testing. A significant difference was also found between G1 and G2 patients in relation to the severity of perfusion defects (258 in G1 vs 602 in G2, respectively, $p < 0.05$).

Conclusions: Persistence of unresected ITA side branches during MINI CABG may account for mild myocardial perfusion defects due to steal phenomena in presence of maximal coronary vasodilation. Stress SPECT appears to represents a valuable tool to assess persistence of postoperative inducible ischemia in off-pump CABG patients

783 The beneficial effect of off-pump bypass surgery in patients with left ventricular dysfunction

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The adverse effects of extracorporeal circulation increase the morbidity and mortality risk of coronary bypass surgery, espacially in patients with poor left ventricular function. The purpose of this study was to provide a comparison of long-term survival and intervention-free outcome between patient groups with poor ventricular function (LVEF < 40% or LVPS≥15) subjected to one-vessel coronary bypass accomplished with or without the use of cardiopulmonary bypass.

From October 1992 to March 1994, 51 patiens, who were operated on at Kosuyolu Heart and Research Hospital, with poor left ventricular function were investigated retrospectively. They were divided in two groups: beating heart group included 26 patients and cardiopulmonary bypass group 25 patients. Mean age (54 ± 9.5 versus 50.5 ± 8; $p > 0.05$) and risk factors were identical. All of the patients operated on only for one vessel (LIMA-LAD).

At 6 year follow up, all patients in both groups were alive. In the early postoperative period the need of cardiac support therapy (inotropic support or IABP) was significantly higher in the cardiopulmonary bypass group than the beating heart group: 8 (32%) patients versus 2 (7.7%) patients, $p < 0.05$. Perioperative myocardial infarction was not seen in any patient. No patient in both groups had anginal or congestive symptoms in the postoperative period (mean 68.5 ± 3.5 months) and required reoperation or reintervention (PTCA or stent). The need of blood products (for FFP 3.63 ± 2.15 u versus 2.5 ± 1.34 u and $p < 0.01$; for packed red blood cells 1.8 ± 0.75 u versus 1.25 ± 0.46 u and $p < 0.01$), the ICU-stay (2.8 ± 1.9 days versus 2.04 ± 0.9 days; $p < 0.05$) and hospital stay (10.64 ± 3.2 days versus 7.92 ± 2.25; $p < 0.001$) were higher in the cardiopulmonary group than in the beating group.

Despite one less graft per patient, survival and cardiac death rates were similiar for both groups. However, more than four times as many patients in the CPB group required inotropic support after surgery. Off-pump bypass surgery conserves the blood constituents. The benefits of both techniques to improve the left ventricular performance skore and EF were similiar, but postoperative extubation time, lenght of ICU and hospital stay were reduced significantly in the beating heart group. With these good results of the beating heart group and the performing coronary revascularization more cheeper, coronary bypass on beating heart can be an alternative to cardiopulmonary bypass technique in selective patient groups.

784 Cardiogenic shock following postinfarction ventricular septal defect: need for immediate surgical repair despite initial stabilization with intraaortic balloon counterpulsation

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Aims The aim of this study was to analyse the potential of intraaortic balloon counterpul-sation to reverse cardiogenic shock and to delay surgical repair in patients with ischemic ventricular septal defect.

Methods and Results Between 1981 and 1997, a total of 25 consecutive patients presenting with cardiogenic shock following postinfarction ventricular septal defect were treated with intraaortic balloon counterpulsation. In all patients hemodynamics improved immediately after initiation of intraaortic balloon counterpulsation with a significant increase in mean aortic pressure from 61 to 84 mmHg (n = 25; $P < 0.01$) and in cardiac index from 1.70 ± 0.32 to 2.08 ± 0.23 $L^{*}min^{-1}{}^{*}m^{-2}$ (n = 16; $P < 0.01$). Simultaneously, left-to-right shunting significantly decreased from 279.9 ± 73% to 175.7 ± 92% (n = 16; $P < 0.01$).

Fourteen patients underwent early surgical repair within 24 (6.5 ± 5.3) hours after insertion of intraaortic balloon counterpulsation because of the extent of shunting and the hemodynamic compromise. In this group, in hospital mortality was 42.9% (6/14 pts). In the remaining 11 patients, initial counterpulsation-related stabilization encouraged to delay operation as an attempt to reduce operative risk. However, in all of these patients, hemodynamics deteriorated within the following days: 5 patients had to be operated within 48 h, 3 patients within 4 days, and the remaining 3 pts who had not been operated died on days 2, 7 and 9 after balloon pump-insertion. Thus, no patient could be stabilized to perform a strategy of delayed repair of septal defect. In patients operated within the first 48 h, in hospital mortality was 47.4% (9 of 19 pts). In contrast, in patients not operated within 48 h, mortality was 100% (6 of 6 pts).

Conclusion Intraaortic balloon counterpulsation enables marked preoperative hemodynamic improvement in patients presenting with cardiogenic shock following ischemic ventricular septal defect. Despite initial stabilization, such patients need immediate surgical repair of septal defect to avoid hemodynamic deterioration.

785 The role of bi-atrial pacing in the prevention of atrial fibrillation after coronary artery by-pass surgery: a randomised control study

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After coronary artery by-pass surgery (CABG) atrial fibrillation (AF) is common and its management problematic. In this setting prophylactic drug therapy has limited success in suppressing AF. Alternative non-pharmacological approaches are therefore required. We have performed a randomised study comparing bi-atrial pacing to a control group of no pacing on the incidence of AF post CABG.

Methods: Patients undergoing first time CABG are included in the study. At the time of surgery temporary pacing wires are placed in the lateral wall of the right atrium and the roof of the left atrium (Bachmanns bundle) to allow bipolar pacing at both sites. After surgery all patients are connected to an external pacemaker (Chorum ELA) that also acts as a Holter monitor. Patients are consecutively randomised to either resynchronised biatrial pacing at a base rate of 80bpm or no pacing (base rate 30bpm) for 4 days. The primary endpoint is an episode of AF lasting longer than 1 hr.

Result: 100 patients have been randomised so far. The incidence of AF in the control group is 36% (18/50) and in the biatrial group 16% (8/50), p = 0.03.

In conclusion: Our initial experience suggests bi-atrial pacing significantly decrease the incidence of AF after CABG. The completed study results will be available at the meeting.

786 The UK trial of transmyocardial laser revascularisation: clinical and cost effectiveness

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TMLR is used to treat patients with refractory angina due to severe coronary artery disease, which is not suitable for conventional revascularisation.

Purpose: The aim of the MRC UK trial was to evaluate the effectiveness of TMLR versus medical management (MM).

Methods: 188 patients were randomised to TMLR plus usual medication (n = 94) or continued medication alone (n = 94), between October 1993 and September 1997. The primary outcome measure was exercise capacity secondary measures were clinical status, radionuclide myocardial perfusion and health related quality of life, which were all assessed at baseline and at 3, 6 and 12 months following surgery (TMLR) or baseline (MM). Detailed health service resource use was recorded for the assessment, follow up care and drug therapy in both groups plus the surgical procedure and hospital stay for the TMLR group.

Results: The trial was powered to detect a clinically significant increase in exercise tolerance: at 12 months, exercise time was 40 seconds (−15 to 94) greater in the TMLR group than in the controls (p = 0.152) and in 25% of TMLR patients there was a significant improvement in physician rated angina. Peri-operative mortality was 5%. Survival rates at 12 months were 89% (83% to 96%) in the TMLR group and 96% (92% to 100%) in the MM group (p = 0.14). Based on detailed itemised costing of 50 of the 94 procedures and using trial centre costs for 1997, the mean cost of a TMLR procedure was £5746 (95% CI £5103 to £6389). Follow-up hospital admissions in the TMLR group were 1.3 (95% CI 1.1 to 1.5) per patient year compared to 1.1 (95% CI 0.9 0 1.3) per patient year for MM patients (p = 0.110). Outpatient visits were 1.5 (95% CI 1.2 to 1.8) per patient year in the TMLR group compared to 1.7 (95% CI 1.4 to 2.0) for MM patients (p = 0.64).

Conclusion: It is clear that the significant cost of the procedure compared to continued medical therapy, together with the perioperative mortality risk and the slim chance of improvement in angina, all lead to the conclusion that on both clinical and cost effectiveness evidence the adoption of TMLR cannot be recommended.

EMERGING TREATMENT MODALITIES IN DILATED CARDIOMYOPATHY

787 Is the clinical course of dilated cardiomyopathy changed over the last 20 years? The experience of the Heart Muscle Disease Registry of Trieste

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Since 1978, 343 pts with idiopathic dilated cardiomyopathy (IDC) were enrolled and sistematically followed up in our Heart Muscle Disease Registry. Ninety-four pts (group 1) were enlisted between 1978 and 1987, while 249 (group 2) between 1988 and 1997.

Changes in the baseline clinical parameters in group 2 included a younger age (43 ± 9 vs 47 ± 10 years, p = 0.01) and a shorter duration of heart failure symptoms before diagnosis (16 ± 15 vs 25 ± 22 months, p = 0.04). Moreover, an increasing use of ACE inhibitors (92% vs 25%, p < 0.0001) and beta-blockers (77% vs 3%, p < 0.0001), while a less frequent treatment with amiodarone (34% vs 61%, p < 0.0001) were evident in the group 2. Two, 5 and 8 year transplant-free survival was respectively 87%, 74% and 67% in group 2 vs 85%, 58% and 50% in group 1 (p = 0.04 after stratification for heart failure severity). Two, 5 and 8 year risk of death due to refractory heart failure or heart transplant decreased in more recent cohort (respectively 8%, 20% and 22% in group 2 vs 11%, 33% and 36% in group 1; p = 0.04), while the incidence of sudden death did not change (2%, 9% and 18% in group 2 vs 4%, 11% and 19% in group 1; p = NS). The risk of primary events related to heart failure progressively decreased, while sudden death tended to increase during long-term follow-up.

The analysis on 343 IDC patients enrolled in our Registry shows that an earlier diagnosis and a clear change in heart failure treatment determined an improvement of transplant-free survival over the last 20 years. These results were partially lost during long-term follow-up because of an increasing incidence of sudden death.

788 Effect of short-term immunosuppressive therapy on chronic inflammatory cardiomyopathy: six-month follow-up results

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The treatment of idiopathic dilated cardiomyopathy (IDCM) remains problematic and therapeutic modalities involving non-selective anti-inflammatory agents continue to be controversial. We hypothesised that criteria for such therapy should be based on immunohistological hallmarks of chronic myocarditis in biopsy specimens, rather than on the Dallas criteria. Accordingly, we prospectively studied 40 patients (pts) with chronic congestive heart failure due to IDCM confirmed by echocardiography, radionuclide ventriculography, coronary angiography and positive immunohistology (expression of HLA-class I and/or II). Mean duration of symptoms was 3.6 years (range: 8 months to 6 years. Mean LVEF was 25.6% (range: 17–35%). NYHA functional class was as follows: II in 12 pts, III in 26 pts, IV in 2 pts. The baseline clinical assessment included physical examination, ECG, 24-hours ECG monitoring, echocardiography, radionuclide ventriculography and coronary angiography. All pts were treated with conventional therapy (digitalis, metocard, captopril and diuretics). Twenty one pts (16 M, 5 F, age 42 ± 4 years) who were randomised to the immunosuppressive therapy group (IT), were also treated with encorton (1 mg/kg/day, for 12 days, then tapered off every 5 days by 5 mg/day until reaching a maintenance dose of 0.2 mg/kg/day) and azathioprine (1 mg/kg/day) for a total 100 days. Nineteen pts (18 M, 1 F, age 40 ± 6) were randomised to the placebo group (CT). Pts were assessed at baseline, 3 and 6 months. Pts in which the LVEF increased >5% (by radionuclide ventriculography), LV fractional shortening increased >5% (by ECHO), LV diastolic diameter decreased >5 mm (by ECHO), and decreased NYHA class were considered as pts who demonstrated clinical improvement. The differences between groups were analysed using the two-tailed Fisher exact test.

The baseline characteristics were similar in both groups. At the time of 3 month follow-up, 16 pts (76%) in the IT group showed clinical improvement compared to 4 pts (21%) in the CT group (p < 0.01). At the time of 6 month follow-up clinical improvement was observed in 17 pts (81%) in the IT group versus 6 pts (31%) in the CT group (p < 0.01). One patient from the IT group withdrew from the study. There was one death in the CT group.

Conclusions. It appears that short duration immunosuppressive therapy may be beneficial in the treatment of chronic myocarditis. However, the qualification of patients for such treatment should be based on immunohistological assessment using endomyocardial biopsy rather than on the Dallas criteria.

789 Immunoadsorption improves cardiac performance in patients with severe dilated cardiomyopathy

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A causative therapy of idiopathic dilated cardiomyopathy (IDC) is not known. In 70% of patients with IDC a pathological level of auto-antibodies directed against cardiac β_1-adrenoceptors (AAB) can be found.

Methods: We wanted to evaluate whether immmunoadsorption has a positive effect on cardiac function and dimension, i.e. left ventricular ejection fraction (EF) and left ventricular internal diameter in diastole (LVIDd). Thirty-four patients with IDC were devided into two groups (I, C) of 17 patients each. Both groups were not statistically different regarding the following parameters: age, sex, NYHA class, EF, LVIDd, level of AAB and drug therapy regarding cardiac insufficiency. After study recruitment all patients who were not on β-blocker medication received these additionally. After synchronisation of both groups, group received immunoadsorption whereas group C was not treated.

Results: Two patients out of group C were transplanted two and five months, respectively, after recruitment. The table shows the results one year after immunoadsorption as compared to the data at the beginning of the study.

	At the time of recruitment			After one year		
	EF [%]	LVIDd [mm]	AAB [LU]	EF [%]	LVIDd [mm]	AAB [LU]
Group I (n = 17)	22 ± 3	75 ± 7	6.0 ± 1.4	38 ± 8	64 ± 6	not detectable
Group C (n = 17)	24 ± 3	76 ± 6	4.7 ± 1.0	25 ± 6 (n = 15)	73 ± 7 (n = 15)	5 ± 1.0 (n = 15)
P-values	n.s.	n.s.	0.0104	0.0001	0.0004	0.0001

In conclusion: Immunoadsorption led to a significant improvement of cardiac function and dimension. AAB directed against cardiac β 1-receptors seem to be a suitable parameter to assess the success of immunoadsorption. The reason why the cardiac function of the control group also improved may be due to the positive effect of the β-blocker therapy.

790 The beneficial effect of beta blockade on cytokine levels in patients with dilated cardiomyopathy

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Numerous studies have suggested a beneficial effect of beta-blocker therapy in patients with dilated cardiomyopathy (DCM). Although circulating levels of tumor necrosis factor-alpha (TNF-α) have been reported to increase in patients with DCM, the effect of beta-blockers on cytokine levels in DCM is unknown. This study was designed to evaluate whether the cytokine TNF-α was reduced with beta-blocker therapy in patients with DCM.

Methods We studied 25 patients with DCM in New York Heart Association functional class III or IV, who had been treated with digitalis, diuretics and angiotensin-converting enzyme inhibitors. In all patients, beta-blockers (metoprolol or bisoprolol) were added. Plasma levels of TNF-α were measured by enzyme-linked immunosorbent assey at baseline and at 12 weeks after the initiation of beta-blockers. Plasma norepinephrine (NE; pg/ml) and brain natriuretic peptide (BNP; pg/ml) were also measured. Left ventricular dimension at end-diastole and end-systole (LVDd and LVDs; mm) and fractional shortening (FS; %) were measured. Ten age-mached subjects with no cardiac disease served as the normal control (NC).

Results The baseline plasma levels of TNF-α were significantly higher in patients with DCM than in normal subjects (DCM; 30.7 $\pm$ 17 pg/ml, NC; 17.8 $\pm$ 4.9 pg/ml, $p < 0.05$). Plasma TNF-α levels significantly decreased after the treatment with beta-blockers. Plasma NE and BNP were also reduced, and left ventricular dimension and function were improved.

	TNF-α	NE	BNP	LVDd	LVDs	FS
Baseline	30 $\pm$ 17	341 $\pm$ 144	253 $\pm$ 462	69 $\pm$ 11	59 $\pm$ 12	15 $\pm$ 6
12 weeks	15 $\pm$ 4§	218 $\pm$ 140§	184 $\pm$ 470§	64 $\pm$ 7*	50 $\pm$ 9*	22 $\pm$ 7*

$^{*}P < 0.001$, $^{\S}P < 0.005$ vs. baseline

Conclusion Our data indicate that beta-blocker therapy lowered circulating TNF-α levels in patients with DCM. The beneficial effect of beta-blockade in DCM may be partly due to a reduction of cytokines such as TNF-α.

791 Treatment of patients with dilated cardiomyopathy with human recombinant growth hormone for 3 and 6 months: effects on left ventricular size and function

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Short term studies suggest that therapy with human recombinant growth hormone (GH) may improve cardiac function in patients with heart failure. We conducted a randomised, double-blind, placebo-controlled study in 50 patients with dilated cardiomyopathy (DCM). The average NYHA class was 2.2 $\pm$ 0.1 and the mean LV-EF was 27 $\pm$ 2%. After 3 months of blind therapy with 2 U/d GH or placebo (P) every patient received 1 U GH daily for 3 months (GH-GH and P-GH group) in an follow-up trial. Cardiac size and function was determined by cine-magnetic resonance imaging. LV mass was calculated from 10 mm slices of the left ventricle in the short axis.

Results: At baseline both groups did not differ in the severity of heart failure measured by NYHA class, 6 minutes walking distance and central hemodynamics. Blood pressure, heart rate and left ventricular ejection fraction were unaltered after 3 and 6 months. The significant increase in LV mass after therapy for 3 months with 2 U GH s.c. daily was sustained with 1 U/d GH. LV mass increased with 1 U/d GH for 3 months to a similar degree compard to the group treated for 6 months with GH. Progressive ventricular dilatation did not occur in both groups.

Summary: Therapy with GH for 3 and 6 months induces left ventricular hypertrophy and no significant decrease of cardiac function. As the cardiac effects of 1 U/d GH are comparable to 2 U/d GH a low dose of GH substitution therapy is sufficient to decrease systolic wall stress.

792 Beneficial effect of angiotensin-converting enzyme inhibitor on dilated cardiomiopathy induced by autoimmune mechanism against β1-adrenoceptor

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We have previously shown that a peptide corresponding to the sequence of 2nd extracellular loop of the human β1-adrenoceptor (β1-peptide) as an autoantigen was able to induce an autoimmune cardiomyopathy in rabbits (JMCC 29: 641, 1997), and β-blockade protected the myocardial injury induced by this autoimmune mechanism (ISHR 1998, Greece). In this study, we investigated the effect of angiotensin converting enzyme inhibitor (ACEI) on β1-peptide induced cardiomyopathy in rabbits.

[Methods] NZW rabbits were divided into 4 groups. 1) control group (n = 6): saline injection, 2) β1-immunized group (n = 8): β1-peptide injection, 3) ACEI group (n = 6): lisinopril (3 mg/day) orally and saline injection, 4) ACEI + β1-immunized group (n = 7): lisinopril (3 mg/day) orally and β1-peptide injection. Study duration was one year. Saline or peptide was injected once a month.

[Results] All rabbits in both β1-immunized groups had the high titre of anti-β1-adrenoceptor autoantibodies in their sera, whereas none of the sera from all rabbits in control and ACEI groups was positive. Rabbits in the β1-immunized group showed an increase in heart weight, wall thinning and dilatation of bi-ventricles. On the other hand, rabbits in ACEI group and ACEI + β1-immunized group had normal heart weight and shape. All rabbits in β1-immunized group showed multifocal degeneration and necrosis of myocardial cells with moderate infiltration of inflammatory cells. In ACEI group, two rabbits showed no histological changes in the heart, but four showed an occasional focus of scant mononuclear cell infiltration with normal myocardial cells. In ACEI + β1-immunized group, five rabbits showed slight mononuclear cell infiltration with mild degeneration of myocardial cells.

[Conclusion] ACEI (lisinopril) protects the myocardium from injury induced by autoimmune mechanism against β1-adrenoceptor.

NITRIC OXIDE IN HUMAN VASOMOTION AND VENTRICULAR FUNCTION

803 Cardiac sympathoexcitatory effects of nitric oxide synthase inhibition in humans

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It is now clear that nitric oxide (NO) plays an important part in the regulation of sympathetic vasoconstrictor outflow to the peripheral vasculature, but little is known regarding its role in the regulation of sympathetic outflow to the heart. To provide such evidence, we examined, in 8 healthy subjects, effects on heart rate and arterial pressure of NO-synthase inhibition by systemic L-NMMA infusion (0.5 mg/kg/min for 10 min), in the presence and absence of parasympathetic blockade (atropine 0.4 mg/m^2 bolus, followed by 0.3 mg/kg/h for 30 min). The major new finding was that L-NMMA infusion which increased mean arterial pressure by roughly 15 percent, had markedly differential effects on heart rate in the presence and absence of parasympathetic blockade; when infused alone, heart rate decreased by 16 $\pm$ 3% ($\bar{X} \pm$ SE, $P < 0.01$ vs. baseline), whereas when infused during atropine infusion, the L-NMMA-induced increase in arterial pressure was accompanied by a 15 $\pm$ 4% increase in heart rate ($P < 0.01$ vs. L-NMMA alone). This chronotropic effect is sympathetically mediated, because it was abolished by coinfusion of propranolol. These findings provide the first evidence for a cardiac sympathoexcitatory effect of NO-synthase inhibition in humans. We speculate that in clinical conditions associated with a defect in NO-synthesis, exaggerated cardiac sympathoexcitation may contribute to augmented cardiovascular morbidity and mortality.

804 Critical role of endogenous nitric oxide on systolic and diastolic function in hypertensive cardiomyopathy

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The role of nitric oxide synthase in the myocardial dysfunction of hypertensive cardiomyopathy is unclear. We used an in vivo model of perinephritic hypertensive (PHT) dogs to linearly correlate changes in cardiac and vascular contractile parameters with NOS activity and sensitivity to NOS inhibitors.

Methods: Echocardiographic and invasive parameters of systolic and diastolic function were acquired in 9 mongrel dogs before and 8 weeks after kidney wrapping. At both time points all measurements were repeated after 48 h intravenous infusion of the NOS inhibitor, L-NAME (10 μg/kg/min) with a mini-pump. NOS activity (^{3}H-citrulline formation) in heart extracts and contraction of coronary and mesenteric macro- and micro-vessels measured by video-microscopy were analysed in additional dogs at 0, 3 and 8 weeks.

Results: In normotensive dogs, 48 h L-NAME induced an increase in BP (mmHg; 116 ± 4 to 128 ± 2°) and SVR (mmHg/ml/min.10E4; 286 ± 43 to 436 ± 25*) while systolic and diastolic functions were unaltered. PHT dogs had severe high BP (141 ± 6°) but normal SVR (289 ± 44). They had increased LV mass (g; 152 ± 5° vs 124 ± 4) with enhanced systolic parameters but impaired diastolic relaxation (T1, msec; 26.6 ± 0.9° vs 22 ± 1).Their coronary and mesenteric vessels displayed maximal contraction to KCl similar to controls, but an impaired endothelium-dependent relaxation to Acetylcholine at 8 w (% max. contraction; 9.1 ± 4.8 vs 32.4 ± 6.5°). Ca-dependent NOS activity was transiently increased at 3 W, but sharply decreased in all 4 heart chambers at 8 w (LV, fmol/min/mg; 16.9 ± 1 down to 0.1 ± 0.1*). In PHT dogs, L-NAME infusion markedly reduced both diastolic (T1; 31.9 ± 1.3*) and systolic (DP40, sec^{-1}; 47.9 ± 2.2° vs 60.6 ± 3.6) functions (°: P < 0.05; *: P < 0.01).

Conclusion: PHT dogs develop a time-dependent impairment of endothelial function and Ca-dependent NOS activity in the myocardium. Their super-sensitivity to NOS inhibitors suggests a critical compensatory role of myocardial NO to maintain systolic and diastolic function in the face of myocardial hypertrophy.

805 Cardiac vagal modulation by endogenous nitric oxide in humans

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The control mechanisms of the cardiac autonomic nervous system remain poorly defined. Animal data suggest that endogenous nitric oxide (NO) modulates this system, acting both as a vagotonic and a sympatholytic agent. We have used heart rate variability (HRV) to assess the role of endogenous NO in the baroreflex modulation of human cardiac autonomic activity.

Fourteen healthy male volunteers, aged 20–36 years (mean = 26), were studied in a single blind, crossover protocol. In random order, we administered equipressor infusions of the nitric oxide synthase inhibitor N^G-methyl-L-arginine (L-NMMA, 3 mg/kg/hr) or a control vasoconstrictor, phenylephrine (Phe, 0.2–1.4 μg/kg/min). Analysis of HRV was performed on 256 beat segments of ECG data digitally recorded under fixed metronomic breathing at baseline (saline infusion) and then at a stable mean arterial pressure (MAP) measured by Portapres during the pressor infusion. This was repeated on each of the two study visits, 2–14 days apart. Time domain indices of high frequency (vagally mediated) HRV included RMSSD and pNN50. Autoregressive modelling was used to assess spectral power at low frequency (LF, combined sympathetic and vagal activity) and at the respiratory frequency (HF, vagal activity) in normalised units (nu). Results are expressed below as the absolute increase from baseline values (mean ± SD):

	MAP (mmHg)	Mean RR (ms)	RMSSD (ms)	pNN50 (%)	HF (nu)	LF (nu)
Phe	11 ± 3	156 ± 110	51 ± 48	14 ± 12	9 ± 8	−9 ± 7
L-NMMA	11 ± 5	100 ± 55	23 ± 32	6 ± 14	−1 ± 7	−2 ± 8
p value*	0.8	0.08	<0.01	<0.05	<0.01	<0.05

*Wilcoxon signed ranked test

In conclusion, L-NMMA infusion significantly attenuated baroreflex mediated increases in HRV indices of cardiac vagal activity compared to a control infusion of phenylephrine. These results suggest that endogenous NO augments cardiac vagal control of heart rate in humans.

806 Diagnostic value of plasma nitrate in patients with septic shock

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In experimental models of sepsis it has been demonstrated that following induction of nitric oxide synthase (iNOS) circulating levels of serum nitrate increase and that inhibition of iNOS by either glucocorticoids or NOS inhibitors decrease nitrate, paralelled by improvement of septic circulatory situation. However, these data could not be reproduced in humans. We therefore aimed to test whether or not nitrate represents a new diagnostic marker for patients with septic circulatory situation. 424 consecutive patients admitted to an intensive care unit (ICU) were studied on a total of 2274 days. Every morning each patients was clinically assessed via a score invented by Bone et al. to confirm or reject the diagnosis of septic shock. In addition, in septic patients the extent of septic circulatory situation was graded using the Düsseldorfer Sepsis Severity Score (DSSS, <7 points: non-septic, and >7 points: septic). Plasma nitrate was determined every day using the Griess reaction after reduction of nitrate to nitrite. Only those patients (n = 159 studied on 1143 observation days) on intravenous standardized nutrition and with serum creatinine levels < 2 mg/dl were included into the final study population. Serum nitrate was higher in patients with septic shock as compared to non septic patients: 51 ± 6 vs 36 ± 2 μmol/L. Plasma nitrate increased with progressive shock. An increase or a decrease in sepsis score was associated with concomitant changes in nitrate: r = 0.46, p < 0.0001. Mortality rate increased with increasing nitrate levels. The probability of dying was highest in those patients with nitrate levels exceeding 50 μmol/L.

Conclusions: Levels of plasma nitrate are increased in patients with septic circulatory situation suggesting sepsis associated induction of nitric oxide synthase in humans. Changes in nitrate are tightly coupled to changes in septic circulatory situation and therefore nitrate may represent a diagnostic parameter to monitor septic shock in individual patients.

807 Calcitonin gene-related peptide induced vasodilation depends on the release of nitric oxide

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Aims: To investigate *in vivo* in man whether nitric oxide (NO) and/or vasodilating prostaglandins (PG) contribute to the vasodilation induced by calcitonin gene-related peptide (CGRP).

Methods: Venous occlusion plethysmography was used to assess the forearm blood flow (FBF) response to increasing infusion rates of CGRP (3-10-30 ng/min/dl forearm) into the brachial artery of 24 healthy subjects. Dose-response curves were constructed before and during the co-infusion of placebo (NaCl 0.9%), the NO-synthase inhibitor N^G-monomethyl-L-arginine (L-NMMA, 0.2 mg/min/dl forearm) and the PG-synthase inhibitor indomethacin (5 μg/min/dl forearm). Forearm vascular resistance (FVR) was calculated (FVR = mean arterial pressure/FBF) and presented as percentage change from baseline in FVR (ΔFVR). Dose-response curves were compared using ANOVA with repeated measures and Wilcoxon's matched-pairs signed-rank tests. Data are presented as mean ± SEM.

Results: CGRP (n = 24) increased FBF from 2.6 ± 0.3 at baseline to 5.4 ± 0.5, 9.8 ± 0.7 and 14.1 ± 1.1 ml/min/dl forearm, respectively (p < 0.001). Repeated infusions of CGRP with placebo (n = 8) or indomethacin (n = 8) showed comparable responses. L-NMMA (n = 8) decreased CGRP-induced ΔFVR (p < 0.001) (Table, NS = not significant).

CGRP (ng/dl forearm/min)	ΔFVR (%) Placebo	Δ FVR (%) L-NMMA	P-value
3	−61 ± 3	−26 ± 5	<0.05
10	−78 ± 2	−57 ± 4	<0.05
30	−84 ± 3	−81 ± 2	NS

Conclusions: The intra-brachial infusion of CGRP results in a dose-dependent and repeatable decrease in FVR. CGRP-induced vasodilation in man does not involve PG but depends, at least in part, on the release of NO.

808 Chronic ace-inhibition modulates vascular extracellular superoxide dismutase activity in patients with coronary artery disease: a new mechanism for increased bioavailability of nitric oxide after ACE-inhibition?

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Endothelial function, including flow-dependent, endothelium-mediated vasodilation (FDD), is impaired in patients with coronary artery disease (CAD). Increased inactivation of nitric oxide (NO) by oxygen free radicals has been suggested as an underlying mechanism. We hypothesized that chronic ACE-inhibition enhances the vascular activity of extracellular superoxide dismutase (EC-SOD), the most important antioxidant enzyme system of the human vessel wall, leading to increased bioavailability of NO.

Methods: Endothelial-bound EC-SOD activity and FDD of the radial artery were determined at baseline and after 4 weeks of ACE-inhibition with ramipril (5 mg bid) in 15 patients with angiographically documented CAD. EC-SOD has a strong affinity to heparin and was released from endothelium to plasma by heparin bolus injection (SOD I: 1000 IE; SOD V: 5000 IE) and was determined in the plasma by a combination of chromatography and a spectrophotometric SOD-assay. High resolution ultrasound (10 Mhz; precision 2 μm) and Doppler (8 Mhz) were used to measure radial artery diameter and blood flow (ml/min) at rest and during reactive hyperemia (diameter change in % representing FDD). To determine the portion of FDD mediated by NO the effect of the NO-synthase inhibitor N-monomethyl-L-arginine (NMMA; 7 μmol/min i.a.) on FDD was determined and the Delta-value was calculated (Delta-FDD = FDD at baseline minus FDD after NMMA).

Results: Endothelial-bound EC-SOD activity and the portion of FDD mediated by NO were significantly increased after chronic ACE-inhibition.

	FDD (%)	FDD-NMMA (%)	Delta-FDD (%)	SOD I (U/ml)	SOD V (U/ml)
Control	6.7 ± 0.5	4.2 ± 0.4	2.6 ± 0.5	0.6 ± 0.2	3.9 ± 1.1
4 weeks	10.7 ± 0.6*	4.3 ± 0.5	6.4 ± 0.5*	2.0 ± 0.3*	14.1 ± 1.3*

(all data ± SEM; *p < 0.01 vs control)

Conclusion: In patients with CAD chronic ACE-inhibition increased vascular activity of EC-SOD, the most important antioxidant enzyme system of the human vessel wall, by up to 350%. This represents a potential underlying mechanism for the increase of the bioavailability of NO.

PERIPHERAL VASCULAR INTERVENTIONS

809 Transluminal recanalization of deep vein thrombosis: long-term results

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Systemic thrombolysis of deep vein thrombosis is contraindicated in patients with recent surgery or major trauma due to the high risk of major bleeding.

Methods: In 28 patients (pts) (15 men, 13women, age 29 ± 12 years) with deep vein thrombosis (clinical duration 8.9 ± 6.3 days) and contraindication against systemic thrombolysis we performed a local low dose thrombolytic therapy. A temporal vena cava filter was placed via a brachial vein to prevent pulmonary emboli, and a perfusion catheter was placed either in the iliac (n = 13) or superficial femoral vein (n = 15). Urokinase was infused in a dose of 30000 IU/h up to 5 days. Doppler measurements were performed daily to control flow in the veins. In addition local fragmentation of the thrombi was done in 16 (57%) pts 24 to 96 hrs after start of the lytic therapy. Hemoglobin and hematocrit were controlled every 6 hrs: no transfusions were necessary. Recanalization was successful after 5 days in all iliac and 11/15 femoral veins. All pts were anticoagulated with a oral phenprocoumon for at least 6 months and were advised to wear compression stockings. A control of the functional results and a vein doppler was performed 12 to 36 months after the thrombosis (21 ± 7.8 months). All venous segments that had been successfully recanalized were still open. A persistent swelling of the leg was observed in 4 pts (14%). None of the pts developed extensive varicosis or hyperpigmentation as a sign of postthrombotic syndrome.

Conclusion: Local intraluminal thrombolysis is a highly effective therapy for patients with deep vein thrombosis and contraindication against a systemic thrombolytic therapy. Long-term results are excellent in these pts.

810 Percutaneous intervention in haemodialysis fistula disease: is it the answer?

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Failing dialysis vascular access sites pose a serious challenge in the management of patients on chronic hemodialysis (HD). Vascular access failure occurs in >30% of cases within 6 months after placement and represents the leading cause of morbidity in the HD population. Prolonged patient survival has added emphasis to the importance of maintaining patent vascular access. Surgical repair consumes the limited vascular sites available. Percutaneous intervention by angioplasty (PTA) is being performed in HD shunts, but has not been adequately evaluated. We present our experience of 5 years in PTA of failing HD vascular access sites. From 1/94 to 12/98, PTA was performed in 288 patients (51% female; mean age 67; range 25–90). Significant co-morbidities included atherosclerotic heart disease in 43%, hypertension in 81% and diabetes in 48%. Vascular access sites treated were 315, of which 40% were Brescio-Cimino arteriovenous fistulas and 60% were PTFE grafts. There was history of prior intervention at the same site, in 32%. The average age of the graft was 16 months (range 1–28 months). Nearly 35% were referred for elevated venous resistance or extremity swelling. The remainder presented with access site thrombosis, which included arterial thrombotic occlusions and multiple stenoses along the arterial and/or venous tracts of the HD fistulas. All patients received IV heparin bolus of 2,000–7,000 U. Adjunctive urokinase was administered in 20.4%. Balloon angioplasty was performed with 3-minute dilatations utilizing 6–8 mm balloons. Stent was deployed in 195 (62%). Once effective flow was restored, all catheters were removed and pressure was applied to the site.

Results: Procedural success was achieved in 99.3%. Clinical success (graft successfully used for HD 3 times or remaining patent for 1 week) was 95.1%. One patient (0.3%) required emergency surgery for vessel rupture. Two dissections resulted in hematomas, which were treated with prolonged balloon inflation; 2 minor dissections healed spontaneously. There was no incidence of pulmonary embolism. Mean hospital stay was 1.59 days. Functional patency of the graft was assessed by flow during dialysis and calculated as a measure of the ratio of urea clearance to dialysis time (k/tv ratio; normal range 1.2–1.4). The mean pre-PTA KTV ratio was 0.42 ± 0.001, which increased to 1.24 ± 0.60 post-PTA. The mean primary patency rate was 86% at 6 months and 72% at 2 years. Only 10.4% of the patients required a repeat intervention during the follow up period (mean 2.4 years). No shunt infection was reported.

Conclusions: (1) The application of endovascular therapies for PTA of the arterial limb and venous outflow stenoses in HD access fistulas can significantly prolong its patency and function. (2) This is helpful in increasing the life span and improving the salvage rate of the access sites. (3) Our series did not demonstrate an increase in infection rate with percutaneous intervention by either PTA or ST.

811 Endoluminal treatment of sub-clavian occlusive diseases: percutaneous angioplasty and stenting

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Purpose: To review feasibility, risks, long term results of PTA of subclavian artery with and without Palmaz stent placement.

Methods: Over 10 years, 135 patients (pts) underwent percutaneous treatment of sub-clavian occlusive diseases. M: 75, F: 60, mean age: 63 ± 11 years (27–87). Indications: superior limb ischemia (n = 70), vertebro-basilar insufficiency (n = 72), vertebro-basilar and superior limb ischemia (n = 30), coronary steal (n = 9). Asymptomatic patients with severe coronary diseases (before internal mammary bypass) (n = 14), 110 stenosed arteries, 25 occluded. Right sub-clavian artery: 19 (11%), left: 112 (83%), innominate: 4 (3%). Mean % stenosis: 80.9 ± 7.4 (70–100). Mean lesion length: 23.5 ± 8.7 mm (10–50). Access way: retrograde femoral (n = 95), brachial artery (n = 26) access or both (n = 14), with balloon dilatation of the lesion. Since 1989 Palmaz stents were implanted for 66 lesions in case of sub-optimal PTA (n = 39), important dissection (n = 9), restenoses (n = 3). Primary stenting performed for 15 lesions.

Results: 122/135 lesions successfully treated (94%), 12 occlusions were recanalized (48%). 3 procedural complications (1.5%): 1 T.I.A., 1 major stroke, 2 arterial thromboses: 1 24 hours after the procedure, treated medically, 1 at 30 days, treated by new PTA. 19 restenoses (14%) were treated by new PTA (n = 5), by PTA + stent (n = 7), by surgery (n = 7). Primary (PI) and secondary patency (PII) for all treated lesions (n = 135) at 8 years follow-up: 76.6 and 83.7%. Without stent, respectively 67.5 and 75.5%, with stent 88.2 and 96.1% (p < 0.01). PI and PII for recanalized lesions (n = 125), 83.1%, 90.8%, without stent: 79.1%, 88.5%, with stent: 88.2% and 96.1% respectively (p = ns).

Conclusion: PTA with/without stenting is safe, effective to treat sub-clavian artery occlusive diseases with good long term patency. Occluded vessels do not respond well to PTA. Stents (implanted only for suboptimal PTA results) do not seem to improve long term results.

812 Efficacy of ultrasound thrombus disruption in vivo

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Recently, we have shown that the *in vitro* treatment of thrombi with continuous low frequency ultrasound (US), in combination with streptokinase (SK) or alone, is a potent method of clot destruction. The present study was aimed at testing efficacy and safety of intravascular (IV) destruction of thrombi *in vivo* by using a novel catheter-based system for US treatment.

Materials and methods. Acute IV thrombosis was modeled on *a. femoralis* in the 15 mongrel dogs. In 2 h after thrombus formation, thrombolysis was performed by: (1) IV catheter-delivered US treatment (22 kHz, 10 W/cm^2); (2) a combined administration of SK (35,000 U/kg) and US of the same intensity. Condition of the thrombus and distal circulation were examined before the thrombus destruction and 1, 5, 40, 90 and 120 min after its destruction, using the methods of angiography, impedance reography and direct measurement of blood AP in the distal to the thrombus formation zone. Blood coagulation parameters were also assayed. Moreover, histological examination of vessel wall was performed after thrombus destruction.

Results. Intra-arterial application of US resulted in fast destruction of the thrombi. Additional administration of SK did not decrease significantly the time of US thrombus disruption (1.5 ± 0.8 min for US, 1.2 ± 0.6 min for US + SK, $p > 0.05$). However, proteolytic cleavage of fibrin was enhanced (9.1 ± 0.8 μg/ml of D-dimers for US, 13.3 ± 3.3 μg/ml for US + SK, $p < 0.05$). After the US treatment, circulation was always restored. However, complete destruction of thrombi, with no signs of thromboembolia of distal microcirculation, was achieved only for combined application of US and SK. Blood coagulation tests revealed an US-induced activation of thrombin system, the effect was less significant in the presence of SK. Histological examination did not show the thermal, cavitational damage of vessel wall, as well as its perforation after US treatment.

Conclusion. Combined administration of US and SK is an efficient and safe method for the treatment of peripheral vessel thromboses.

813 Infiltration-thrombolysis with recombinant tissue-type plasminogen activator and prostaglandin E1 in alternating order for recanalisation of peripheral arterial occlusions

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Background: The efficacy, duration and dosages for intra-arterial thrombolytic treatment is still under discussion, especially for the recanalisation of chronic peripheral artery occlusions. The combination of low dose recombinant tissue-type plasminogen activator (rt-pa) and prostaglandin E1 (PGE1) for long-term intra-arterial thrombolysis has not been described before. We did a retrospective analysis to look for the use of the continuation of the local intra-arterial thrombolysis if a short-term thrombolysis up to 3 h during an intervention was not successful.

Methods: From 323 patients with peripheral arterial occlusions 142 could be effectively thrombolysed with intra-arterial rt-pa in the first 3 h. In 119 patients the thrombolysis was continued as a long-term therapy (3 mg rt-pa in 3 h followed by PGE1 (2.1 ml/h for 3 h, concentration: 20 microgram/50 ml NaCl) in alternating order). Treatment times ranged from 1 to 13 days (2.8 ± 2.2). If necessary, angioplasty was performed after a wire was passed through the lumen.

Results: Long-term thrombolysis succeed in complete recanalisation in 72 (61%) patients and partial recanalisation in 28 (23%) out of the 119 patients. Recanalisation at all occurred up to the 7th day whereas 91.7% showed racanalisation within the first 4 days. 10 patients suffered from severe bleedings. All bleedings occurred in the first 24 h after extraction of the catheter. No bleeding occurred during thrombolytic treatment.

Conclusion: The combination of low dose rt-pa and PGE1 for infiltration-thrombolysis is useful for long-term thrombolysis in patients with peripheral arterial occlusion. Treatment can reach up to the 4th day without increasing the risk of complications.

814 A new cerebral protection device for carotid angioplasty and stenting: first clinical experience with the percusurge GuardWire™

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Purpose: To study feasibility and safety of carotid angioplasty and stenting with cerebral protection with the new PercuSurge GuardWire™ device.

Methods: The device consists of a 0.014″ GuardWire™ with protection balloon incorporated into its distal segment. The proximal end of the hypotube wire incorporates a Microseal™ allowing inflation/deflation of occlusion balloon. Angioplasty + stenting are performed under cerebral protection. The dilated area is then cleaned before deflation of the protection balloon, either by aspiration, or by a flushing, derivating flow towards external carotid artery. Blood samples are analyzed. 35 carotid angioplasty + stenting procedures performed using this technique in 31 high-risk pts (M: 25, F: 6, mean age: 70.8 ± 6.7 years (56–86)) with implantation of 30 Palmaz stents, 8 Expander stents. Mean % stenosis: 82.2 ± 8.3 (70–96), mean lesion length: 16 ± 8.4 (6–50). 19 calcified lesions, 22 ulcerated, 18 echolucent on Dupplex scan. Contralateral internal carotid artery was stenosed (n = 8) or thrombosed (n = 2).

Results: Immediate technical success in all patients. Very good tolerance of occlusion (34/35). 1 case of intolerance (patient with contralateral carotid occlusion). No neurological complication. Occlusion balloon was deflated between pre-dilatation and stenting in 11 patients. Mean pre-dilatation occlusion time: 324.7 ± 141.1 sec (162–540). Mean stent implantation occlusion time: 602.5 ± 212.5 sec (372–905). In 29 cases occlusion balloon remained inflated during the whole procedure. Mean occlusion time: 550.4 ± 212.7 sec (245–991). Debris aspirated in all patients.

Conclusion: Cerebral protection with the PercuSurge GuardWire™ device seems safe/efficient to reduce risk of cerebral embolization during carotid angioplasty with stent implantation. It is easy to use, and should be developed in the near future to enlarge carotid angioplasty indications and make the procedure safer and an alternative to surgery. Larger studies are expected.

RISK FACTOR MANAGEMENT

826 Does the provision of support by a cardiac rehabilitation liaison nurse within the immediate discharge period improve patient's recovery at 6 months following first myocardial infarction?

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Introduction: There is increasing evidence that comprehensive cardiac rehabilitation (CR) programmes following acute myocardial infarction (MI) can reduce mortality and morbidity, reduce psychological distress, enhance secondary prevention and improve quality of life. In contrast when such a service is not provided there is evidence of poor progress and recovery from disease, which may result in a preoccupation with physical symptoms, a general loss of confidence, and often inappropriate use of health services. The immediate post discharge period has been identified as a problematic time for the patient (and partner), when they require but do not necessarily receive support from health care staff. This may be exacerbated by a lack of information transferred by the health care staff to the primary care sector. This study therefore aims to evaluate whether the provision of education and support by a specialist CR Liaison nurse in the immediate discharge period improves recovery.

Subjects and Methods: 100 patients admitted to Ninewells Hospital with a definite diagnosis of MI have currently entered the study and been randomly assigned to either normal care or the intervention group. Those assigned to normal care will receive CR via the existing programme i.e. individual education and counselling by the CR nurses during the in-patient phase and an invitation to attend the out patient educational programme. All these patients will receive telephone follow up in the normal manner within 1 week of discharge and they will have access to the rehabilitation advice line. In the intervention group the patients will be seen by CR liaison nurse at home within 1 week of discharge, again on week 3 of discharge and contacted by telephone on week 5. These patients will also have access to the rehabilitation advice line. A comparison of risk factor modification, mood, knowledge, health status and quality of life will be made between the two groups at 6 and 12 months. Health service utilisation will also be evaluated.

Results: The results of the 6 month outcomes of these two groups of patients will be presented to determine any differences in outcomes in terms of mood, knowledge, health status, quality of life, risk profiles and health service utilisation.

Conclusion: These results will be used to inform clinicians and managers within primary and secondary care of the impact of the CR liaison nurse service on recovery following MI. This will contribute to the development and provision of a high quality CR service to meet the varied needs of patients following first MI.

827 Age and preoperative comorbidities as factors influencing, on the lenght of icu stay for cardiac surgery patients

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The improvement in quality of life and a more public-health education have contributed to increase the elderly population who undergo cardiac surgery. In order to know the relationship of the age and the preoperative comorbidites with the length of ICU stay, we perfomed a descriptive, transversal, and retrospective study for patiens after cardiac sugery.

Methods: 376 patients, which a postoperative lenght of stay > 3 days were selected from the population treated during the last three years, 1996–98. They were divided into four groups base on the age: <60, 60–69, 70–79 and >80 years. The datas colletion were categorized into the following sections. Demographic characteristics, preoperative factors, operative variables and postoperative complications.

Results: there has been an increase in the lenght of ICU stay, being of 3.08 in 1998, however the proportion of patients >80 years has risen as well. The observed preoperative risk factors influencing the length of stay were: creatinine > 2 mgrs/dl, ejection fraction < 50%, diabetes mellitus, and hypertension, along with atrial fibrillation and need for supplemental oxigen

Years	High outcomes patients	Stay average	Readmiting	Cases per year > 3 days			
				<60	60–69	70–79	>80
1996	699	2.71	32 OF 28	27	37	43	2
1997	731	2.66	37 OF 33	29	46	39	8
1998	749	3.08	28 OF 25	25	48	56	11

In conclusion, the elderly and comorbidities increase the risk of postoperative complications and the length of ICU stay, therefore a more intense nurse care is required.

828 Experience of and need for cardiac rehabilitation care after cardiovascular disease in 490 women

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Background: Despite the high incidence of cardiovascular disease in women, there is a paucity of nursing research that addresses women's needs for cardiac rehabilitation care. Women are less prone to attend cardiac rehabilitation programs than men are, they also have a higher drop out rate before completion of the rehabilitation programs. Few studies have investigated the reasons why.

Objective: The purpose of this study was to survey women's reported experience of and need for rehabilitation after AMI, PTCA or CABG.

Method: An exploratory study was carried out. A sample of 490 eligible women who had suffered from AMI, or undergone PTCA or CABG took part in the study. A 282-item questionnaire at an ordinal scale level was used.

Results: The 490 women attended one or more parts of a cardiac rehabilitation program; in a physical training group n = 182 (37%), in a dietary modification group n = 48 (10%), in a conversation group n = 73 (15%), in a smoking cessation group n = 5 (1%) and in a stress modification group n = 35 (7%). Smokers were n = 54 (11%) and ex-smokers n = 153 (31%). Smoking cessation group was considered as the most important part of cardiac rehabilitation program and in decreasing order of importance physical training group, stress modification group, dietary modification group and last the conversation group.

Conclusion: Smoking cessation group was considered to be the most important part in cardiac rehabilitation program, however only 1% of the smokers and ex-smokers had attended a smoking cessation group.

829 Risk factors, clinical and angiograpic characteristics in young patients (≤45 years) recovering from acute myocardial infarction

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AMI in young adults is rare. There are few data regarding the angiographic findings in young AMI pts compared with older ones.

Methods: We compared the baseline characteristics, risk factors and angiographic findings of 761 consecutive pts with AMI; 120 young (age ≤ 45 yrs) and 641 older (age > 45 yrs) pts hospitalized between 1986–1996. Coronary angio was performed within the first 100 days after AMI. CAD was defined as ≥50% stenosis.

Results (see table; numbers are percentages):

	Age ≤ 45 yr	Age > 45 yr	p value
Age, yrs (mean ± SD)	41 ± 4	61 ± 9	<0.0001
Males	92	77	0.003
No. Risk factors (mean ± SD)	2.1 ± 1.1	1.9 ± 1.2	ns
Current smokers	68	31	<0.0001
Positive family history	43	29	0.003
Hypertension	18	37	<0.0001
Diabetes mellitus	13	21	0.02
Hyperlipidemia	50	50	ns
Obesity (BMI > 28 kg/m^2)	19	26	0.1
Inferior location	57	42	0.003
Q-wave MI	83	67	0.008
Thrombolysis	57	42	0.003
Angiographic findings:			
Normal/Nonobstructive	8	2	
Single vessel disease	46	20	<0.0001*
Multiple vessel disease	46	78	
Lesions per patient† (mean ± SD)	2.4 ± 1.8	3.4 ± 2.0	<0.0001
Proximal lesions‡	67	83	<0.0001
Proximal LAD	39	63	<0.0001

*Comparing between the 3 categories of diseased vessels. †No. of segments with stenosis ≥ 50%, using a 17 coronary segments/pts model. ‡Significant stenosis in ≥1 of the proximal segments of LAD, LCx, RCA.

Conclusions: Compared with older pts, young pts with AMI are more often current smokers, with a family history of CAD. They presented more often with first AMI, Q-wave MI, inferior location and had a better residual LV function. They had less diffuse CAD and had less often proximal coronary lesions.

830 Presence of risk factors and risk factor modification in women undergoing coronary revascularization

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Findings suggest that effective secondary prevention programs to control cholesterol in women after revascularization should include smoking cessation and weight loss components. The aim of our study was to determine to which extent those women of our area modify their risk factors.

Methods: Risk factors for CAD were examined in 182 women (mean age 62.4 ± 9.6 years) at the time of coronary angiography and at least one year after revascularization (113: CABG, 69: PTCA). Presence of risk factors at the time of coronary angiography were as follow: total cholesterol > 200, 65.6%; and 45% were taking statins; smoking (current), 8.24%; diabetes, 20.3%; hypertension, 36.3% obesity (BMI > 30%, 21.4%; BMI > 25% and <30%, 37.5%; family history, 14%. All except one were postmenaupausal

Results: Risk factor modification at least one year after intervention was assessed in all 182 women and lipids were measured in 119 women. Antihypertensive and antidiabetics drugs were used by all women stating they had hypertension or diabetes respectively. 25% of women did not quit smoking after intervention. During follow-up 87% of women had TC < 200 mg/dL and under statin treatment were 71% and in none the target level of LDL cholesterol < 115 mg/dL was reached. Decrease of at least 20% in BMI was achieved by 5 women. None was taking hormone replacement therapy Almost all women (85%) were taking low-dose aspirin and b-blockers (55.5%).

Conclusions: The inadequate cholesterol management is due to insufficient LDL lowering and not from failure to initiate statins. Smoking and obesity in women of our area do not constitute common risk factors compared to other countries.

831 Adults in Poland underestimate cardiovascular risks of sedentary life style and profits of regular physical activity

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The aim of our study was to assess knowledge about life style habits predisposing to cardiovascular (CV) diseases and arterial hypertension (HT) among adults in Poland. Thus, we conducted a cross-sectional survey based on a questionnaire interview on a representative sample of 1664 men and women aged 18 years and over. The subjects were selected from Polish population by stratified and cluster random sampling with quotas. In all of them blood pressure and anthropometric parameters were measured. The respondents answered the following questions: What causes of HT and CV diseases do you know? What methods of prevention of HT and CV diseases do you know? The results were analysed according to age, sex, education, income, place of living, presence of hypertension and/or obesity.

Respondents mentioned the causes of HT and CV diseases in the following order: stress (39%), overeating (37%), alcohol abuse (25%), smoking (22%), coffee (9%), salt excess in diet (8%), sedentary life style (7%), oral contraceptives (5%), heredity (4%). A list of preventive methods started with "taking drugs" (50% !!!). The subjects also mentioned regular style of life (22%), limitation of fat in diet (23%), weight reduction (14%), alcohol restrictions (14%), giving up smoking (13%), regular physical activity (13%), and reduction of salt intake (10%). They have learnt about these preventive methods from physicians (43%), radio and TV (34%), newspapers and magazines (34%), and from relatives (21%). School was hardly ever mentioned (<1%). The results show that adults in Poland underestimate cardiovascular profits of regular physical activity and risks resulting from lack of exercise. Our study univocally points out the tasks relevant to education and prevention of HT and CV diseases in Poland.

LONG-TERM OUTCOME OF PERCUTANEOUS INTERVENTIONS

841 A randomized comparision of elective stenting versus balloon angioplasty with two years follow-up

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Angioplasty or Stent (AS) Trial is a Polish multicentre, randomized comparision of elective, high pressure PS 153 stenting (S) without IVUS guidance with balloon angiolpasty (BA) of single de novo lesions in native coronary arteries.

Patients: between Feb and Dec 1996 a total of 388 pts were enrolled, 192 in S group and 196 in BA group. Both groups were well matched with regard to all clinical and angio parameters. Ticlopidine 250 mg bid and ASA 300 mg/day were used in both arms.

Results: the procedural success did not differ significantly (96.35% vs 95.41%, p. = NS). There were no stent thrombosis. At six months on angio restudy MLD was 1.82 ± 0.63 mm (S) vs 1.57 ± 0.58 mm (BA), p. = 0.004; restenosis rate (>50% diam) was 18.82% (S) vs 24.74% (BA), p. = 0.05.

At two years adverse event (AE) rates were as followed:

AE	S	BA	p =
Death	0.052%	0	NS
Cerebrovacs. accident	0	0	NS
QMI	1.04%	1.02%	NS
Target lesion rev. (TLR)	16.15%	24.5%	0.05

The event-free survival (no death, cerebrovascular accident, QMI or TLR) at 6, 12 and 24 months was: 86.77% vs 78.84%, 84.13% vs 76.70% and 83.07% vs 73.54%, p. = 0.0172 (Log-Rank), for S group and BA group respectively.

Conclusion: High pressure elective coronary stenting with antiplatelets regimen eliminates stent thrombosis. In comparision to balloon angioplasty angiographic restenosis rate is significantly lower at six month. During two years of follow-up event-free survival of the stented patients was better because of 34% reduction in repeat revascularization rate.

842 Minimal invasive bypass surgery versus stentimplantation in proximal high-grade lesions of the left anterior descending coronary artery

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Background: Minimal invasive bypass surgery (MIC) has been shown to yield comparable results to conventional bypass grafting with less operative trauma. Therefore it may be considered an alternative treatment to stentimplantation (S) in patients with proximal high grade lesions of the Left Anterior Descending Coronary Artery (LAD).

Methods: 136 patients (P) with high grade lesion of the proximal LAD were randomized between MIC (65) and S (71). Clinical symptoms were assessed by CCS-class. After 6 months P underwent repeat coronary angiography, coronary lesions were measured by quantitative coronary angiography.

Results: At baseline all P had stress induced angina pectoris (CCS: MIC: 2.6 ± 0.8; S: 2.7 ± 0.9). After revascularization 98% of P were free of angina pectoris. During MIC 3 P (4.6%) were converted to conventional bypass surgery with sternotomy and 2 P (4%) required repeat operation due to stenosis of the distal anastomosis within one week. Acute stent thrombosis occurred in 2 P (3%) after S. After 6 month 18/50 P (36%) in the S-group showed in stent restenosis > 50%, 14 P (28%) underwent re-PTCA. In the MIC-group 5/33 P (15%) showed stenosis > 50% of the distal anastomosis, 3 P (9%) required PTCA (p = 0.05). Relieve of angina at 6 months was more complete in MIC as compared to S (CCS: 0.21 ± 0.54 vs 0.73 ± 1.13; p < 0.05), although physical work capacity did not differ between the groups (S: 120 ± 35 Watt; MIC: 130 ± 33 Watt; p: n.s.)

Conclusion: In P with high grade stenosis of the proximal LAD both MIC and S yield excellent results with few clinical events. Relieve of angina pectoris is more complete in MIC. In the face of reduced operative trauma, MIC may be considered an alternative treatment to S in these P.

843 Continued benefit of coronary stenting versus balloon angioplasty: five-year clinical follow-up of BENESTENT-I trial

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Objectives: This study sought to determine the 5-year clinical follow-up of patients included in the BENESTENT-I trial.

Background: The BENESTENT-I trial is a randomized study comparing elective Palmaz-Schatz stent implantation with balloon angioplasty in patients with stable angina with a single de novo lesion. Seven-month follow-up data have shown a decreased rate of restenosis and fewer clinical events in the stent group. It is not established whether this favourable clinical outcome is maintained for longer periods or whether coronary stenting defers restenosis and its subsequent clinical manifestations.

Method: To clarify this uncertainty, we updated clinical information on 491 of 516 patients (25 patients are still pending) enrolled in the BENESTENT-I trial at least 5 years after the intervention.

Results: Major Adverse Clinical Events (MACE) in descending order of severity:

	Events per patient		*p-value*	Ranking	
	BA (243)	S (248)		BA (243)	S (248)
Death (D)	3.3%	6.0%	0.20	3.3%	6.0%
Cardiac D	1.6%	2.8%	0.54	1.6%	2.8%
Non-cardiac D	1.6%	3.2%	0.38	1.6%	3.2%
CVA	1.2%	0.4%	0.37	1.2%	0%
Q-wave MI	3.3%	7.7%	0.046	2.9%	7.3%
Non-Q MI	2.5%	1.2%	0.34	2.5%	1.2%
CABG	9.5%	12.1%	0.38	8.2%	10.1%
TLR	27.2%	17.3%	0.009	21.4%	10.1%
No MACE	60.5%	65.3%	0.30	60.5%	65.3%

Conclusion: The original difference of 10% in TLR observed at 7 months (23.3% for BA vs 13.5% for S) has remained unchanged at 5 years (27.2% vs 17.3%) emphasizing the extraordinary long-term stability of the dilated or stented target site. In the stent group, the relatively high proportion of non-cardiac death and the Q-wave MI potentially unrelated to the deterioration of the target lesion may have dampened the global long-term benefit of stenting (no MACE, log rank test: p = 0.18).

844 Stent implantation after successful balloon angioplasty of a chronic coronary occlusion (SARECCO): 2 years follow-up

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The restenosis rate after angioplasty for chronic total coronary occlusion is much higher compared to coronary stenoses. The long-term benefit of stent implantation after successful recanalization is unknown.

110 Patients were randomized after successful balloon angioplasty of a chronic coronary occlusion (vessel diameter ≥ 2.5 mm) to "stent" implantation or to "no stent". The baseline characteristics of both groups showed no difference. Follow up (FU) angiogram was performed after 4–6 months and clinical follow-up obtained for 2 years.

	No stent	Stent	P
MLD post (mm)	1.85 ± 0.44	2.54 ± 0.53	<0.01
MLD FU (mm)	1.15 ± 0.73	1.81 ± 0.9	<0.01
Reocclusion FU	14%	2%	<0.05
Restenosis (>50% FU)	62%	26%	<0.01
Event free survival (2 yrs.)	48%	74%	<0.05

Conclusion: The beneficial effect of stent implantation after successful recanalization and balloon dilatation of a chronic coronary occlusion is maintained after 2 years.

845 Argentine randomized study optimal coronary balloon angioplasty and stenting versus coronary bypass surgery in multiple vessel disease (ERACI II): acute and mid term outcome

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Purpose: The use of stents during coronary interventions reduce acute complications and late restenosis. The aim of this study was to compare coronary angioplasty with stents (PTCA) vs coronary by pass surgery (CABG) in patients with multiple vessel coronary artery disease (CAD).

Methods: From November 1996 to September 1998, 450 pts with multiple vessel CAD were included and randomized to PTCA (225 pts) or CABG (225 pts). The end point of this study was to compare major adverse cardiac events (MACE) defined as death, myocardial infarction (AMI) and requirement of repeat, PTCA/CABG (TLR) at 30 days, one, three, and five years after the randomization. At 30 days stroke was also included as MACE.

Results: Basal demographic and angiographic characteristics were similar, Unstable Angina class II, III, and C 83% vs 90.2% in PTCA and CABG groups respectively.

	PTCA	CABG	P
Death (30 days)	0.9%	5.7%	= 0.012
AMI (30 days)	0.9%	5.7%	= 0.012
Death + AMI (30 days)	1.8%	11.4%	= 0.0002
Stroke (30 days)	0%	1.8%	NS
MACE (30 days)	3.6%	12.5%	= 0.003
Death + AMI (6 Months)	4.5%	13.3%	= 0.007
TLR (6 Months)	13.7%	4.8%	= 0.005

Conclusions: Patients randomized to PTCA Group had significantly lower, 30 days MACE than patients randomized to CABG group. At 6 months freedom from death and AMI was also better in PTCA arm.

846 GABI-II: 1 year follow up of a prospective, multicenter study for the treatment of patients with symptomatic multivessel disease

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Patients (pts.) with symptomatic multivessel coronary disease benefit from both percutaneous angioplasty (PTCA) and aortocoronary bypass grafting (CABG). In the GABI trial (GABI-I) which randomized pts. to either PTCA or CABG in the years 1986–1991 the symptomatic improvement in both treatment groups was not significantly different, however, after one year of follow up pts. in the PTCA arm required more reinterventions than pts. randomized to CABG.

In order to evaluate the impact of current technology including coronary stents the GABI-II trial included pts. according to the initial GABI criteria. Between 2 '1996 and 10 '1997 136 pts. (79% male, mean age 63 years) with symptomatic multivessel coronary disease were enrolled, 98.5% underwent PTCA for 2.1 ± 0.6 vessels. Stents were deployed in 74% of the pts., 7% of the pts. underwent rotational atherectomy and 7% of the pts. received abciximab. During initial hospitalization no patient required emergency bypass operation (vs. 8.5% in GABI-I, $p < 0.01$). After 12 months, 19% of the pts. remained symptomatic with a CCS-class > II vs. 29% in the PTCA-arm of GABI-I ($p = 0.05$). The incidence of q-wave myocardial infarction was 1.5% after 12 months vs. 5% in the PTCA arm of GABI-I (n.s.). Within the first year 7% of the pts. had undergone CABG (vs. 21% in GABI-I, $p < 0.001$) and 23% underwent Re-PTCA (vs. 23% in GABI-I). The total reintervention rate was reduced by 32% ($p < 0.05$) but remained higher compared to the CABG-arm in GABI-I ($p < 0.001$).

Conclusions: PTCA in pts. with coronary multivessel disease is still associated with a higher reintervention rate compared to CABG. However, compared to the PTCA arm of GABI-I, the reintervention rate is significantly lower, which is mainly driven by the reduced necessity for CABG. This is most probably a result of intracoronary stents.

INTRACORONARY IRRADIATION: BASIC MECHANISMS

852 The effects of external beam irradiation in stented pig coronary arteries

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Background: External beam irradiation (EBI) has some potential advantages for vascular radiotherapy and has been shown to reduce neointima formation and lumen loss in balloon injured pig coronary arteries at a dose of 21 Gy. However in stented coronary arteries, EBI failed to show any benefit at 8 Gy. We therefore investigated the effects of EBI at the higher dose of 21 Gy in pig coronary arteries after stent implantation.

Methods: Intracoronary stent implantation was performed in all 3 epicardial vessels of 15 pigs. Pigs were randomized to receive EBI at 21 Gy delivered to the entire heart or placebo. Quantitative coronary angiography (QCA) was performed at implantation and at 28 days just prior to harvest. Sections were prepared by saw-and-grinding after plastic embedding and lumen area, neointimal area, injury score and maximal neointimal thickness were measured by computer-assisted histomorphometry.

Results: On QCA, there were no differences in reference vessel diameter, balloon to artery ratio or post stent lumen diameter between treated and control groups at baseline. EBI resulted in a significant decrease in late lumen loss compared to controls; (0.08 mm vs 1.21 mm, $p < 0.05$) respectively. The histomorphometry results are shown below.

	Lumen area	Intimal area	Intima/injury score	Intimal thickness
Control	4.69 ± 1.87	3.67 ± 1.94	2.90 ± 1.44	0.76 ± 0.36
21 Gy EBI	7.40 ± 1.40	0.39 ± 0.60	0.36 ± 0.57	0.12 ± 0.13
p-Value	0.003	<0.001	<0.001	<0.001

Conclusions: In stented pig coronary arteries, external beam irradiation at 21 Gy significantly reduced neointima formation and lumen loss. EBI by linear accelerator for clinical in-stent restenosis prevention warrants further investigation.

853 Impairment of isolated coronary reactivity one month post-angioplasty and irradiation in the pig

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The effects of post-angioplasty (PTCA) radiation therapy for restenosis prevention on coronary vasomotion and endothelium-dependent regulation is unknown. To address this issue, vascular reactivity was assessed following PTCA and intracoronary radiation therapy (ICRT) in pigs.

Methods: PTCA and ICRT (using a β-emitter, Sr/Y90) were performed using a non-centered 5F closed end catheter alternatively to the LAD or Cx arteries. A dose of 16 Gy to a depth of 2 mm from the source center was delivered over 3 cm segment. At 6 weeks, the pigs were sacrificed and treated coronary arteries were isolated. Rings were mounted on a myograph to record isometric changes in tension. Data are expressed as mean ± SEM. Using a Student's t test, p was considered significant <0.05.

Results: Rings were stretched to 5 g and allowed to reach their baseline tension. Tension stabilized at 1.28 ± 0.09 g in the control group (CG) (n = 7) but was lower in treated animals (0.42 ± 0.12 g, P < 0.05), indicating a weakening in the stiffness of the vascular walls. The initial contractions induced by a depolarizing solution (40 mM KCl) and PGF2α (40 μM) were similar in the 2 groups. After 4 hours, PGF2α-induced contraction was blunted (1.5 ± 1.5% 40 mM KCl response, P < 0.05) compared to the response of time-control arterial rings (16 ± 5% 40 mM KCl response). In preconstricted depolarized vessels, substance P (0.1 μM)-induced relaxation was negligible (1.7 ± 1.7%, P < 0.05) compared to CG (33 ± 5%), indicating a lack of NO release, effect or production. Sodium nitroprusside (SNP, 1 nM-10 μM)-induced relaxation was facilitated by endothelial denudation in the CG (P < 0.05) due to the increase in guanylate cyclase sensitivity associated with the loss of endothelium-derived NO. In the treated group, SNP-induced relaxation was similar to the denuded CG further suggesting decreased NO bioavailability 6 weeks post-PTCA and ICRT.

Conclusion: PTCA and ICRT in pigs resulted in a decrease in arterial wall stiffness, a weakening of smooth muscle cell contractility and a loss of endothelium-derived NO effect.

854 Edge stenosis after "low dose" radiation therapy using a Re-188 liquid-filled balloon system

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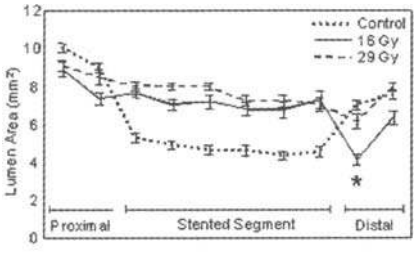
Background: Early clinical results with the 3–6 mCi ^{32}P-stents showed instances of restenosis at the ends of the radiation zones creating a "candy wrapper" appearance. In addition, pig studies with balloon injury have demonstrated that low dose radiation therapy may promote proliferation. Edge stenoses after radiation therapy with a liquid-filled balloon have not been reported yet.

Methods: 24 pig coronary arteries (RCA and LAD) were radiated at 0, 16 and 29 Gy at 0.5 mm tissue depth using a Re188 liquid-filled, 20 mm long balloon. Subsequently, 17 mm long stents were placed with oversizing. At follow up, the stents and the edges were systematically evaluated by angiography and intravascular ultrasound (IVUS).

Results: Within the stented segment, radiation therapy produced a significant dose-dependent reduction of intimal thickening. By angiography, the minimal luminal diameter tended to be at the distal portion of the radiated stent segments compared with diffuse in-stent restenosis seen in controls. At 16 Gy, IVUS demonstrated a significant, focal decrease of the lumen area at the distal edge of the stent. At this site intima proliferation was increased by >200% as compared to controls (p < 0.01).



IVUS analysis.

Conclusions: Increased injury at the distal stent edge due to vessel tapering, in combination with insufficient radiation dose due to rapid dose fall-off at the balloon ends, may enhance intima proliferation. This paradoxical event may be prevented by the use of longer radiation balloons to fully cover the injured segment.

855 Effects of endovascular irradiation on platelet recruitment in ballon-injured coronary arteries

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Background: Endovascular irradiation (EI) is effective in animals in preventing neointima formation after balloon angioplasty and early clinical data on restenosis prevention appears promising. However, little is known about the vascular biological consequences of EI. In this study we examined the effect of EI at therapeutic and supra-therapeutic doses on platelet deposition in coronary arteries at serial time points after angioplasty.

Methods: Adult Yucatan miniature pigs received balloon angioplasty in all 3 epicardial arteries. They were immediately treated with doses of 0 (controls), 15, or 30 Gy at 2 mm from the source center. Autologous platelets were isolated from whole blood and labeled with ^{111}In-oxine (labeling efficiency was consistently >90%) then reinjected the same day or 1, 3, 7 or 28 d after angioplasty. Two hr after injection hearts were harvested and perfusion fixed; coronary arteries were excised and radioactivity determined in a -counter. Platelets/vessel was determined from activity and platelet counts of whole blood sampled at the time of tissue harvest.

Results: EI had no effect on platelet recruitment compared to control except 30 Gy at 28 d (table). Means and SD are shown.

Time	Number of platelets/vessel segment/10^{-6}		
	Control	15 Gy	30 Gy
2 hr	32.6 (21.0)	6.8 (4.6)	14.5 (7.3)
1–3 d	8.7 (11.0)	12.6 (7.7)	22.5 (36.7)
7 d	4.4 (0.9)	15.7 (24.9	5.8 (2.3)
28 d	2.1 (0.6)	5.1 (2.8)	15.3 (8.6)*

*P = 0.03 compared to 28 d control

Conclusions: EI at a dose (15 Gy) within the range currently employed in clinical trials had no effect on platelet recruitment in pig coronary arteries through 1 month after angioplasty. However with twice this dose (30 Gy) in this initial series, more platelets were recruited at the angioplasty site at one month after the procedures. Caution needs to be exercised in using higher dose EI for restenosis prevention. Studies are ongoing to extend these data.

856 Gallium-68 positron radiation effectively reduces neointima proliferation in the porcine coronary overstretch model

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Background: We have recently proposed the use of Ga-68 for liquid-filled balloon brachytherapy since it combines anti-proliferative efficacy in cell culture assays with markedly superior safety in case of balloon failure, based on its short half-life (68 min). This study investigates the impact on neointima proliferation in the porcine coronary overstretch model.

Methods: 25–50 mCi 68-GaCl3 eluted from a Ge-68/Ga-68 generator was delivered into the fluid port of conventional autoperfusion balloon catheters and used to irradiate sites of coronary overstretch (B:A ratio = 1:3, n = 25) in juvenile farm pigs (n = 15). Therapeutic doses were directed to a prescription point 1 mm beyond the intimal surface and included groups of arteries treated with 8 Gy, 12 Gy, 16 Gy, and 24 Gy. Overstretched but unirradiated arteries served as control. Animals were sacrificed 28 d later and hearts were perfusion fixed. Serial sections were evaluated by histomorphometric analysis. Intimal area (IA), intimal area to fracture length ration (IA/FL), and maximal intimal thickness (MIT) were measured.

Results:

	n	IA (mm^2)	IA/FL (mm)	MIT (mm)
Control	9	0.51 ± 0.04	0.47 ± 0.06	0.40 ± 0.05
8 Gy	5	0.75 ± 0.15	0.68 ± 0.10	0.62 ± 0.08*
12 Gy	3	0.46 ± 0.16	0.34 ± 0.12	0.32 ± 0.11
16 Gy	3	0.07 ± 0.04*	0.05 ± 0.03*	0.09 ± 0.01*
24 Gy	3	0.07 ± 0.02*	0.05 ± 0.02*	0.08 ± 0.04*

Data are mean ± SEM, *p < 0.05 vs. control.

Conclusion: Ga-68 positron radiation significantly reduces neointima formation in the porcine model in both high dose groups. Since Ga-68 is effective, safe, and available from a generator, it should be considered as an isotope optimally suited for liquid-filled balloon brachytherapy.

PAEDIATRIC ARRHYTHMIAS/ELECTROPHYSIOLOGY

873 Molecular and ionic mechanisms of complete congenital heart block

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An important advance in the description and understanding of congenital heart block (CHB) came in the 1970s with the observation that mothers of affected infants frequently had autoimmune diseases and, in particular, that many maternal sera contained antibodies to SSA/Ro and SSB/La ribonucleoproteins. While the molecular biology of the candidate antigens has been extensively defined, the arrhythmogenic and electrophysiologic effects of their cognate antibodies on the human fetal and rat heart are unknown.

Methods and Results: Here we provide evidence that IgG-enriched fractions and anti-52 kD SSA/Ro antibodies affinity purified from sera of mothers whose children have CHB induce complete atrio-ventricular (AV) block in the human fetal and rat heart perfused by the Langendorff technique and in multicellular AV nodal preparation, inhibit L-type Ca currents at the whole cell and single channel level. Confocal immunofluorescent studies showed sarcolemmal staining of the isolated myocyte to IgG containing anti-Ro/La antibodies but not to normal IgG. Double staining using both Ca channel anti-alpha1 subunit antibody and IgG showed areas stained by both antibodies. Immunization of female BALB/c mice with recombinant SSA/Ro protein generated high titer antibodies which crossed the placenta during pregnancy and were associated with varying degrees of AV conduction abnormalities, including complete AV block, in the pups.

In conclusion, these findings strongly suggest that maternal autoantibodies from mothers of children with CHB are causally related to the development of CHB. The data suggest that sarcolemmal Ca channel subunits and/or associated regulatory proteins could be the possible binding sites for the maternal antibodies. Taken all together, the present data provide new insights into the pathogenesis and etiology of CHB.

873 QT interval prolongation in infants with maternal anti-SSA/Ro antibodies

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The neonatal lupus syndromes are characterized by anti-SSA/Ro positivity and AV conduction defects. To our knowledge, a prolonged QT interval has not been described in these patients. We have reported a positive infant with QT interval prolongation (QTc = 473 msec) that persisted during the first year of follow-up. To confirm this finding, we retrospectively analyzed the electrocardiograms of 21 SSA/Ro positive infants and of 10 infants who did not receive antibodies from their positive mothers. None of the infants had extreme bradicardia in the fetal period or AV conduction defects after birth and all possible causes of prolonged repolarization had been excluded. QTc was greater in the positive infants (442 ± 35 vs 403 + 16 msec, p = 0.001), while QT interval dispersion expressed as QTcmax-min and coefficient of variation of QTc did not differ. When we analyzed the individual values of QTc, we observed that 9/21 (43%) of the positive infants (range 441–529 msec) and none of the negative infants had a QTc greater than 440 msec. In 5 infants with prolonged QTc on the standard ECG a 24-hour Holter ECG was recorded and automatic QT analysis from 2880 30-sec segments (ELA Medical) confirmed the QT interval prolongation that remained constant throughout the 24 hours. Since a higher mortality has been reported with QT prolongation during infancy, a prophylactic treatment with beta-blockers was started in these newborns who remained free of arrhythmias or symptoms during follow-up. Thus, a significant portion of infants who received anti-SSA/Ro antibodies from their mother and did not develop AV conduction defects, showed a prolongation of the QT interval that persisted in the following months. Since most of these infants were treated prophilactically with beta-blockers we do not know if life-threatening arrhythmias might have occurred. However, QT interval should be measured in the first months of life in this population. The observation that none of the negative infants born from positive mothers had a prolonged QT interval may suggest that anti-SSA/Ro antibodies may interfere with ventricular repolarization during development.

874 Electrophysiologic characterisation and radiofrequency ablation of atrial tachycardia in patients after fontan surgery using a non-contact mapping system

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Atrial tachycardia (AT) is a common late complication of surgical procedures involving the atria used to palliate certain forms of congenital heart disease. Suture lines, surgical incisions, prosthetic material and distorted anatomy all create the substrate for these complex arrhythmias, which are believed to be macroreentry in nature. Mapping by conventional techniques is difficult and time consuming.

We have used a non-contact multielectrode array (EnSite 3000, Endocardial Solutions Inc.) to construct isopotential and isochronal maps of the systemic venous return ("right atrial") chamber in 3 patients with AT after Fontan surgery. The multi-electrode array allows reconstruction of over 3300 unipolar electrograms which are superimposed on a 3-D model of the endocardial surface. The low amplitude electrical activity in the dilated, diseased atrium challenges the accuracy of this new technology. Nevertheless, AT reentry circuits could be identified in 2 pts and an ectopic atrial focus in 1. Known features of the Fontan anatomy could be correlated with the chamber geometry and isopotential maps. The path of activation was determined by atriotomy scars, cardiac structures or patch tissue. The radiofrequency ablation catheter was guided by a locator signal superimposed on the map and used to create focal or linear lesions. This abolished AT in 2 patients. In the third patient the chronic AT was initially terminated but remained inducible, although with a longer cycle length (420 msec vs 340 msec) and has not clinically recurred.

Conclusion: Non-contact mapping of the systemic venous atrium after Fontan surgery can characterise AT. It may be superior to conventional mapping techniques and allow successful catheter ablation of these complex arrhythmias.

875 Medical treatment of children with atrial ectopic tachycardia and tachycardia-induced cardiomyopathy

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Due to its good results, radiofrequency ablation has been advocated as a first line therapy for children with atrial ectopic tachycardia (AET) and cardiomyopathy (CMP). The purpose of this study was to assess the efficacy and tolerance of antiarrhythmic drugs in these patients.

From 1990 to 1997, 8 children aged 3 mths to 12 yrs (m: 4.5 ± 4.7 yrs) were admitted for AET with severe CMP (SF < 10%). All pts had cardiac failure, 3 being referred for heart transplantation. All had permanent AET with heart rate 160 to 400 bpm. Oral antiarrhythmic drugs were given in all cases and success was defined as achievement of a stable sinus rhythm with normal ventricular function. Main trials included amiodarone (*Amio:* 250 mg/m^2), propranolol (*Pr:* 2–3 mg/kg), digoxine (*Dig:* 10–15 μg/kg) and flecaïnide (*Fleca:* 3–8 mg/kg), alone and in combination.

	Dig	Amio	Dig + Pr	Amio + Pr	Amio + Pr + Dig	Fleca	Fleca + Pr
Failure	3	2		2	2	1	
Success	0	3	1	2	2	1	2
Trials	3	5	1	4	4	2	2

100% of pts achieved successful treatment without side effect. Follow-up is 2–years (m: 5.1 ± 3 yrs) and all pts have permanent sinus rhythm with normal echocardiography. AET has totally resolved in 5 cases within 2 to 5 years and the treatment has been reduced in 3 others.

Conclusions. In children with AET resulting in CPM, restoration of sinus rhythm and normal echocardiography can be achieved with medical treatment. Spontaneous resolution of AET is expected. Due to the possible late complications of ablation, we recommend a conservative approach in all children with AET, including those with severe CPM.

876 Radiofrequency catheter ablation in children

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Radiofrequency ablation therapy is the current therapy of choice in adults with some types of supraventricular and ventricular tachycardias. The aim of this study was to evaluate the efficacy and safety of radiofrequency ablation therapy in children.

Methods: radiofrequency ablation therapy was used in 40 consecutive children with a mean age of 11.8 ± 3.4 years (range = 3–15). Twenty-seven patients had Wolf-Parkinson-White syndrome, 7 had atrioventricular node re-entry tachycardia, two had atrial tachycardia and four had idiopathic ventricular tachycardia. Follow-up clinical data, electrocardiograms and 24-h Holter monitors were obtained and analysed.

Results: all patients were alive, and none were lost to follow-up after a mean follow-up of 46 months (range 3 to 85). Success at last follow-up included accessory pathways in 25 (92.5%) of 27 patients, atrioventricular node re-entry in 6 (85.7%) of 7, atrial tachycardia in 1 (50%) of 2, ventricular tachycardia in 3 (75%) of 4. Seven recurrences were observed within one month of ablation (three with accessory pathway-mediated tachycardia, three with AV node re-entry and one with idiopathic ventricular tachycardia). Five patients were successfully ablated by second trial. First degree AV block followed the procedure in 2 patients.

In conclusion, radiofrequency ablation therapy is effective and safe in paediatric patients with supraventricular and ventricular tachycardia and should be considered as the therapy of choice in this group of patients.

877 Long-term results using epicardial stimulation with "autocapture" in children

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An automatic adaptation of the pulse amplitude to the measured threshold is provided by the "Autocapture" algorithm, thereby providing low-energy stimulation. A reliable performance of this function has been schown with endocardial leads. We studied for the first time the long-term effectivity and reliability of Autocapture in children, using epicardial leads.

Methods: In 14 children, age 38 ± 10 month (1 day to 10 years) weight 12.2 ± 2.5 kg (1980 g–29.3 kg) a VVIR-Pacemaker (PM) with Autocapture-function (9 Regency SR+, 5 Microny SR+, Pacesetter) was implanted together with a steroid-eluting bipolar epicardial electrode (10366, Medtronic). Threshold values and measured data were obtained pre-discharge and after 3, 6 and 12 months.

Results: The mean follow-up time is 9 ± 1.8 months. Holters have been performed in 11/14 pts., showing a correct PM function without loss of capture. Autocapture functioned as specified due to reliably epicardially measured evoked potentials with a low polarisation in 12/14 pts. (86%). Low evoked potentials precluded the activation of the algorithm in 2 pts.. For both devices life spans of 7.8 ± 1.4 (Microny) and 21.1 ± 1.6 y (Regency) have been calculated. Measured values:

	Discharge	3 months	6 months	
Evoked potential (mV)	11.0 ± 2.1	12.8 ± 2.4	9.6 ± 2.7	n.s.
Pulse amplitude (V)	1.1 ± 0.3	1.2 ± 0.2	0.9 ± 0.3	n.s.
Pulse width (ms)	0.31 ± 0.06	0.36 ± 0.03	0.36 ± 0.03	n.s.

Conclusion: In the majority of children epicardial stimulation with Autocapture is feasible. Autocapture saves energy, extending battery service life, and providing high stimulation safety.

BASIC AND CLINICAL ASPECTS OF INOTROPIC MODULATION

888 Mechanism underlying the stronger positive inotropic effects of LND-623 a new cardotonic drug: exclusion of cellular sites of contractile control and specific inhibition of Na,K-ATPase isoforms or digitalis receptors

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LND-623 is a new aminosteroid analog of ouabain with a greater separation between efficacy and toxicity than ouabain and digoxin. To precise its mechanism of action, we studied its biochemical and physiological effects on human red blood cell sodium transports, on different cellular structures regarded as sites of contractile control and we compared its relative efficacy to ouabain in rat heart preparations and in membrane bound fractions with purified Na,K-ATPase isoenzymes. The responsiveness to ouabain was evaluated in Langendorff-perfused hearts and on purified membrane-bound Na,K-ATPase.

Results: LND-623 was 6.8-fold more efficient than ouabain in inhibiting the human Na + pump (IC_{50} = 0.098 ± 0.001 μM vs IC_{50} = 0.67 ± 0.02 μM ($p < 0.0001$). LND-623 did not have effects on the following cellular functions: Na-Ca exchange, Na-K cotransport, Ca-ATPase, slow calcium channels, adenylate cyclase system, phosphodiesterase and calcium sensitivity of the contractile protein system. The dose response curve for the positive inotropic effect and the inhibitory efects on rat cardiac isoenzymes produced by LND-623 were clearly biphasic. The amplitude of the maximun inotropic effect, without any toxic effect, was up to 3-fold higher with LND-623 than with the same dose of ouabain ($p < 0.05$).

Conclusion: The strong positive inotropic effect of LND-623 in rat could be related to a specific inhibition of the two rat cardiac isoforms of the Na,K-ATPase and not to myocyte sites of contractile control.

889 Pyruvate acts positive inotropic and does not change economy of myocardial contraction in rabbit and human myocardium

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The glycolysis metabolite pyruvate has been shown to act as a positive inotropic agent in several animal models. Recent investigations from our group showed a marked increase in cardiac output when 3–6 mM pyruvate was given intracoronary to patients with severe cardiogenic shock. The long term use of many other positive inotropic agents, especially catecholamines, is limited because of an overproportional increase in myocardial energy demand. Therefore we investigated the effect of pyruvate on contractile force and on economy of isometrical contraction in isolated multicellular myocardial preparations from rabbit hearts and from explanted human failing hearts. The measurements were performed with a recently developed microelectrode technique for quantification of myocardial oxygen consumption in muscle preparations.

Developed force increased after addition of 20 mM sodium-pyruvate by 65% (from 7.10 ± 1.15 to 11.73 ± 3.17 mN/mm^2 in rabbit preparations, $n = 7$, $p < 0.05$) and by 116% (from 8.71 ± 0.35 to 18.9 ± 0.51 mN/mm^2, $n = 8$, $p < 0.01$) in preparations from human failing myocardium.

At the basic stimulation rate of 1 Hz, 37° and 2.5 mM calcium the oxygen consumption was 1.77 ± 0.52 ml O_2/min · 100 g. After addition of 20 mM pyruvate the oxygen consumption increased to 3.18 ± 0.76 ml O_2/min · 100 g ($p < 0.01$) in rabbit myocardium and increased from 2.87 ± 0.17 to 4.47 ± 0.19 ml O_2/min · 100 g ($p < 0.01$) in human failing myocardium. Economy of myocardial contraction was calculated as the ratio of active developed force-time-integral to oxygen consumption. We observed a slight but non significant ($p = 0.13$) improvement in economy of contraction in presence of 20 mM pyruvate compared to control values (124.3 ± 52.6 N s m/ml O_2 at control, 145.8 ± 46.9 N s m/ml O_2 at 20 mM pyruvate, rabbit myocardium, similar results in human myocardium). In contrast to the unchanged economy values basal metabolism (the absolute amount of oxygen consumption in absence of mechanical energy demand) increased to 347% of control in presence of 20 mM pyruvate (from 0.70 ± 0.27 to 2.41 ± 1.18 ml O_2/min · 100 g, $p < 0.01$) in rabbit myocardium, similar results were obtained in human myocardium.

We conclude that pyruvate causes an increase in the energy costs for basal metabolism but does not change economy of myocardial contraction while acting directly postive inotropic. As mechanism of action we hypothesize an increase in cytosolic phosphorylation potential by improved mitochondrial ATP produktion.

890 Gingerol, ouabain and isoproterenol normalize impaired post-rest-behaviour but not force-frequency relation in failing human myocardium

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Potentiation of twitch force after a rest interval is considered to be an index for Ca^{2+}-uptake capacity of the sarcoplasmic reticulum (SR). Post-rest potentiation of force is blunted and frequency-dependent increase in force is absent in failing human myocardium. These alterations were related to changes in intracellular Ca^{2+}-handling. We investigated whether inotropic agents with different subcellular mechanisms can normalize these pathological alterations.

Methods: Isolated muscle strips, isometric contractions (1 Hz; 37°C; post-rest behavior: rest intervals: 1–240 s; force-frequency relation: stimulation frequencies: 0.5–3 Hz). We tested the influence of the β-adrenoceptor agonist isoproterenol (10^{-8}–10^{-6} M; n = 35), the Na^+/K^+-ATPase inhibitor ouabain (3×10^{-8} M; n = 11) and [10] gingerol, which specifically stimulates SR Ca^{2+}-ATPase (10^{-5} M; n = 13;). In addition, the specific inhibitor of SR Ca^{2+}-ATPase thapsigargin was used (10^{-5} M; n = 14). Furthermore, Ca^{2+}-uptake in crude myocardial homogenates was measured for gingerol (n = 6).

Results: Isoproterenol, ouabain and gingerol significantly increase twitch force which can be prevented by blocking SR Ca^{2+}-ATPase with thapsigargin. In addition, all inotropic agents greatly improve post-rest behavior. In contrast, force-frequency relation was only slightly improved by low concentrations of isoproterenol or gingerol. In contrast, blocking SR Ca^{2+}-ATPase deteriorates both post-rest behavior and force-frequency relation. The specific stimulation of SR Ca^{2+}-ATPase with gingerol could also be shown by Ca^{2+}-uptake measurements in crude myocardial homogenates.

Conclusions: The blunted post-rest potentiation of twitch force and force-frequency relation in failing human myocardium result from altered intracellular Ca^{2+}-handling. Stimulation of SR Ca^{2+}-uptake normalizes post-rest behavior but not force-frequency relation in failing human myocardium.

891 Endothelin-1 antagonises β-adrenergic stimulation in human right atrial myocardium

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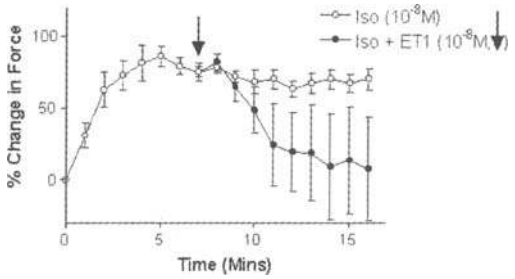
Endothelin (ET1) and isoprenaline (ISO) are known to have positive inotropic effects on human myocardium. However, beta-adrenergic stimulation in human right atrium increases adenyl cyclase (AC) activity while ET1 has been shown to reduce AC activity in isolated tissue homogenates. This study examined the functional significance of this opposing effect.

Methods: Human right atrial tissue was obtained from right atrial appendage during routine coronary by-pass surgery in patients with no evidence of left ventricular dysfunction (n = 6). Small trabeculae were dissected (0.5–0.9 mm diameter, 3–4 mm length), mounted for isometric tension measurement and stimulated at 1 Hz at Lmax. Preparations were allowed to equilibrate for 1–2 hours and repeatedly stimulated with ISO until stable responses were obtained.

Results:



ISO (10^{-8} M) alone produced a maximum increase in isometric force of 63.4 ± 6.2% from baseline after 4–5 minutes while ET1 (10^{-8} M) alone produced an initial fall in force (2.6 ± 2.4%) after 1–2 minutes followed by a 14.2 ± 12.1% increase after 7–9 minutes. However, in the presence of ISO (10^{-8} M), addition of ET1 (10^{-8} M) to the bathing solution (arrow, see figure) resulted in a reduction in developed force of 16 ± 9.6% (n = 5, P = 0.07).

Conclusions: ET1 attenuates the positive inotropic effects of ISO in isolated human right atrial myocardium. The functional significance of this is unclear, however it may be of importance in conditions where both the ET and adrenergic systems are activated such as heart failure. Furthermore, the effects of ET antagonists, which are currently in clinical trials, on this mechanism are unknown and require further examination.

892 Influence of amlodipine and diltiazem on contractility and force-frequency behaviour in isolated human myocardium from ischaemic and dilated cardiomyopathy

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The long-acting Ca channel antagonist amlodipine (Amlo) does not adversely affect outcome of heart failure patients and may even be beneficial in dilated (DCM) but not ischemic (ICM) cardiomyopathy. We tested the direct effects of Amlo on contractile behavior of isolated muscle strips from 26 end-stage failing human hearts (14 DCM, 12 ICM). Diltiazem (Dil) was investigated for comparison.

Methods: Left ventricular muscle strips, isometric contractions, electrical stimulation (1 Hz, 37°C). Cumulative concentration-response curves for Amlo and Dil (0.01–100 μM). In a subset of muscles, the influence of the compounds on intracellular Ca transients (aequorin method) or sarcoplasmic reticulum (SR) Ca content (rapid cooling contractures) was characterized. Furthermore, systolic and diastolic force-frequency behavior (0.5–3.0 Hz) before and in the presence of the compounds was established.

Results: Amlo and Dil concentration-dependently depressed isometric twitch force in a similar fashion. With both compounds, the negative inotropic effect started at 0.1 μM and was maximal at 100 μM (decline by 89 ± 2 and 93 ± 3%, respectively, $p < 0.05$). The IC50 values were 4.63 μM (CI 1.96–7.30 μM) for Amlo, and 5.58 μM (CI 3.09–8.10 μM) for Dil (differences not significant). These negative inotropic effects were related to parallel declines in aequorin light emission and rapid cooling contractures. There was no difference between myocardium from ICM or DCM hearts. Preincubation with Amlo (0.44 and 8.8 μM, n = 14) or Dil (0.1 and 3 μM, n = 14) slightly improved the pathological inverse force-frequency relation. This was attributable to a clear improvement in diastolic function in the subset of muscle strips with increasing diastolic tension at higher stimulation rates (e.g., diastolic tension increased by 58 ± 9% before, and by 18 ± 12% after Amlo, $p < 0.05$, upon increasing stimulation rate from 0.5 to 3.0 Hz; n = 8).

Conclusion: Amlo and Dil exert similar direct negative inotropic effects in human ventricular myocardium with no differences between ischemic or dilated cardiomyopathy. The negative inotropic effects are associated with parallel declines in intracellular Ca transients and SR Ca content, and both compounds may improve diastolic dysfunction. Therefore, potential differences in the tolerability of Amlo and Dil in heart failure patients are not related to their direct effects on the myocardium, and Ca channel antagonists may prove especially beneficial in patients with predominant diastolic dysfunction.

893 β-Endorphin improves left ventricular systolic function in patients with mild chronic heart failure

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The evidence of opioid receptors on ventricular myocytes in experimental models and of high plasma levels of β-endorphin (BE), an endogenous opioid peptide, in patients with congestive heart failure (CHF) led to suppose that BE might play some role in regulation of the cardiovascular system in humans. This study was designed to investigate on the effects of BE on left ventricular systolic function in patients (P) affected by mild CHF.

Eight P (5 M/3 F; age: 47.4 ± 8.3 yrs, M ± SD; BMI: 25.9 ± 0.4 kg/m^2; HR: 84 b/min; SBP: 111 ± 9 mmHg; DBP: 79 ± 6 mmHg) affected by idiopathic dilated cardiomyopathy (IDC) and in II–III NYHA functional class, were enrolled in the study; all were treated with diuretics, digitalis and/or ACE-inhibitors until 72 h before the starting of the study. Seven sex-, age-, and BMI-matched healthy subjects served as controls (C). All subjects received an infusion of synthetic human BE at a constant rate of 500 μg/h for 1 h. In all subjects two dimensional and pulsed Doppler echocardiographic scans were performed at baseline and during BE infusion, and blood pressure (BP) and heart rate (HR) were measured even 5 min during BE infusion. ANOVA analysis for repeated measures was performed for statistics.

At baseline, plasma levels of BE in P were significantly higher than in C (5.6 ± 2.1 vs 2.9 ± 1.0 pmol/L, p = 0.008). When infused, BE plasma levels reached pharmacological concentrations (~400 pmol/L) in both groups. BE infusion induced a significant increase in stroke volume, cardiac output and left ventricular ejection fraction (basal vs steady-state: 64.7 ± 12.3 vs 74.4 ± 11.7 mL, p = 0.008; 5.4 ± 1.0 vs 6.0 ± 1.0 L/min, p = 0.030; 29.7 ± 2.7 vs 34.2 ± 3.1%, p = 0.008, respectively) and a significant decrease in systemic vascular resistance (1384 ± 371 vs 1227 ± 264 dyn•sec•cm^{-5}, p = 0.031) in P, no significant changes in C, and no significant variations of BP and HR in both groups.

In conclusion, these data suggest that high doses of BE for short periods might improve ventricular systolic function in P affected by IDC with mild CHF.

NEW INSIGHT IN HEART TRANSPLANTATION AND GRAFT DISEASE

894 Clinical significance of haptoglobin polymorphism on the development of cardiac transplant vasculopathy

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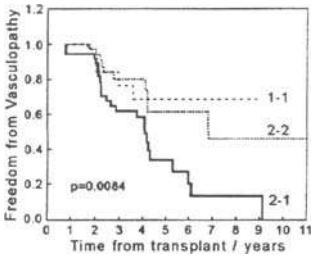
Haptoglobin polymorphism (HP) confers phenotype-dependent modulation of free haemoglobin binding, oxidative stress, immune responses, prostaglandin synthesis and angiogenesis. Clinically HP has been associated with the prevalance and clinical evolution of atherosclerosis and autoimmune diseases. We investigated the effect of HP on the development of cardiac transplant vasculopathy (CTV).

Methods: Haemoglobin (10%) was added to plasma of 131 cardiac graft recipients. Agar electrophoresis with peroxidase dye identified HP. Haptoglobin was measured by immunonephelometry. Angiographic data were available for 93 patients (78.5% male, mean age at transplant 45.6 ± 1.3). Analysis was by a Kaplan-Meier actuarial curve and log rank.

Results: Phenotype 1-1 was found in 18.3%, 2-1 in 44.3%, and 2-2 in 37.4% with haptoglobin levels of 2.1 (± 0.58), 1.78 (0.88), 1.3 (± 0.81) g/l respectively. Patients with the 1-1 phenotype had the lowest incidence of CTV; individuals with a 2-1 phenotype had the highest rate of CTV (p = 0.0084). The results were independent of other clinical variables.



Conclusions: Haptoglobin polymorphism may be important in the pathogenesis of CTV. Differing functional properties of the 3 phenotypes may explain the increased prevalence of CTV in the 2-1 cohort. Manipulation of haptoglobin expression may be an important new area for therapeutic intervention of CTV.

895 Peripheral endothelial dysfunction after heart transplantation: possible role of proinflammatory cytokines

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Conflicting results have been obtained regarding nomalization of peripheral endothelial dysfunction after heart transplantation. We therefore examined microvascular endothelium-dependent vasodilatation together with acknowledged markers of endothelial dysfunction (von Willebrand factor (vWf), plasma NO_2^- + NO_3^- (NO) and big-endothelin), and further explored the possible role of proinflammatory cytokines in this process.

Methods: The vasodilatory responses to acetylcholine (Ach) (endothelium-dependent) and sodium nitroprusside (SNP) (endothelium independent), were evaluated by forearm skin laser Doppler perfusion measurements in 63 clinically stable HTx pts (56 ± 1 years, mean ± SEM), 6 (range 1–13 years) years after HTx, and compared with 20 age- and sex-matched healthy controls. The HTx pts received standard immunosuppression. Plasma vWf, NO, big-endothelin and cytokines were measured by enzyme immunoassay.

Results: Vascular responses to both Ach and SNP were significantly attenuated in the HTx patients compared to healthy controls ($p < 0.001$ and $p = 0.02$, respectively). Plasma VWf, NO and big-endothelin, were also significantly raised in HTx pts, further supporting endothelial dysfunction in these patients. HTx pts also had significantly raised plasma levels of the proinflammatory cytokines TNF-a, IL-6 and IL-1b, and as for TNF-a, the level was significantly correlated with raised b-ET levels ($r = 0.34$, $p = 0.007$) and impaired Ach response ($r = -0.36$, $p < 0.001$). In contrast, there were no correlation's between markers of endothelial dysfunction and neither, lipid-levels, hemodynamics, time since HTx, age, aetiology of heart failure, or serum levels of ciclosporine.

Conclusion: Endothelial dysfunction in long term follow-up of HTx pts was in periods with no rejection or intercurrent illness, demonstrated by both impaired endothelial-dependent vasodilatation as well as by raised levels of markers of endothelial activation. This endothelial dysfunction may be related to enhanced activation of proinflammatory cytokines in these patients.

896 Absence of L-arginine effect on the coronary hypersensitivity to serotonin in cardiac transplant recipients

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Background. Coronary hypersensitivity to serotonin (5HT) promotes platelet aggregation and therefore, the progression of the atherosclerotic process. This abnormality occurs in the early stages of coronary atherosclerosis (CA) when the responses to bradykinin (Bk) are still preserved.

Methods. To determine whether such changes also occur early after cardiac transplantation (Tx), intracoronary injections of Bk and 5HT were performed in 7 control patients (CTRL), in 19 patients with dyslipidemia (CA) and 15 cardiac Tx recipients. Coronary angiography was normal in the 3 groups. In the segments where 5HT effects were the most pronounced, the diameter changes (expressed as % of baseline) were measured by quantitative angiography.

Results.

	Bk 60 ng	Bk 200 ng	Bk 600 ng	5HT 3 μg	ISDN 200 μg
CTRL (n = 7)	108 ± 2	117 ± 2	122 ± 2	107 ± 3	125 ± 5
CA (n = 19)	106 ± 2	113 ± 4	116 ± 2	81 ± 2*	127 ± 2
Tx (n = 15)	103 ± 1	113 ± 2	115 ± 2	85 ± 3*	121 ± 3

*P < 0.05 vs CTRL; ISDN = isosorbide dinitrate

After selective infusion of L-arginine (40 mg/min for 12 min) the 5HT-induced constriction was significantly attenuated in CA group (from 82 ± 3 to 95 ± 4%, n = 8) but not in Tx group (from 83 ± 3 to 77 ± 6, n = 9).

Conclusions: In the early stages of the graft vasculopathy, the response to Bk is preserved. However, in contrast to patients with CA, the absence of L-arginine effect on the responses to 5HT suggests that other mechanisms than reduced EDNO availability are involved in the abnormal response to this amine. Immune process promoting the release of EDCFs such as endothelin and/or, superoxide anion might play a role.

897 Evidence of myocardial blood supply: demand uncoupling in non-rejecting orthotopic heart transplant recipients

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Experimental models demonstrated impaired metabolic efficiency of chronically denervated myocardium. Concentric left ventricular hypertrophy (LVH) develops early after orthotopic heart transplantation (OHT). Further, LVH reduces wall stress and is associated with impaired contractile function. Aim: To measure in OHT recipients myocardial blood supply together with indices of oxygen consumption, i.e. peak LV wall stress and indices of contractility in order to answer the question, whether the myocardial blood supply – demand relationship is altered in OHT recipients.

Methods: In 10 OHT recipients (11 ± 4 months after surgery) and 15 healthy volunteers (matched to donor's age and sex) coronary sinus flow (CSF) was measured by a cine phase contrast (PC) MR technique (TR/TE 20/7 ms, temporal and spatial resolution 40 ms and 1.25 × 0.8 mm^2, respectively) at rest and during hyperemia (dipyridamole 0.56 mg/kg). In order to obtain estimates of myocardial blood flow (MBF) in ml/min/g, CSF was divided by LV mass. Additionally indices of LV loading (end-systolic and peak-systolic wall stresses) and contractile function (afterload-corrected midwall circumferential fiber shortening: cFS_{norm}) were determined. Results: In OHT recipients the left ventricle was concentrically hypertrophied (LV mass: 203 ± 30 vs 149 ± 25 g in controls; $P < 0.0001$). Meridional peak-systolic LV wall stress (mS_{peak}) was reduced in OHT recipients (178 ± 32 vs 236 ± 31 kdyn/cm^2 of controls, $P < 0.0003$) as was cFSnorm (17.8 ± 4.0 vs 23.6 ± 3.0% in controls, $P = 0.0005$). CSF was increased in OHT recipients (174 ± 25 vs 71 ± 18 ml/min in controls; $P < 0.0001$) as was MBF (0.86 ± 0.11 vs 0.49 ± 0.13 ml/min/g, $P < 0.0001$); MBF corrected for rate-pressure product in OHT recipients was not different from controls ($P = 0.33$). However, correlations of cFS_{norm} and mS_{peak} versus MBF/beat in OHT recipients were shifted towards higher flows ($P < 0.0001$ vs controls). When MBF was corrected for these two parameters, again the regression line of the patients was shifted upwards ($P < 0.0001$). This shift reflected the degree of blood supply – demand imbalance and showed a direct correlation ($r = 0.74$, $P = 0.023$) with blood cyclosporine levels measured on the day of the MR study. Coronary flow reserve was reduced in OHT recipients (2.0 ± 0.5 vs 3.9 ± 1.3 in controls, $P < 0.001$).

Conclusions: In relation to major determinants of oxygen demand MBF is elevated in OHT recipients suggesting an uncoupling of blood supply and oxygen demand in transplanted human hearts. Cyclosporine seems to modify this supply – demand relationship.

898 Expression of molecular markers of apoptosis during acute rejection after heart transplantation

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The role of apoptosis in acute rejection after heart transplantation has not been adequately defined. In an attempt to clarify this we have investigated the changes in several molecular markers of apoptosis and proteins involved in the regulation of the apoptotic pathway.

Methods: Ten patients were prospectively followed for 3 months after heart transplantation. Biopsies were performed at 1, 2, 3, 4, 5, 6, 8, 10 and 12 weeks and on clinical indication of rejection and a total of 108 biopsies were obtained. The International Society of Heart & Lung Transplantation (ISHLT) grades of rejection were no rejection in 60, Grade 1A in 26, Grade 1B in 6, Grade 3A in 12, Grade 3B in 2 and Grade 4 in 2. Fas, bax, bak, bclxs and CPP32 act as pro-apoptotic regulators whereas bcl-2 acts as an anti-apoptotic regulator. All biopsies were examined for expression of bax, bcl-2, bclxs, bak, Fas and CPP32 using immunocytochemistry. The C-terminal deoxynucleotydyl transferase-mediated dUTP-fluoroscein nick end labelling (TUNEL) technique was applied to biopsies from patients before and during episodes of moderate/severe acute rejection to detect evidence of apoptosis.

Results: The TUNEL technique detected occasional foci of apoptotic cells in biopsies before rejection and an increase in the number of apoptotic cells during rejection. Fas, bax, bclxs and bak were strongly expressed in cardiac myocytes both prior to and during episodes of rejection, but expression did not appear to change with rejection. CPP32 (pro-apoptotic) and bcl-2 (anti-apoptotic) were not expressed during no rejection, but were weakly expressed in cardiac myocytes during rejection episodes. Strong CPP32 and bcl-2 staining was seen in inflammatory cells during moderate/severe rejection.

Conclusions: Apoptosis appears to play a role in acute cardiac allograft rejection, but rejection is accompanied by variable expression of different apoptotic markers.

899 Clinical usefulness of pulsed-wave tissue Doppler imaging in the non-invasive follow-up of patients with transplant coronary artery disease

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Graft coronary artery disease (TxCAD) is the major factor that limits the long-term results of cardiac transplantation. Routine annual coronary angiography, in combination with intracoronary ultrasound (ICUS), is generally accepted as the only means for the detection of early disease. Nevertheless, noninvasive detection of signs for TxCAD development or aggravation continues to be a challenge. We designed the present study to investigate the usefulness of the pulsed-wave tissue Doppler imaging (PWTD) velocity and time parameters in the detection of functional abnormalities due to TxCAD.

Methods: Twohundred heart transplant recipients underwent PWTD before and/or after a combined examination of coronary angiography and ICUS. In all patients endomyocardial biopsies were also performed. The registration of a phonocardiogram simultaneously with the PWTD from the posterior wall allowed us to measure not only the peak early systolic and diastolic velocities, but also the systolic and diastolic time intervals.

Results: As expected, the incidence of diastolic dysfunction was significantly higher ($p < 0.01$) in patients with TxCAD, but more striking were the differences with regard to the PWTD parameters during systole. The mean peak early systolic velocity in the 51 patients without TxCAD (12.7 ± 1.9 cm/s) was significantly higher ($p < 0.001$ and $p < 0.01$, respectively) than in the 67 patients with severe disease (9.6 ± 2.2 cm/s), as well as in the 82 patients with only moderate TxCAD (10.7 ± 1.9 cm/s). Significant differences ($p < 0.001$ and $p < 0.01$, respectively) were also found for the time from the onset of the first heart sound to the peak of the systolic wave. With a cut off value of less than 9.6 cm/s, the specificity and the positive predictive value of peak myocardial contraction velocities for TxCAD were 97.8% and 98.3%, respectively. The same specificity and positive predictive value for TxCAD was found also with a cut off value of less than 70 cm/s^2 for the systolic wall acceleration.

In conclusion, the PWTD provides important information, which improves the diagnostic value of the noninvasive follow-up, for the detection and monitoring of functional changes produced by TxCAD.

LESSONS FROM GENE MUTATIONS IN ATHEROSCLEROSIS: FOCUS ON ANGIOTENSIN-CONVERTING ENZYME AND NITRIC OXIDE SYNTHASE GENE

904 Large-scale test of hypothesized associations between the ACE I/D polymorphism and MI in over 10,000 cases and controls

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Background: The original report of a possible association between MI and the I/D polymorphism of the ACE gene indicated an odds ratio with the DD genotype of 1.34 (95% CI 1.05–1.70), and the association appeared to be particularly strong in a retrospectively defined "low risk" subgroup. Subsequent investigations reached varying conclusions, but all were small, and a much larger study is needed to test these hypothesised associations.

Methods: Comparison of ACE I/D genotypes in 4629 cases who had presented to hospital with confirmed MI, and were enrolled in the ISIS-3 study of thrombolytic therapy in MI, with 5934 controls, first-degree relatives of MI survivors or spouses of such relatives, who had no history of cardiovascular disease.

Fiindings: The DD genotype was found in 1359 (29.4%) of the MI cases and in 1637 (27.6%) of the controls (odds ratio 1.09; 95% CI 1.00–1.19). No clear association between MI and the DD genotype was observed in the subgroup defined as low risk by previous criteria (232 [28%] of 832 cases and 914 [28%] of 3256 controls: odds ratio 0.99; 95% CI 0.84–1.17), or in any other subgroup. Nor was ACE I/D genotype associated with subsequent survival.

Interpretation: The present study involved about ten times as many MI cases as the previous largest study of this polymorphism, but did not confirm the existence of any substantial risk of MI with the DD genotype. So, although an increase in risk of up to about 20% cannot be ruled out, more extreme risks can be – and in particular, there is not an especially strong association in subgroups previously selected for emphasis. These findings demonstrate the need for such studies of candidate genes to be conducted in much larger populations than is currently customary.

905 No association of the I/D polymorphism of the angiotensin-converting enzyme with myocardial infarction in 4941 probands

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The DD genotype of the angiotensin converting enzyme (ACE) gene polymorphism has been found to be associated with cardiovascular diseases including myocardial infarction (MI). However, sample sizes of many studies showing positive association were small and data were inconsistent.

Methods: Genotype distribution was analysed in 1328 patients who had had an MI below 60 years of age and in 2398 individuals from a survey of the general population in Augsburg. In addition, to condensate genetic factors, 707 siblings of MI patients affected with MI and 883 siblings with no known coronary artery disease were genotyped.

Results: Compared with the general population MI patients did not show a higher frequency of the D allele of the DD genotype:

	II (%)	ID (%)	DD (%)	Freqency of D-allele
MI	21.9	51.0	27.1	52.6
General population 20.3	48.6	31.1	55.4	

Genotype distributions were similar in affected and unaffected siblings. This result was unchanged when men and women were analysed separately. In addition, a low risk group (male, body mass index < 26, total cholesterol/HDL-ratio < 5) selected from MI patients displayed a similar frequency of the D allele (52.4%;n = 85) as a control group selected from the general population (55.4%;n = 167).

This study included thus far the largest number of MI patients and a population based sample for comparison, but no association of the D allele of the ACE I/D polymorphism with myocardial infarction could be observed.

906 12/15-Lipoxygenase deficiency results in delayed atherosclerotic lesion initiation and progression in vivo

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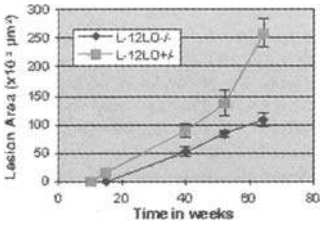
Background: 12/15-Lipoxygenase (12/15-LO)has been implicated in oxidative modification of LDL and in atherogenesis. The relative contribution of macrophage-expressed 12/15-LO to atherogenesis in vivo remains controversial.

Methods and Results: 12/15-LO deficient (L-12LO−/−) mice, generated by targeted gene disruption, were cross-bred with atherosclerosis-prone apoE knockout (apoE−/−) mice. Mice were fed a normal mouse chow diet and atherosclerotic lesion development was studied at 10, 15, 40 weeks, and 12 and 15 months of age. Lesion areas in the whole aortas (en face preparations)developed earlier in apoE−/−/L-12LO± mice than apoE−/−/L-12LO−/− double-knockout mice (at 10 weeks: 677 ± 365 vs. 52 ± 52 square-micrometer, mean ± SEM, n = 10, P = 0.03 (Mann-Whitney test)) respectively, and lesion progression was enhanced in the heterozygous mice as compared to the double-knockout mice (258696 ± 24374 vs. 108075 ± 11964 square-micrometer, n = 9, P = 0.002) at 15 months of age. The total plasma cholesterol levels and lipoprotein profiles were not significantly different between genotypes at any given time point.



12-LO-pict.

Conclusions: Lipoprotein oxidation via enzymatic action of 12/15-LO is a major component of atherogenesis in apoE−/− mice, and this animal model provides in vivo evidence for the importance of 12/15-LO in the initiation and propagation of atherosclerotic lesions.

907 ecNOS-polymorphism is associated with coronary endothelial dysfunction

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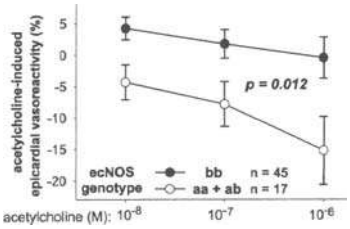
Nitric oxide (NO) plays a central role in endothelium-dependent dilation of coronary arteries. The a allele of the 4a/b polymorphism of the endothelial NO-synthase (ecNOS) was shown to be associated with an increased risk for atherosclerosis. Therefore in 63 patients with an angiographically normal or only minimally diseased (<30% focal stenosis) left coronary artery or left circumflex, we examined the impact of the ecNOS-polymorphism on coronary endothelial vasodilator function. Endothelium dependent vasoreactivity was assessed by i.c. infusion of acetylcholine (Ach 10^{-8}–10^{-6} M), endothelium independent vasoreactivity was analyzed by i.c. infusion of nitroglycerine (NTG 200–300 µg).

Results: Coronary arteries of patients with the aa/ab genotype of the ecNOS poly-morphism had an enhanced epicardial vasoconstriction to Ach compared to patients with the bb genotype. NTG-induced vasodilation was also reduced in patients with the aa/ab genotype (26 ± 3.8% [mean ± SEM], n = 17 versus bb genotype 37 ± 3.5%; n = 45; p = 0.05).



Conclusion: These results point towards a functional relevance of the ecNOS-polymorphism, a gene encoding for an enzyme producing nitric oxide, on coronary vasotonus regulation.

908 High CA repeat numbers in intron 13 of the endothelial nitric oxide synthase gene and increased risk of coronary artery disease

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Background: Endothelial nitric oxide synthase (eNOS) plays a key role in vascular homeostasis. As its product, nitric oxide, possesses vasodilatory and antiatherogenic properties, an altered eNOS function could promote atherosclerosis. We investigated the association between variations in CA repeat copy number ((CA)n polymorphism) in intron 13 of the eNOS gene and the risk of coronary artery disease.

Methods: (CA)n polymorphism was investigated in 1000 consecutive patients with angiographically confirmed coronary artery disease and 1000 age- and gender-matched controls by a PCR based fragment length calculation.

Findings: 28 different alleles were identified containing 17 to 44 CA repeats. Presence of one allele containing more than 38 repeats was associated with an excess risk of coronary artery disease (odds ratio: 1.94; 95% confidence interval: 1.31–2.86; p = 0.001). Carriers of alleles containing more than 38 CA repeats were, in particular, overrepresented in the subgroup without common cardiovascular risk factors, odds ratio 3.39 (95% confidence interval: 1.30–8.86, p = 0.009). Logistic regression analysis disclosed, that the (CA)n polymorphism proved to be an independent risk factor (relative risk: 2.17; 95% confidence interval: 1.44–3.27, p = 0.0002).

Interpretation: Our findings indicate that high numbers of CA repeats in intron 13 of the eNOS gene are associated with an excess risk of coronary artery disease.

ENDOTHELIUM DYSFUNCTION IN DIABETES

910 Non-insulin-dependent diabetes mellitus subjects exhibit an increase in lipid peroxidation and augmented endothelial dysfunction in response to post-prandial lipaemia

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Secondary markers of lipid peroxidation are elevated in diseases with increased oxidative stress. Elevated levels of malondialdehyde (MDA)-LDL complexes are thought to suggest plaque instability in coronary artery disease patients and 4-hydroxynonenal (4-HNE) has been implicated in vascular smooth muscle mitogenesis and atherosclerosis. We therefore studied the effect of post-prandial lipaemia (PPL) on lipid peroxidation and endothelial function (EF) in NIDDM.

Methods. 15 NIDDM patients (8 M, 7 F, mean age 47.7 yrs) with moderate glycaemic control (Av. HbA1c 8.2%) were studied following a 12 hour overnight fast and 4 hours after a standard fatty meal and were compared with 15 healthy controls (7 M, 8 F, mean age 42.3 yrs) with normal EF. EF was assessed by measuring flow-mediated vasodilatation (FMD) in the brachial artery and expressed as % change in brachial artery diameter. A commercially available (R&D Systems) colorimetric assay for products of lipid peroxidation was used, to measure MDA and 4-HNE from plasma frozen at −70°C.

Results. [Mean + S.D.] There were significantly greater amounts of MDA and 4-HNE in NIDDM subjects compared to healthy controls (8.75 ± 4.7 vs. 5.55 ± 2.7 p < 0.05) in association with endothelial dysfunction (ED) (3.4 ± 1.7% vs 6.25 ± 1.3%, p < 0.05) at baseline. PPL results in augmented ED (3.4 ± 1.7% to 1.6 ± 1.1%) and significantly higher TG levels (3.1 ± 2.1 to 7.9 ± 7.9 mmol/L) and MDA/4-HNE (8.75 ± 4.7 to 10.38 ± 4.7 µmol/l) at 4 hours (both p < 0.05).

Conclusions. NIDDM subjects have enhanced lipid peroxidation in association with ED compared to healthy controls. Furthermore PPL augments ED associated with an increase in MDA and 4-HNE. This data offers a possible mechanistic explanation for the markedly raised macrovascular disease risk in NIDDM and the deleterious effects of PPL.

911 Increased soluble E-selectin expression in diabetics with acute coronary syndromes

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Diabetes Mellitus (DM) is associated with chronic endothelial dysfunction. Diabetic patients presenting with acute coronary syndromes have a worse prognosis than non-diabetics. An acute inflammatory reaction at the site of coronary plaque rupture with increased expression of surface and soluble cellular adhesion molecules (CAMs) is a pathological feature of acute coronary syndromes. We set out to characterise the expression of soluble CAMs in diabetics and non-diabetics presenting with unstable angina (UA) and subendocardial infarction (SEMI).

Methods: Patients presenting with UA and SEMI had serum samples taken at presentation, 72 hours and 3 months after discharge. Levels of soluble ICAM-1, VCAM-1 and E-selectin were measured using an ELISA technique.

Results: 87 patients entered the study, 15 diabetic (M/F = 13/2, mean age 65 ± 14 yrs) and 72 non-diabetics (M/F = 57/15, mean age 61 ± 11 yrs). Levels of soluble E-selectin were elevated in diabetics in comparison to non diabetics at all measured time points (74 ± 10 ng/ml vs 53 ± 2 ng/ml, $p < 0.035$ at T = 0 hrs, 53 ± 5 ng/ml vs 45 ± 2 ng/ml, $p < 0.1$ at T = 72 hrs and 68 ± 12 ng/ml vs 55 ± 2 ng/ml, $p < 0.14$ at T = 3/12 respectively). There was no significant difference in levels of soluble ICAM-1 and VCAM-1 between diabetics and non-diabetics at any measured time point.

Conclusion: Levels of soluble E-selectin are significantly elevated in diabetic patients presenting with UA and SEMI in comparison to non-diabetics. This enhanced endothelial activation may contribute to the adverse prognosis of diabetics with acute coronary syndromes.

912 Ciprofibrate blunts post-prandial lipaemia and attenuates the associated endothelial dysfunction and oxidative stress in non-insulin-dependent diabetes mellitus

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Elevated fasting and post-prandial (PP) triglyceride (TG)-rich lipoproteins predict the severity and progression of coronary artery disease. Post-prandial lipaemia (PPL) causes endothelial dysfunction (ED) in healthy individuals and attenuated by vitamin C. We recently reported exaggerated PP oxidative stress and ED in NIDDM in association with increased PP hypertriglycerideamia. Fibrate therapy lowers fasting TG, VLDL and increases HDL-C. We therefore studied the effects of 3 months of ciprofibrate on the above parameters.

Methods 20 NIDDM subjects with moderate control (Av.HbA1c 8.4), were studied, assessing endothelial function (EF) and oxidative stress in response to a fatty meal, and were randomised in a double-blind placebo controlled manner to Ciprofibrate therapy 100 mg od. for 3 months. Subject responses to a fatty meal were then reassessed with measurements of EF and FR's. EF was assessed non-invasively by flow-mediated vasodilatation (FMD) of the brachial artery; Venous FR's were measured by electron spin resonance spectroscopy. 3 patients withdrew, 9 were enrolled into the ciprofibrate arm and 8 into the placebo arm.

Results (mean ± SD) Ciprofibrate reduced both fasting and post-prandial TG (3.0 ± 2.1 to 1.5 ± 0.8 mmol/l) and (7.1 ± 6.5 to 2.9 ± 1.13 mmol/l) respectively both $p < 0.05$. It improved both fasting and post-prandial FMD (4 ± 2.1 to 4.9 ± 1.2%) and (1.77 ± 1.4 to 3.4 ± 1.2%) respectively both $p < 0.05$. These effects of ciprofibrate were associated with an attenuation of the PP rise in free radicals (1.5 ± 1.1 pre to 0.3 ± 0.6 arbitrary units after therapy) $p < 0.05$.

Conclusions Ciprofibrate therapy lowers pre and post-prandial TG levels in NIDDM and blunts the rise in FR and worsening ED associated with a fatty meal. This confirms work implicating TG-rich lipoproteins in this process.

913 Atorvastatin attenuates glucose-induced increases in superoxide anion formation in coronary endothelium

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Increased vascular superoxide anion ($O_{2\cdot-}$) formation contributes to the pathogenesis of atherosclerosis. Chronic hyperglycemia induces endothelial dysfunction, probably due to increased formation of reactive oxygen intermediates. The aim of the present study was to characterize the localization, modulators and molecular mechanisms of vascular O_2^--formation during hyperglycemia in native coronary arteries.

Methods and Results: In porcine coronary segments, high-glucose (25 mM, 48 h) significantly increased O_2^--formation (measured by lucigenin -enhanced-chemiluminescence) vs. controls and isoosmotic sucrose. This effect was completely blocked after removal of the endothelium. Endothelial-dependence of glucose-induced increase in O_2^--formation was also demonstrated by staining with nitro-blue-tetrazolium. Coincubation with atorvastatin (1, 10 μmol/L), a lipophilic inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, attenuated both basal and glucose-induced O_2^--formation. This effect was reversed by mevalonic acid. Furthermore, high-glucose significantly increased expression of the oxidase subunits $p22^{phox}$ and $gp91^{phox}$ measured by RT-PCR. Atorvastatin prevented the glucose-induced increase in $gp91^{phox}$ expression and reduced $p22^{phox}$ expression even below control levels.

In conclusion, these data demonstrate for the first time that glucose-induced increase of vascular O_2^--formation is endothelium-dependent and may be mediated by increased oxidase subunit expression. Beneficial effects of statins in diabetic patients may be explained in part by attenuation of vascular O_2^--formation independent of lipid lowering.

914 Does type of diabetes and metabolic control have influence on antioxidative status in diabetics?

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High endogenous lipid peroxidation and altered antioxidative status are considered to be important for accelerated atherosclerosisis in diabetes mellitus (DM). It is not quite clear whether antioxidative status in diabetics is influenced by the type of DM and quality of metabolic control. This study was aimed to compare antioxidative profile in patients with DM type 1 (DM1) and DM type 2 (DM2), regarding metabolic control.

Methods: in 21 patiens with DM1 and 29 with DM2 antioxidative profile was estimated by: Erythrocyte Superoxid Desmuthase (E-SOD) and Erythrocyte Glutation Peroxidase (E-GPx) activity and Plasma Total Antioxidative Status (P-TAS). All parameters were determined by spectrophothometric methods. Marker of metabolic control, HbA1, was determined colorimetricaly. Groups were similar in duration of DM (about 10 years), patients ages (35–50 years) and sex ratio (female: male -= 1:1). All patients were non-smokers.

Results: are shown in table.

		DM type 1			DM type 2		
		HbA1 < 8% (n = 9)	vs.	HbA1 > 8% (n = 12)	HbA1 < 8% (n = 18)	vs.	HbA1 > 8% (n = 21)
E-SOD	(U/gHb)	999.0 ± 78.9	vs.	767.2 ± 164.4**	902.3 ± 132.0	vs.	812.3 ± 131.7*
E-Gpx	(U/gHb)	27.67 ± 5.18	vs.	29.7 ± 10.58	24.66 ± 4.03	vs.	25.95 ± 6.63
p-TAS	(nmol/l)	1.39 ± 0.03	vs.	1.25 ± 0.19*	1.51 ± 0.28	vs.	1.21 ± 0.10**

* $p < 0.05$; ** $p < 0.01$.

Comparing antioxidative profile between well controled DM1 and well controled DM2, significant difference was founded only in E-SOD activity ($p < 0.05$). In poor controlled diabetics there were no significant differences in antioxidative profile between DM1 and DM2. Correlation (linear regression model) between HbA1 and markers of antioxidative activity was significant among: HbA1 and E-SOD in DM1 ($r = 0.56$; $p < 0.01$), HbA1 and P-TAS in DM2 ($r = -0.54$; $p < 0.01$) and HbA1 and E-SOD in poor controlled DM2 ($r = 0.54$; $p < 0.05$).

Conclusion: Our results suggest that metabolic control influence atioxidative profile in both types of DM, specially E-SOD and P-TAS activity. However, it seems that type of DM has little influence on antioxidative activity, except on E-SOD, but only when DM is well controlled.

915 Does a glass of red wine improve the endothelial function?

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The objective of this study was to examine the acute effect of red wine and de-alcoholised red wine on endothelial function. High frequency ultrasound was used to measure blood flow and percentage brachial artery dilatation after reactive hyperemia induced by forearm cuff occlusion in twelve healthy subjects, less than 40 years, without known cardiovascular risk factors. The subjects drank either 250 ml de-alcoholised red wine or 250 ml of red wine during 10 minutes according to a randomization procedure. Another two examinations of the brachial artery dilatation were done 30 and 60 minutes after the subjects finished the drinking. The second study of the subjects were performed within a week in a cross-over design.

After red wine the resting brachial artery diameter, resting blood flow, heart rate and plasma-ethanol increased significantly. After de-alcoholised red wine these parameters were unchanged. Flow-mediated dilatation of the brachial artery was significantly higher ($p < 0.05$) after drinking de-alcoholised red wine (5.6 ± 3.2%) than after drinking red wine (3.6 ± 2.2%) and before drinking (3.9 ± 2.5%).

Thus, after ingestion of red wine the brachial artery dilated and the blood flow increased. These changes were not observed following the de-alcoholised red wine and were thus attributable to ethanol. These hemodynamic changes may have concealed an effect on flow-mediated brachial artery dilatation which did not increase after drinking red wine. Flow-mediated dilatation of the brachial artery increased significantly after de-alcoholised red wine and this finding may support the hypothesis that antioxidant qualities of red wine, rather than ethanol in itself, may protect against cardiovascular disease.

IMPROVED NON-INVASIVE QUANTITATION OF VALVULAR LESIONS

920 Aortic valve stenosis assessment by Doppler echocardiography: simplified or more complex calculations?

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New simplified and less time-consuming Doppler-echocardiography (DE) methods have been proposed during recent years to evaluate the severity of aortic valve stenosis. The aim of the study was to investigate the value of new simplified and classic DE methods.

Methods: We studied 70 consecutive patients with aortic valve stenosis in sinus rythm (69 ± 10 years, 32 females). DE studies were performed 1 hour prior to cardiac catheterization. The selected gold standard was the Gorlin formula and severe aortic valve stenosis was defined if aortic valve area (AVA) was <0.75 cm^2. The selected DE methods included more complex calculations as AVA either by planimetry in short-axis parasternal view (2D) or continuity equation (CE) and aortic valve resistance (AVR). More simplified calculations were: Percent stroke work loss (PSWL), fractional shortening-velocity-ratio (FSVR), the velocities ratio between outflow tract and vena contracta (V1/V2) and the acceleration time and ejection time ratio in the vena contracta flow (AT-ET).

Results: Mean AVA (Gorlin) was 0.8 ± 0.4 cm^2. The cut-off values, the number of valuable studies (N), agreement (kappa) with Gorlin formula and sensitivity and specificity for each method were as follows:

	N	Kappa	Gorlin < 0.75 cm^2	
			Sensitivity	Specificity
AT-ET, >0.34	70	0.23	81%	66%
V1/V2, <0.2	70	0.50	78%	80%
FSvR, <0.4	64	0.45	77%	79%
2D, <0.75 cm^2	53	0.41	87%	70%
CE, <0.75 cm^2	70	0.53	95%	75%
AvR, >300	70	0.65	85%	85%
PSWL, >25%	70	0.51	88%	77%

In conclusion, continuity equation and aortic valve resistance were the best methods in our study. Among simplified calculations, PSWL and V1/V2 exhibited best sensitivity and specificity.

921 Reproducibility of Doppler echocardiographic measures of aortic stenosis

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Background. Several "new" Doppler echocardiographic measures of aortic stenosis severity have been recently introduced and validated in addition to the traditional *"flow-corrected"* indexes, that are continuity equation (CE) and aortic valve resistance (AVR). These "new" indexes are 1) *"pressure-corrected"*: stroke work loss (SWL = mean gradient/mean gradient + cuff systolic blood pressure); 2) *"function-corrected"*: fractional shortening-velocity ratio (FSVR = left ventricular fractional shortening/4 $Vmax^2$) and ejection-fraction velocity ratio (EFVR = ejection fraction/4 $Vmax^2$). The additional usefulness of these indexes is still under discussion; there is however little information about the reproducibility of each of these measures.

Methods. One hundred consecutive patients with aortic stenosis (53 males, 47 females, aged 72 ± 11 years, mean valve area 0.8 ± 0.4 cm^2) were studied by Doppler echocardiography within 1 hour by two experienced investigators in a blinded, independent fashion. The observer variability for each index was calculated using coefficients of variation. Furthermore the two investigators classified all patients into two groups (respectively with severe and nonsevere aortic stenosis, using the same previously validated cut-off values for each index) and the respective levels of agreement were assessed.

Results. The coefficients of variation were significantly higher for "flow-corrected" indexes (CE = 28%, AVR = 33%) rather than for "pressure-" and "function"-corrected ones (SWL = 11%, FSVR = 20%, EFVR = 14%); this could be explained by the coefficients of variation observed for the respective correcting factors (cardiac output = 29%, cuff systolic blood pressure = 5%, ejection fraction = 7%). The best agreement between the investigators in the classification of severity was obtained using EFVR (93%); lower agreement levels were oberved considering FSVR (89%), SWL (86%), AVR (80%), CE (72%). The dimentionless CE (obtained considering a costant value of left ventricular outflow tract diameter = 2.0 cm) allowed to improve the inter-observer agreement in the classification of severity from 72% to 86%.

Conclusion. "Pressure-corrected" and "function-corrected" indexes not requiring left ventricular outflow tract measurements (such as SWL, EFVR, FSVR) are more reproducible than flow-corrected indexes (CE and AVR). The knowledge of these findings could be relevant in order to assess which index could be best applied in clinical practice.

922 A novel echocardiographic method for quantification of orifice area using colour Doppler of the proximal convergence zone: in vitro validation and automated analysis

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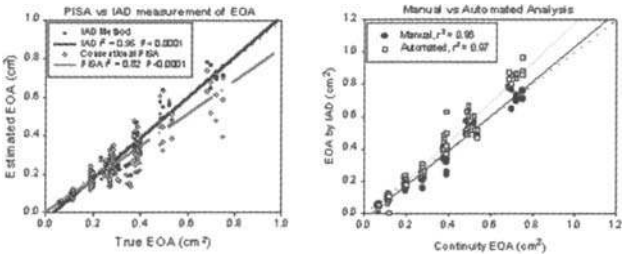
Non-invasive measurement of regurgitant orifice area can be performed using proximal convergence analysis (PISA), but requires localization of the true orifice to measure the radius of the first aliasing contour. Errors in estimating the orifice location lead to errors in orifice area measurement. To avoid this, we examined a method using the interaliasing distance (IAD), the distance between the first and second aliasing contours, to calculate orifice area.

Methods: Using a model of continuous flow through circular orifices (0.05–0.8 cm^2), color M-mode recordings of the proximal convergence zone were made for measurement of the first aliasing contour radius and the IAD. Flow was calculated from these measurements. Using flow velocity by CW Doppler, effective orifice area (EOA) was determined by PISA and IAD methods. EOA measurements made by both methods were compared with those by continuity. An automated method of IAD analysis was compared with the manual method. The effects of varying aliasing velocity and orifice size were examined.

Results: EOA estimated by the IAD method correlated more closely with that obtained by continuity (r^2 0.95, $p < 0.0001$) than did PISA (r^2 0.82, $p < 0.0001$). Aliasing velocity affected EOA measurement by PISA ($p < 0.0001$), but not by IAD ($p = 0.39$). EOA derived by automated analysis of color M-modes to yield IAD values correlated well with true EOA (r^2 0.97), but tended to overestimate EOA with larger orifices.



EOA by IAD, PISA and automated IAD.

Conclusions: In vitro, the IAD method measures orifice area accurately and with less variability than PISA due to independence from the aliasing velocity and to elimination of errors associated with orifice localization. Automated analysis using the IAD method is feasible and this promising method deserves further investigation.

923 A new method for calculation of mitral valve area based on colour flow Doppler imaging of the vena contracta

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The vena contracta is the narrowest portion of the regurgitant or stenotic jet that occurs just downstream from the orifice and reflects the size of that orifice. Vena contracta width (VCW) as determined by doppler color flow mapping has emerged recently as a simple echocardiographic marker of the severity of mitral regurgitation. We hypothesized that this method also can be used to calculate stenotic orifices. Therefore, this study was performed to assess the accuracy of VCW in evaluating the severity of mitral stenosis (MS) and (2) compare mitral valve area determined by VCW with other more traditional echocardiographic methods.

Methods: We studied 38 patients (29 females, 41 ± 15 years) with MS. VCW was measured from the apical four chamber view by Doppler color flow mapping. The narrowest sector angle that allowed visualization of the MS vena contracta was used to maximize color flow imaging frame rate. In all pts, VCW was seen clearly, and its largest diameter during diastole was measured for at least three cardiac cycles and averaged. Mitral valve area was calculated from the following equation: constant pi × r^2, where r = VCW/2. Mitral valve area was also determined by planimetry, the pressure half time method, and by the Gorlin formula. The results for all methods were compared.

Results: Mitral valve area by VCW (1.31 ± 0.45 cm^2) showed good correlations and was not significantly different from three comparative techniques: 1)cross-sectional area by planimetry (1.33 ± 0.40 cm^2, p = 0.92, mean difference = 0.22, r = 0.79, SEE = 0.28 cm^2, p < 0.001); 2) area derived from the Doppler half-time (1.26 ± 0.36 cm^2, p = 0.26, mean difference = 0.22, r = 0.77, SEE = 0.29 cm^2, p < 0.001); 3) area derived from the Gorlin equation in the 18 patients who underwent catheterization (1.27 ± 0.35 cm^2, p = 0.63, mean difference = 0.19, r = 0.81, SEE = 0.25 cm^2, p < 0.001).

Conclusion: These findings suggest that Doppler color flow imaging of the vena contracta of the MS jet can provide an accurate estimation of mitral valve area and appears to be potentially applicable to the assessment of the severity of MS.

924 Validation of a simplified method based on the proximal flow convergence to estimate the severity of the mitral regurgitation

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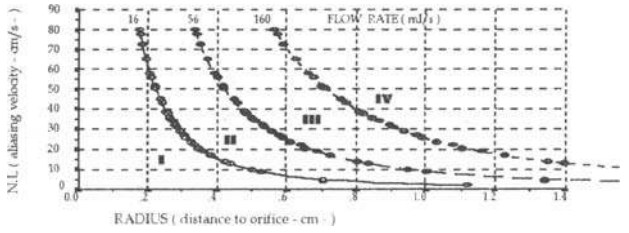
Background: The proximal flow convergence (PFC) is an useful method in the cuantification of the mitral regurgitation (MR), even though its application in the daily clinical practice is not widespread due to its complex and time-consuming calculation.

Objectives: To simplify the cuantification of MR by the PFC, with the elaboration of a nomogram. Afterwards this method is validated through its application in the clinical practice.

Methods and results: We studied 58 patients (pats) with MR, which afterwards were going to be studied by angiography. The maximum regurgitation flow (MRF) was established by the method of the PFC { MRF = 2 × π × (radius obtained)^2 × Nyquist limit (NL) used}. The values of MRF that gave the best predictions of the degrees of angiographic severity from I to IV were estimated by ROC curves (cut points in 16, 56 and 160 ml/second). Maintaining those MRF values constant and applying in the ecuation the most used NL, we obtain the corresponding values of radius, that linked determine three curves. These curves define well-determined areas that represent the angiographic severity degrees.



We applied this nomogram in 24 new pats. with MR. Afterwards they were studied by angiography, with an excellent degree in agreement between PFC (nomogram) and angiography with a weighed kappa value (κ_p) of 0.93. The inter and intraobserver variability presented a κ_p = 0.89 and 0.91 respectively.

Conclusions: 1) The quick estimation of the severity of the MR by the PFC is possible in the daily clinical practice with the use of this simple nomogram. 2) This method has a very good degree in agreement with the angiographic severity of the MR. 3) The variability inter and intraobserver shows an appropiate reproducibility of the PFC method.

925 Direct calculation of regurgitant orifice area in patients with aortic regurgitation by omniplane transoesophageal echocardiography: comparison with angiographic data

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Aim: The aim of the study is to determine the value of direct calculation of Regurgitant Orifice Area (ROA) by omniplane transesophageal echocardiography (OTE) in comparison with angiography (ANGIO). At our best knowledge this is the first clinical study in which is attempted the direct visualization of effective regurgitant orifice in patients with aortic regurgitation (AR).

Methods: We enrolled 28 consecutive pts in a prospective study, (14 men and 14 women, mean age 61.3 yrs, range 43–79, ±10 SD), with chronic AR; all patients underwent to OTE and ANGIO within 25 days. ANGIO was performed by the usual semi-quantitative grading (in four degrees). We calculated by OTE the ROA in oblique cross-sectional views, in order to detect the orifice by means of color Doppler signal; we also performed the color Doppler standard evaluation of AR. The analysis were performed blindly and by two experienced cardiologists for each method, in case of disagreement a third observer was introduced. ROA was calculated off-line on SVHS videotape.

Data Analysis: The pts were divided into four groups according to the angiographic grade of AR. We calculated ROA and the normalized value of ROA to body surface area (nROA).

Feasibility: We were able to perform ROA calculation in 22/28 pts (78%).

Results: ROA clearly detected pts with severe aortic regurgitation (ROA 2.25–2.72 mm^2, nROA 0.8–1.39 mm^2) with 0.8 mm^2 as cut-off value. Pts with trivial AR were also recognized by ROA (ROA 0.16–0.98 mm^2, nROA 0.144–0.058 mm^2) with 0.144 mm as cut-off value. We found an overlapping of ROA in pts with other grade of AR.

Conclusions: According to our results ROA allowed to a new quantitative evaluation of pts with AR and in our hands this method showed a good correlation with angiographic data.

LEFT VENTRICULAR LONG-AXIS FUNCTION

926 Tissue Doppler imaging, standard echo-Doppler and haemodynamic evaluation of left ventricular function in coronary artery disease patients with normal ejection fraction

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Tissue Doppler Imaging (TDI) is a promising technique for non invasive evaluation of left ventricular (LV) function through the analysis of the mitral anulus lenghtwise movement; nevertheless data in healthy and diseased heart are still not conclusive. We performed a combined haemodynamic and echo-Doppler (standard and TDI) study of LV function in a group of 16 patients (mean age 52 ± 9) affected by coronary artery disease (CAD) without previous myocardial infarction, with preserved LV ejection fraction and in a control group of 7 age and sex matched subjects. In each subject we simultaneously recorded two main tracings: 1) the LV pressure curve through a micromanometer-tipped catheter, 2) the TDI tracing of the mitral anulus movement examined in four different sites around the mitral anulus, or alternatively with the standard Doppler signal of transmitral diastolic flow.

Mitral anulus displacement and peak Em (TDI) resulted significantly greater in control subjects than in CAD patients (1.6 ± 0.1 vs 1.3 ± 0.2 cm; p < 0.01 and 17 ± 1 vs 12 ± 2 cm/s; p < 0.01 respectively). Peak Em occurred earlier than peak E obtained with standard Doppler during diastole; in CAD patients time from peak Em to peak E was significantly shorter than in control subjects (9 ± 9 vs 23 ± 8 ms p < 0.005). In CAD patients the invasive indexes of isovolumic contraction (max dP/dt+ and dP/dt/P) and relaxation (max dP/dt−) were significantly lower (p < 0.05) whereas τ was significantly higher (p < 0.05) than in control. LV volumes and ejection fraction were similar in both groups.

In conclusion, subtle systolic and diastolic abnormalities in CAD patients can be detected through high fidelity haemodynamic as well as TDI (mitral anulus velocity) evaluations. The earlier occurrence of peak Em vs peak E supports the concept that a suction effect of the left ventricle promotes the blood inflow across the mitral valve. Such an effect was still evident but significantly reduced in our CAD patients in comparison to control subjects. Furthermore, the correlation we found in all subjects between mitral anulus displacement and invasive contractility indexes, was lacking when comparing mitral anulus displacement and relaxation indexes.

927 Left ventricular long-axis changes in early diastole are closely related to systolic function

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Measurement of movement of the mitral valve annulus either by tissue Dopler imaging (TDI)or by M-mode represents LV long axis (LAX) changes and this has been used to assess LV diastolic and systolic function. Frequently, there is discordance between mitral inflow velocities during early diastole (E and A wave) and those measured by long axis changes. We hypothesised that the long axis movement during early diastole (Em) may reflect more the recoil due stored forces from the previous systole and not the LV filling pressure gradient. Therefore, in a prospective within-patient study we have compared LV long axis changes in diastole with those in systole and with LV ejection fraction (LVEF)measured by 2D-echo in a large group of subjects with a wide range of LV function.

Methods: 265 subjects (106 normal) age range 20–89 yrs were studied with TDI and M-mode. mean LAX was measured from 4 positions (septal, lat.,inf.,and sup-basal);LVEF was measured by 2-D (Simpsons)and LV systolic LAX excursion. Mitral Doppler velocities were measured in the usual way.

Results: LVEF varied from 0.18 to 0.88. In diastole 51% had a normal mitral Doppler pattern, 36% an abnormal relaxation pattern, 7% restrictive, and 6% pseudo-normal. There was a strong correlation between LVEF and LAX E (Em) $r = 0.81$, $p < 0.0001$ by M-mode and $r = 0.63$ $p < 0.0001$ by TDI. There was no significant correlation bewteen Mitral E and LAX Em ($r = 0.88$, $p = 0.16$). Suprisingly LAX Am also correled with LVEF ($r = 0.74$, $p < 0.0001$).

Conclusion: There is a strong relationship between the early LAX changes in diastole and systolic function and probably the LAX Em is reflecting the stored energy from the previous systole and thus LV recoil. TDI LAX and mitral Doppler measurements are reflecting completely different processes in diastole.

928 Factors related to left atrioventricular plane displacement in a mixed population of patients with suspected or proven cardiac disease

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Left atrioventricular plane displacement (AVPD) is an uncomplicated, highly reproducible, reliable, and clinically useful echocardiographic method for the determination of left ventricular function. AVPD is strongly related to the prognosis in patients with heart failure. AVPD reflects both left ventricular systolic and diastolic performance, and is a different measure of left ventricular function compared to ejection fraction. Factors influencing AVPD are insufficiently characterised, and we aimed to identify such factors.

Methods: We examined 357 consecutive patients with suspected or definite cardiac disease (age 67 (12) years, 33% women) by echocardiography/Doppler. Cardiac dimensions, left ventricular ejection fraction and filling, AVPD, and valvular function were assessed.

Results: We identified 10 factors explaining 68% of the AVPD variability, and these were included in a multiple regression analysis. AVPD correlated independently with left ventricular ejection fraction (standard coefficient (SC) 0.67, $p < 0.0001$), age (SC −0.20, $p < 0.0001$), body surface (SC 0.19, $p < 0.0001$), left ventricular end diastolic diameter/m^2 (SC 0.19, $p = 0.0004$), left ventricular mass/m^2 (SC −0.18, $p = 0.0001$), maximum velocity of early/atrial (E/A) transmitral diastolic flow (SC −0.10, $p = 0.004$), but not with left atrial end systolic diameter or degree of mitral, aortic, and tricuspid regurgitation.

Conclusion: AVPD was most closely correlated with systolic function expressed as ejection fraction, but also with age, body surface, left ventricular size and mass, and left ventricular filling. When aiming to assess left ventricular systolic function by AVPD, these factors must be considered. However, no adjustment for valvular regurgitation has to be made.

929 Accuracy and preload-dependency of diastolic mitral annular velocity parameters for the assessment of "pseudonormal" left ventricular relaxation

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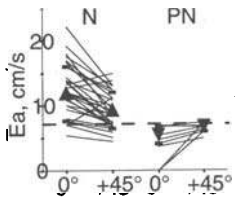
Background: The purpose of this study using transesophageal echocardiography in 40 individuals with normal hearts (N, age 44 yrs), and in 13 patients with LV hypertrophy but normal, age-corrected transmitral Doppler flow pattern ("pseudonormal" group, PN, age 53 yrs) was to test the preload-dependency and the accuracy for the detection of PN of the following parameters: early (Ea) and late (Aa) diastolic mitral annular motion velocity and deceleration time (Ea-dt), mitral annular isovolumetric relaxation time (IVRTa), and the early transmitral flow velocity (E) to Ea ratio.

Methods: All mitral annular velocity parameters were measured using Doppler tissue imaging with the PW sample volume at the inferior annulus. Measurements were performed using a tilt-table during horizontal (0°) and upright (+45°) body position. Preload-dependency (f (prl)) was defined as a significant change of a variable following posture shift from 0° to +45°.

Results:



Variables determining PN	Sens	Specif	f (prl)
Ea < 7 cm/s	100%	90%	no
Ea/Aa < 0.8	100%	53%	yes
Ea-dt > 120 ms	67%	51%	yes
E/Ea < 8	69%	70%	yes
IVRTa > 75 ms	62%	55%	no

Abbreviations: Sens = sensitivity, Specif = specificity

Conclusions: Early diastolic mitral annular motion velocity is probably the most accurate of several annular velocity parameters for the correct detection of falsely normal transmitral flow velocity patterns. It also appears to be relatively insensitive to cardiac preload changes.

930 Strain rate imaging by ultrasound in diastolic function of the left ventricle

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Aims: Strain rate in the left ventricle can be assessed by mapping of longitudinal velocity gradients obtained by colour Doppler; Strain Rate Imaging. Regional diastolic function by this, during early (E) and late (A) filling is characterised both by peak strain rate and propagation velocity of the wave of stretching from base to apex. The aim of this study was to establish normal values and to study the changes with minimal diastolic dysfunction.

Methods: 20 normal subjects (mean BP 119/75, mean HR 61 and mean EF 55%) and 23 hypertensive patients (mean BP 154/80 on treatment, mean HR 61 and mean EF 55%) were studied. Deceleration time of mitral flow was measured as an index of diastolic function.

Real-time SRI colour cine-loops were obtained with a GE Vingmed system 5 scanner in apical 2- and 4-chamber and long axis views. Peak early (PESR) and peak late (PASR) diastolic strain rate were measured in all 16 segments of the left ventricle. Propagation velocity of early (PVE) and late (PVA) diastolic strain were measured off-line in the six walls.

Results: Results are summarised in table I. There were no differences between apical, midwall or basal segments in PSR, and no significant differences between walls in PVE or PVA in normals. When the patients were separated by HR, to see the effect of betablockade, there were no significant differences in PVE, PVA or PESR, but PASR was significantly lower in the group with HR < 60; 1.42 vs. 1.82 Hz, P < 0.02.

Table I

	Age	IVSd (mm)	dec-t (ms)	PESR (Hz)	PASR (Hz)	PVE (cm/s)	PVA (cm/s)
Normals	37	8	175	2.30 (0.86)	1.39 (0.66)	57.8 (16.8)	94.5 (35.4)
Patients	66	11	258	1.43 (0.56)	1.64 (0.70)	28.2 (9.6)	66.9 (19.0)
P:	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

Group characteristics and results. P values are T-test for differences between patients and normals, SD in parenthesis.

Conclusion: The present study shows that diastolic function is a result of peak strain rate, a measure of local relaxation, and the propagation of this relaxation. This gives new information about the physiology of diastole. Even for very moderate hypertrophy and diastolic dysfunction, changes are profound, with decrease in both peak E and E/A ratio, increase in peak A, but most profound reduction in propagation velocity of E. Changes are partly due to differences in age, but this does not alter the pathophysiologic implications.

931 Doppler tissue imaging for the assessment of regional myocardial function after aortic valve replacement

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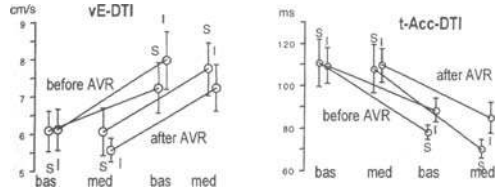
Background: With regression of left ventricular hypertrophy (LVH) changes in global diastolic and eventually systolic function take place. Little is known about the range of these adaptations and their possible regional distribution. Doppler Tissue Imaging (DTI) allows regional evaluation of diastolic and systolic myocardial function, mitral inflow (MIF) and pulmonary venous flow (PVF) are surrogates of global diastolic function. The aim of this study was therefore 1. to evaluate the usefulness of DTI in the assessment of regional relaxation and 2. to look for possible regional differences in patients with regressive LVH after surgery for aortic stenosis (AS).

Methods: In 15 men with sinus rhythm, undergoing elective aortic valve replacement (AVR) for isolated AS, echocardiography including DTI was performed the day before AVR and one month thereafter. In DTI the sample volume was placed on the mitral annulus (bas) and 2 cm beyond the annulus (med) in septal (S) and inferior (I) wall segments.

Results: One month after surgery reduction in LVH took place (from 200 g/m^2 to 162 g/m^2), mainly due to reduction of septal wall thickness (from 18 to 15 mm). Left ventricular ejection fraction improved from 62% to 68% ($p = 0.04$). In MIF, isovolumetric relaxation time (IVRT) shortened form 93 to 70 ms ($p = 0.03$), PVF remained unchanged. In DTI E-wave velocity (vE-DTI) increased in all regions, acceleration time of contraction (tAcc-DTI) decreased in all regions (all $p < 0.05$, two-tailed): cf. graphic.



Conclusions: DTI shows early regional changes in systolic and diastolic function in patients with decreasing LVH. Especially the velocity of early passive relaxation (vE-DTI) and systolic acceleration time (tAcc-DTI) can be used as indicators. Using conventional surrogates of global diastolic function, MIF was superior to PVF in detecting early changes.

PROGRESS IN ULTRASONIC PERFUSION IMAGING

937 A parametric study of peak negative acoustic pressure field distribution and its implications for contrast echocardiography

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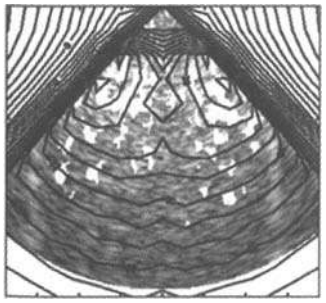
Aim: To determine the relation between peak negative acoustic pressure (PNAP) across an acoustic field and bubble destruction.

Methods: The PNAP distribution occurring within the elevation- and scan planes of a phased array transducer was calculated by computer simulation. The influence of the following parameters on PNAP distribution was investigated: central frequency and bandwidth of the transmitted pulse, position of both axial and elevation focus and number and pitch of the crystals in the phased array. Bubble destruction was studied by scanning contrast-containing phantoms with a 2.5 MHz phased array transducer. Radio-frequency data was acquired for post-processing.



PNAP map vs bubble destruction (white).

Results: Simulations showed that both amplitude of PNAP and its homogenicity within the image increased with decreasing frequency but were independent of transmitted bandwidth. Highest PNAP's were located laterally at 4–5 cm depth. PNAP's were not directly related to propagation distance, being higher in the lateral image lines at the same distance from the transducer. Reflectivity analysis showed that bubble destruction increased with decreasing transmit frequency. Correlation analysis showed that bubble destruction was highest in lateral image regions. The distribution of bubble destruction (white) and PNAP (solid lines) agreed well (cf. figure).

Conclusions: PNAP's have a direct influence on bubble destruction: by decreasing the transmitted frequency the average field PNAP increases. Thus the average rate of bubble destruction within the acoustic field will increase but because of the non-uniform delivery of PNAP across the field bubble destruction is greater in the lateral regions. This has major implications on methods of quantifying contrast images based solely on bubble destruction.

938 Is pulse inversion technique or harmonic power Doppler more tolerant to attenuation-induced reduction of transmission power?

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Objective: In the clinical setting of myocardial perfusion studies, tissue attenuation (AT) is a major factor limiting the nonlinear microbubble response to insonation with a constant mechanical index (MI). Little is known about the relation of the latest imaging modalities to the nonlinear microbubble effect and their tolerance for AT. We studied this relation in an in vitro experimental setting using 3 different contrast agents and varying degrees of MI and AT for the comparison of harmonic power Doppler (HPD) and pulse inversion technique (PIT).

Methods: With a beaker model and a magnetic stirrer, the acoustic energy delivered to the microbubbles at 9 cm depth was reduced incrementally to −42 dB by using increasing layers of castoroil (0, 2, 4, 6 and 8 cm) and reducing MI (1.3, 0.9, 0.6, 0.4, 0.2 and 0.1). Levovist (0.7 ml, 300 mg/ml), Sonovue (0.3 ml) and Optison (0.03 ml) were studied with intermittent imaging at 0.5 Hz using an ATL HDI 5000 with a broadband transducer. Signal intensities (SI) in the digital data sets were measured in dB with a research tool analysis program (HDI lab).

Results: As expected, SI increased with increasing acoustic energy in all imaging modality data sets and contrast agents ($r = 0.87$). HPD demonstrated less tolerance for AT with the onset of SI response to increasing acoustic energy at −25 dB (Levovist) and −29 dB (Sonovue and Optison) compared to PIT: −27 dB (Levovist), −32 dB (Sonovue) and −30 dB (Optison).

Conclusion: These data suggest that the pulse inversion technique is inherently more tolerant for tissue attenuation than harmonic power Doppler. The extent of this effect is modified by the specific bubble composition.

939 Accurate quantification of absolute flow rate by contrast echocardiography using harmonic power imaging combined with dual triggering

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Ultrasound pulsing variation turns out to be promising for myocardial blood flow assessment by contrast echocardiography. Since it has been suggested that contrast agent detection is improved by Harmonic Power Imaging (HPI), we hypothesized that HPI combined with contrast agent and dual triggering provide accurate quantification of absolute flow rate.

Methods: A myocardial tissue mimicking phantom was perfused by a saline solution at flow rates (range: 2–15 ml/min). Trans-sectional echocardiography was performed by using an HDI3000 system with a P3-2 probe. NC100100 was continuously injected in the system. ECG was simulated at 60 bpm by an external device. The first trigger (the destruction pulse) was increased from 550 to 900 ms before the subsequent q wave (second fixed trigger) for each flow rate. Images were digitized and analyzed from the fixed trigger. Pixel intensities were plotted with the delay (TD) between the two triggers (8 configurations from 550 to 900 ms) and the curve slope was calculated for each flow rate. Correlation analysis was performed between slopes and flow rates.

Results: For each flow rate, we observed a highly significant signal decrease always associated with a TD decrease ($R = 0.91$). As long as the flow rate was increased, the corresponding curve slope decreased (table). Most importantly, there is a high relationship between the flow rate value and curve slope changes ($R = 0.98$), providing an accurate quantification of the flow rate from the pixel intensities.

Flow rate (ml/min)	2	5	8	10	12	15
Slope	8.44	7.92	6.34	5.7	4.07	2.82
R	0.95	0.97	0.92	0.91	0.89	0.84

Conclusion: Dual trigger combined with contrast HPI is a reliable indirect method to quantify absolute flow rate.

940 Protection of microvascular reflow by endothelin antagonist treatment: evaluation with fluorescent microspheres and myocardial contrast echocardiography

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Background: A progressive deterioration of microvascular flow has been observed after ischemia-reperfusion. We hypothesized that an endothelin ETA selective receptor antagonist, administered at the time of reperfusion, improves post-ischemic microvascular reflow. Also, we tested the efficacy of myocardial contrast echo (MCE) in detecting pharmacologically-induced changes in microvascular flow.

Methods: In 16 dogs, the LAD was occluded for 90 min and then reperfused for 180 min. Five min before LAD reopening, 5 mg/kg of LU-135252 (Knoll-AG) were infused intravenously in 8 dogs and vehicle was infused in 8 control dogs. Microvascular blood flow (BF) was assessed by fluorescent microspheres at baseline (BSL), during occlusion (OCC), 5, 90 and 180 min of reperfusion (RP). At the same time-points, MCE was performed with Imagent® (Alliance) infused i.v. (4 mg/min). The heart was imaged in short axis in ECG-gated harmonic mode. Background-subtracted videointensity and BF were expressed as LAD/LCx ratio and presented as% of baseline values.

Results: No differences in flow between the two groups were observed at BSL, OCC, 5 and 90 min of RP. At 180 min RP flow was decreased in controls (70 ± 7.4% of bsl) and remained stable LU-135252 treated animals (89 ± 4% of bsl, *p < 0.05 vs control). MCE followed closely the changes in flow observed in the two groups and significantly correlated with BF, r = 0.74, p < 0.0001).

Conclusions: The intravenous administration of LU-135252 at the time of reperfusion limited the progressive decrease in post-ischemic microvascular reflow. MCE with intravenous Imagent® allowed a reliable evaluation of pharmacologically-induced changes in microvascular flow. These data hold promises in the treatment of reperfusion injury and its non-invasive assessment by MCE.

941 ST-segment changes in patients with acute myocardial infarction treated with PTCA are less predictive for functional recovery than myocardial contrast echocardiography and coronary flow reserve

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In 25 patients (pts) with acute first myocardial infarction (11 anterior, 14 inferior) myocardial contrast echocardiography (MCE) was performed prior to primary PTCA and 24 h later, using i.v. NC100100 (Nycomed-Amersham). The endocardial border length corresponding to the contrast defect was measured for each MCE in the apical views. The sum of ST-segment elevation (in mm) in 12-lead ECG was measured pre PTCA, at 1, 2 and 4 hours after PTCA. Coronary flow reserve (CFR) was measured in the infarct related artery using a Doppler guidewire and intracoronary adenosine immediately after PTCA and 24 h later. Depending on the CFR at the 24 h follow-up two groups were defined: Group A (CFR > 1.5, n = 17) and Group B (CFR ≤ 1.5, n = 8). Regional wall motion score index (RI) was calculated pre PTCA and after 4 weeks.

Results:

	Group A	Group B	P
CFR early after PTCA	1.62 ± 0.42	1.51 ± 0.37	NS
CFR after 24 h	2.11 ± 0.46	1.40 ± 0.21	P < 0.0001
MCE defect pre PTCA (cm)	6.0 ± 5.3	6.5 ± 4.5	NS
MCE defect at 24 h (cm)	4.1 ± 5.8*	9.2 ± 6.2	P = 0.058
ST-elevation pre PTCA (mm)	9.3 ± 6.4	13.5 ± 10.1	NS
ST-elevation after 1 hour (mm)	2.7 ± 2.6	6.5 ± 5.6	P < 0.05
ST-elevation after 2 hours (mm)	2.1 ± 1.9	4.4 ± 4.8	NS
ST-elevation after 4 hours (mm)	2.1 ± 1.8	3.1 ± 3.2	NS
RI pre PTCA	2.7 ± 0.5	2.8 ± 0.1	NS
RI after 4 weeks	2.0 ± 0.5#	2.6 ± 0.4	P < 0.05

#p < 0.0001 vs. RI prePTCA, *p < 0.05 vs. MCE defect prePTCA

Conclusion: Pts with reduced CFR 24 h after PTCA showed no reduction or even an increase in MCE defect size at 24 h follow-up and an impaired functional recovery. Reduction of ST-elevation was comparable for both groups. Thus, i.v. MCE may be more precise to predict success of reperfusion therapy in comparison to routine ECG-recordings.

COMPUTER DEMONSTRATIONS

D945 Analyzation of clinical or experimental vascular section with a relational database

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Clinical and experimental vascular sections from online (IVUS, MR angiography) or offline analyzation methods are performed increasingly. Digital relational analysis enable enhanced studies of various parameters.

Methods: To compare different parameters adequately a relational digital image analysis procedure was developed and used that allows easy-to-use digital data transfer. The system files all clinical and histological data and all calculated data after acquisition. Microscopic or macroscopic images are scanned with a 3-chip CCD camera and digitally transferred to the processor. Using a sufficient software environement, digital analyzation of morphometric parameters and image processing is performed (NIH Image). A database (Cumulus, Canto Software Inc.) connected to a spreadsheat developed in a 4th Dimension environment (ACIUS, France) combines an easy to use interface with powerful analyzation features. This allows the relational analysis of nearly all clinical, experimental, macro- and microscopical features. All parameters can be used for further analysis and several calculations with correlated values.

In conclusion: Digitally assisted image analyzation and comparison in referal centers can be performed by several blinded experts after digital data transfer. This allows to bild a net of experimental and clinical data for research and education that is affordable, easy-to-use and standardized.

D946 Myocardial tissue characterization by echocardiography: a new totally digital method using the grey level histograms, the co-occurrence matrix and the fractal dimension

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There are two methods for quantitative approach of myocardial texture (T); one based on the radiofrequency signal analysis and the other one called "videodensitometry", needs a video interface for analysis.

Aims: presentation of a original new tool and a home made software for tissue characterization. We try to prove that it is possible to describe the T with the grey level histogram and with methods of quantifiication of the heterogeneity of the T: the cooccurrence matrix and the fractal approach.

Methods: the study population was composed of 34 normal volunteers. The conventional echocardiography was optimized with a 2.5 Mhz phased array transducer. The texture analysis was done in parasternal long axis; without zoom, ROI of 10*12 pixels, and with zoom, ROI of 20*10 were manually positioned in the interventricular myocardial region. Ten measures were done for each patient over the cardiac cycle. To describe the myocardial texture 9 values from 3 treatments were tested:

(1) the grey level histogram (parameters: mean, median, variance, skweness)
(2) A orthogonal biplane cooccurrence matrix (parameters: mean, variance, energy, contrast).
(3) The fractal approach (fractal dimension)

Results: there was a good intra-observer reproducibility except fractal dimension (intra-classe correlation coefficient ICCC > 80, results confirmed by Bland and Altman graphics). There was cyclic variation of each parameter over a cardiac cycle. The normalization of each measure by the value of the left ventricle cavity was not totally correlated with results without normalization.

Conclusion: tissue characterization by echocardiography is a difficult challenge. Our new tool is homemade, easy to use with images treated by the echo machine like in this study but also with radio-frequency signals.

CORONARY INTERVENTIONS: MISCELLANEOUS

P947 Value of the American College of Cardiology/American Heart Association coronary artery stenosis morphology classification for predicting acute outcomes in the era of coronary stent angioplasty

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Background: The American College of Cardiology/ American Heart Association (ACA/ AHA) stenosis morphology classification was developed for transluminal coronary balloon angioplasty in the 1980s. The aim of our study was to assess the value of this classification to predict the in-hospital outcomes in the era of stent angioplasty.

Methods: From June 1998 to January 1999 we classified 1220 coronary lesions during 807 consecutive angioplasty procedures into ACC/AHA type A, B and C. Angiographic success was defined as <50% residual stenosis after balloon angioplasty and <25% residual stenosis after stent angioplasty. In-hospital major adverse cardiac and cerebral events (MACCE) were registered at discharge.

Results: Of the 731 patients (74% males) 69% were treated because of stable and 31% because of unstable ischemic coronary syndromes. The lesion morphology distribution was as follows: type A 15%, type B1 20%, type B2 42% and type C 23%. Of the latter 46% constituted chronic total occlusions. Stents were implanted in 73% of type A, 81% of type B and 88% of recanalised type C lesions. Angiographic success rates were significantly lower for lesions with complex morphology: type A 100%, type B 96% and type C 81% (55% for chronic total occlusions). MACCE occurred in 17 patients (2.1%): 2 deaths, 4 Q-myocardial infarctions, 1 patient developed disabling stroke and 1 cardiac tamponade due to guidewire perforation, acute bypass surgery was performed in 6 patients and acute re-angioplasty in 3. The MACCE rate in single lesion procedures (n 480), two lesion procedures (n 232) and multi lesion procedures (n 86) were 1.5%, 3.4% and 2.2%, respectively (NS). Freedom from MACCE in single lesion procedures with morphology type A (n 67), B (n 293) and C (n 118) was 100%, 99% and 97%, respectively (NS). The procedural success rates (combined angiographic success and freedom from MACCE) of the lesions were 100%, 95% and 66% ($p < 0.001$, type A and B vs. type C).

Conclusions: 1) The ACA/AHA lesion morphology classification predicts angiographic success after coronary angioplasty even in the era of stenting, 2) stent use increases with lesion complexity, 3) the frequency of major adverse in-hospital clinical events is not related to the number of lesions treated per procedure and only tends to increase with lesion complexity, 4) a high procedural success for morphology type A lesions encourages to consider out-patient angioplasty treatment of these lesions.

P948 American College of Cardiology/American Heart Association stenosis morphology classification is a strong predictive factor of procedural success and late angiographic and clinical outcome after coronary stent implantation

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ACC/AHA lesion morphology is predictive of success rates after PTCA but little is known on its value in predicting the procedural and late angiographic and clinical outcome after coronary stenting.

Methods: The study includes 2944 consecutive patients (pts) who underwent coronary stenting. Only pts with acute myocardial infarction before stenting were excluded. There were 264 pts (9%) with type A, 634 (22%) with type B1, 1152 (39%) with type B2 and 894 (30%) with type C lesions. Lesions of type B2 and C were combined to form the group of complex lesions. All pts had a 1-year clinical follow-up; death, myocardial infarction (MI) and target lesion revascularizations were recorded as adverse events. Six-month angiography was performed in 2296 pts (82% of the eligible pts). All angiograms were assessed with QCA.

Results:

	B2/C type (n = 2046)	A/B1 type (n = 898)	P
Procedural success, %	97.6	98.9	0.02
Thrombosis rate (30-day), %	2.7	1.3	0.02
Death or MI (30-day), %	2.6	1.2	0.02
Angiographic late lumen loss, mm	1.19 ± 0.83	0.99 ± 0.73	<0.001
Angiographic restenosis rate, %	33.2	24.9	<0.001
Event-free survival (1-year), %	75.6	81.1	0.001

In multivariate analysis, B2/C pts had an increased risk of restenosis with odds ratio of 1.33 [95% CI, 1.07–1.64] and of adverse clinical events at 1 year with hazard ratio of 1.27 [1.06–1.52] compared to A/B1 pts.

Conclusions: ACC/AHA lesion morphology classification has a strong predictive value not only for the procedural success rate but also for early and late angiographic and clinical outcome after coronary stent placement.

P949 Prolonged balloon inflations decrease elastic recoil during coronary angioplasty: a quantitative angiographic and intracoronary ultrasound study

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To determine the angiographic, procedural and intracoronary ultrasound (ICUS) factors related to elastic recoil during balloon angioplasty (PTCA), 36 coronary arterial narrowings in 35 patients (pts) were analyzed. Reference diameters (RD) and minimum lumen diameters (MLD) were measured by edge detection method before and after PTCA. Angiographic balloon diameters (BD) were measured along the length of the balloon and average value was utilized for calculation of stretch (BD-pre MLD/RD) and recoil BD-postMLD/RD).

Morphologic characteristics of the dilated lesion (length, eccentricity, Ambrose morphology, calcification, thrombus, postprocedure dissection, bend > 45°) were evaluated visually. ICUS images were obtained using a 3.5 F, 30 mHz catheter. Plaque area, total vessel area (TVA) at the reference and stenotic site, eccentricity index and calcification were recorded before and after PTCA.

The average BD was 2.97 ± 0.43 mm and the balloon/artery ratio was 0.94 ± 0.16. The average stretch was 0.62 ± 0.18 (1.97 ± 0.53 mm) and the recoil was 0.29 ± 0.15 (0.92 ± 0.46 mm). Smaller MLD correlated to higher stretch ($r = 0.66$, $p < 0.01$) but not to recoil. Higher BA ratio was associated with more stretch ($r = 0.79$, $p < 0.01$) and recoil ($r = 0.65$, $p < 0.01$). Discrete (≤5 mm) lesions showed less recoil ($p = 0.04$). The length of the inflation, but not the inflation pressure, was inversely correlated to recoil ($r = -0.49$, $p < 0.01$). No ICUS characteristics including calcification, eccentricity or TVA diminution at the stenosis site were correlated to recoil.

In conclusion, longer lesions are more prone to elastic recoil. Elastic recoil could be reduced by prolonged balloon inflations.

P950 A logistic regression model to determine the probability of achieving an optimal angiographic and physiologic result with balloon angioplasty alone

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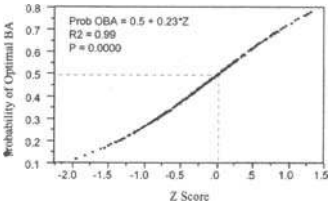
The DESTINI trial is a prospective randomized evaluation of primary stenting (PS) compared to Doppler-guided balloon angioplasty with conditional stenting (G-BA). The population of this analysis consisted of patients with a single lesion who were randomized to the G-BA arm (n = 301). Of this population, 138 pts (46%) achieved an optimal balloon angioplasty (OBA) result (DS < 35% and CFR > 2.0) and 163 pts (54%) had suboptimal result and proceeded to conditional stenting (CS).

Results: Among all clinical, angiographic and procedural variables, only the following was predictive of OBA by logistic regression: reference diameter (RD)(smaller vessels), lesion length (LL) (shorter lesions), and lesions that yielded at a lower inflation pressure (Pres). The regression equation {$Z = 3.59 - 0.546 * (RD) - 0.061 * (LL) - 0.12 * (Pres)$, $P < 0.0001$} was used to calculate the probability of achieving an OBA result using the formula ($Prob = 1/1 + e^{(-z)}$). As shown in the figure below, a Z score = 0 predicts a 50/50 chance of obtaining OBA; for every 0.2 increase in Z score there is a 5% absolute increase in the probability of achieving OBA.



Conclusions: Optimal balloon angioplasty, as defined angiographically and physiologically, depends primarily on lesion substrate. This is more likely to be achieved in pts with shorter lesions located in smaller vessels that yield at lower inflation pressure.

P951 Prognostic implication of concomitant non-critical stenosis in patients with single vessel coronary disease

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Patients with a single critical vessel disease may or may not have additional non critical stenosis on the same vessel or in other coronary arteries. The prognostic implications of presence or absence of these non critical stenosis is currently unknown. We have studied 275 patients who underwent coronary angiography because of stable or unstable angina pectoris. The affected coronary artery was the LAD in 156 (57%), the right coronary artery in 78 (28%), the circumflex coronary artery in 41 (15%). Of the 275 patients 224 (81%) were treated with PTCA. In 200 (73%, group A) of them no additional lesions, beside the single critical one, were observed. The remaining 75 (group B) patients had one or more non critical lesions within the same vessel (n = 32, 43%) or on other coronary arteries (n = 43, 57%).

During the follow-up of 45 ± 8 months occurrence of major lethal and non lethal myocardial infarction (MI) and minor (revascularization) events were recorded. Seventy-two (26%) patients had events and group B had a higher incidence of total events when compared with group A ($c2 = 6.8$), resulting primarily from minor events. Of interest, is the fact that in LAD lesion group the presence of additional non critical stenosis was associated with a higher incidence of major events ($p < 0.05$) when compared with the patients who had LAD lesion without other concomitant non critical stenosis.

In conclusion, in patients with single vessel disease the concomitant presence of non critical lesions within the same vessel or on other coronary arteries is associated with a higher risk for MI or need of revascularization in the follow-up. Furthermore, the coexistence of additional no critical lesions with a critical stenosis on the LAD identifies a subgroup of patients at higher risk for lethal and non lethal MI.

P952 Quantitative coronary angiography: a three-dimensional as compared to the two-dimensional approach

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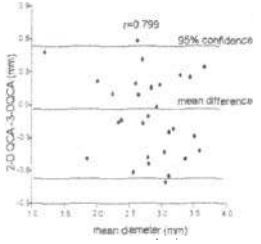
Goals: 1. Validation of an accurate method for 3-dimensional quantitative assessment of volumes, lengths and diameters of coronary vascular branches and segments from biplane angiographic projections (3-D QCA). 2. Comparison of diameter measurements using 3-D QCA as compared to 2-dimensional QCA (2-D QCA).

Methods: The accuracy was tested in a complex phantom. In-vivo, inter- (n = 31) and intraobserver agreement (n = 31) were assessed by analysis of routine angiograms. The sensitivity was evaluated using angiograms of patients having diagnostic vasoactive pharmacological intervention. 2- D QCA and 3-D QCA were compared concerning the accuracy of diameter evaluation.

Results: 3-D QCA yields accurate results (<3% error) even based on non-orthogonal views, provided that projections parallel to the object are avoided. Inter- and intraobserver variability is <5%. Significant ($p < 0.01$) changes of the volume (36%–39%) and the diameter (19%–21%) are detected following pharmacological intervention. 2-D QCA and 3-D QCA agree only in short matched segments without foreshortening (see Bland-Altman plot).



Conclusion: 3-D QCA permits an accurate, reproducible and sensitive comprehensive 3-dimensional geometric analysis of the coronaries and is superior to 2-D QCA with respect to diameter evaluation in foreshortened segments.

P953 Left atrial pump function in patients with coronary artery disease assessed by digitized cineangiography

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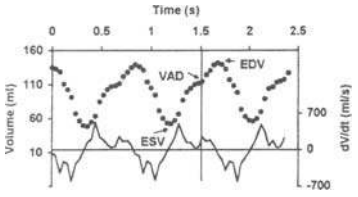
Left atrial (LA) contribution to left ventricular (LV) filling in patients with LV dysfunction due to coronary artery disease was studied in 75 patients (pts) with single vessel disease (43 pts with left anterior descending (LAD), 15 pts with left circumflex (LCx) and 17 pts with right coronary artery (RCA) disease). Furthermore, 15 subjects with normal coronary arteries served as controls (C).

Methods: A computerized technique for the calculation of instantaneous LV volume from digitized cineangiographic data which was developed in our institution was used. LA contribution was estimated by LA filling fraction (LAFF = [LVEDV − LVVAD]/LVVAD, where LVVAD = LV volume at the end of atrial diastasis and LVEDV = LV end-diastolic volume)

Results: LV ejection fraction was decreased in all patients compared with controls ($p < 0.01$). LA contribution was augmented in 39 pts with lesion of LAD, in 7 pts with distal lesion of LCx and in 13 pts with distal lesion of RCA compared with controls, as indicated by increases in LAFF (LAD: 23.1 ± 3.3, LCx: 20.8 ± 3.6, RCA: 19.5 ± 4.6, vs C: 12.7 ± 2.4%). In 8 pts with proximal lesion of the LCx and 4 pts with proximal lesion of RCA, LA ischemia depressed LA contribution, as indicated by decreased LAFF (LCx: 4.5 ± 0.7, RCA: 5.5 ± 1.1%). In 4 pts with lesion of LAD who had severely impaired LV ejection fraction (28.8 ± 7.5%) and symptoms of congestive heart failure LA contractility was also decreased (LAFF: 2.2 ± 0.5%).



Conclusion: Ischemia renders LV performance dependent on augmented LA transport. LA contribution to LV filling may be depressed by LA ischemia. Furthermore, LA contribution was compromised in patients with advanced heart failure.

P954 Angiographic predictors for coronary dissection after coronary stening

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Coronary artery dissection is an unavoidable complication in coronary stenting. Dissection following stent implantation may increase the number of devices used and total procedural time, resulting in an increased procedural cost. We reviewed the incidence of post stent dissection in 1678 patients (2215 lesions) from September 1996 to January 1999. This cohort consisted of de novo, non occlusive lesions only. Dissection occurred in 250 lesions (11.29%) after initial stent implantation, of which 200 lesions (9.03%) received at least one additional stent. Using univariate and multivariate analysis, we evaluated the eight possible baseline angiographic characteristics including calcifications, bifurcation, vessel tortuosity, tandem lesion, lesion shape (eccentric, concentric), vessel size, diameter stenosis and lesion length. Results are as shown below:

Variable	Univariate p value	Multivariate p value
Calcifications	0.08	0.12
Bifurcated Lesion	0.003	0.005
Tortuosity	0.08	0.03
Tandem Lesion	0.05	0.22
Lesion Shape	0.69	0.74
Smaller vessel size	0.0025	0.0007
Diameter Stenosis	0.97	0.88
Longer Lesions	0.026	0.03

Conclusion: Patients with tortuous vessels, smaller vessels, longer lesions, or bifurcated lesions are at higher risk of sustaining dissections after stent implantation.

P955 Comparison of the extent of revascularization and event free survival in the angioplasty arms of two randomized trials of coronary angioplasty versus surgery for multivessel coronary artery disease

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The CABRI trial (Coronary Angioplasty Bypass Revascularization Investigation) randomized patients (pts) with multivessel disease (MVD) to surgery (CABG) or angioplasty (PTCA). Less than 1% of pts were treated with stented angioplasty (SA). In the ARTS trial (Arterial Revascularization Therapy Study) SA was the per protocol treatment in the angioplasty cohort. CABRI was conducted from 1988 to 1992 and ARTS from 1997 to 1998. We sought to determine the influence of completeness of revascularization (CR) on subsequent event free survival (EFS) (absence of death, myocardial infarction (MI), cerebral event or re-revacularization).

Methods: In CABRI as opposed to ARTS equivalence of revascularization between CABG and PTCA was not obligatory. In both studies inclusion was based on consensus between cardiologist and surgeon. We compared the number of diseased vessels (>50% diameter stenosis, reference diameter > 1.75 mm), CR and EFS at 1 month follow-up in the angioplasty cohorts of both trials.

Results: Baseline demographics were not different in both study populations. The table summarizes angiographic data, procedural outcome and EFS at 1 month and 6 month (CABRI).

Outcome in angioplasty arms ARTS/CABRI

	N	Segments diseas-dilated	CR	EFS	Death	MI	Rerevasc	FU
CABRI	541	1815–983	26%	90.2%	1.2%	2.1%	6.5%	1 m
				69.5%	3.3%	3.3%	24.0%	6 m
ARTS	600	1782–1636	73%	92.1%	1.6%	2.5%	3.3%	1 m

diseas = diseased, FU = follow-up, rerevasc = repeat revascularization

Conclusion: Although the extent of disease did not differ between both studies, revascularization was much more complete in ARTS, this was not reflected in a higher EFS at 1 month f-up. There was a trend towards more re-revascularizations in the CABRI trial, reflecting the lower rate of CR. Six month follow-up data from the ARTS will be available soon.

P956 Overlapping coronary stents result in an increased neointimal hyperplasia response: insight from a porcine coronary stent model

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Clinical experience suggests that overlapping coronary stents result in an increased in-stent restenosis. This study investigates the underlying mechanisms in a porcine coronary model. Single or two overlapping self-made stainless steel single wire sinusoidal helical coil stents were randomly deployed in the right coronary artery of 20 crossbred pigs (weight 20–25 kg). The pigs underwent a control angiogram at 6 weeks and were then sacrificed.

Quantitative coronary analysis before, immediately after stent implantation and at 6 weeks, was performed using the semi-automated Polytron 1000™ system. Morphometry was performed using a computerized morphometric program.

Angiographic analysis revealed a decreased recoil in the overlapping group (1% vs. 4%: $p < 0.02$) and a significantly larger minimal stent lumen diameter at follow-up in the single stent group (2.87 ± 0.16 vs. 2.58 ± 0.22 mm: $p = 0.005$). Histopathology showed a significantly increased injury (1.27 ± 0.43 vs. 0.83 ± 0.44, $p = 0.042$) and a significantly increased inflammatory reaction surrounding the stent filaments (1.51 ± 0.11 vs. 1.09 ± 0.54: $p = 0.035$) in the overlapping stent group. Morphometric analysis showed a significantly higher neointimal hyperplasia (3.34 ± 0.68 vs. 2.16 ± 1.48 mm^2: $p = 0.034$) in the overlapping stent group.

Conclusion: Overlapping stents result in more pronounced coronary vessel injury resulting in more inflammation and neointimal hyperplasia compared to single stents.

P957 A new unique low-pressure coronary stent design in a porcine model

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We tested a new unique low pressure stent (LP Stent, InterVenventional Technologies, Inc.) in a minipig model (62 stents in 26 arteries: 22 LAD, 21 Cx and 18 RCA normal coronary arteries; average diameter: 2.52 mm) using standard QCA, angioplasty/stenting and histomorphometric techniques. The device is a stainless steel tubular stent with a configuration of interconnected multiple circumferential serpentine elements and trapezoid strut cross tensile section, fabricated with photomask/chemical etching/electropolishing technique. Mechanical characteristics: tensile strength 120K psi, crush resistance 60.3 g, plasticdeformity 50 psi. We delivered the stent over non-compliant PET balloons. Hypothesis: the trapezoid strut facilitates the stent deployment at lower pressures and this may reduce intimal proliferation.

Results: All stents on the balloon were successfully deployed with a maximum inflation pressure of 6 or 8 atm within 30 sec. The stent on the balloon easily tracked the normal coronary arteries. No stent migration or side branch occlusions were observed.

Follow-up time	Overdilatation	QCA	Histomorphometry	*
24 hours (n = 17)	19.0 ± 6.5	3.9 ± 3.2	8.7 ± 10.5	0
5 days (n = 8)	16.5 ± 9.4	8.8 ± 4.6	9.4 ± 8.5	0
3 weeks (n = 6)	17.0 ± 12.7	7.1 ± 11.3	32.5 ± 16.2	1
1 month (n = 19)	13.0 ± 11.9	14.0 ± 12.4	43.5 ± 13.2	5
6 months (n = 12)	6.9 ± 18.7	6.0 ± 9.1	28.3 ± 15.7	2

Overdilation: mean ± SD of angiographic overdilation in%; QCA: mean ± SD angiographic diameter renarrowing in%; Histomorphometry: mean ± SD histomorphometric area stenosis in%. The highest angiographic restenosis was 45%. The numbers in the * column indicate the number of arteries where the area restenosis was >50%.

The highest histomorphometric restenosis was 69.77% after a 29% overdilation.

Conclusions: 1) LP Stent has outstanding mechanical characteristics; 2) It can be fully deployed with 8 atm inflation pressure with 30 sec; 3) It induced no angiographic restenosis; 4) The histological proliferation primarily correlates with the original overdilation.

P958 Emergency coronary artery bypass grafting for failed percutaneous transluminal coronary angioplasty: changes with the evolution of coronary stenting

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Acute or subacute vessel closure have been the most common complications requiring emergency coronary artery bypass graft surgery (eCABG) following PTCA. The introduction of coronary stenting and its developments have the potential of changing the need of eCABG for failed PTCA. The purpose of this study was to evaluate the impact of technical and procedural evolutions in stenting on the need and reasons to perform eCABG following PTCA.

Methods and results: From January 1993 through December 1998, at our institution, 58 out of 4213 (1.38%) patients undergoing PTCA required eCABG because of failed PTCA. Stent were used in 2775/4213 (65.8%) of the procedures. Overall indications for eCABG were: 1) coronary, dissection with threatened closure or acute closure in 40/58 (69%) patients; 2) coronary perforation in 12/58 (20.7%) patients; 3) mechanical device failure (device trapping or rupture) in 6/58 (10.3%) patients. The study population was divided in two groups according to the date of procedure: Group A from 1993 to 1996 and Group B from 1997 to 1998.

Results:

	Group A PTCA	Group B PTCA
Total patients w/PTCA	2497	1716
Total procedures w/Stent	1586/2497 (63.5%)	1189/1716 (69.3%)
Overall eCABG rate	52/2497 (2.1%)	6/1716 (0.35%)
eCABG for acute or threat. closure	38/52 (73.1%)	2/6 (33.3%)
eCABG for coronary perforation or device trapping or device rupture	14/52 (26.9%)	4/6 (66.7%)

Conclusions: 1) There has been a decrease in the incidence of emergency CABG for failed PTCA, likely related to the widespread use of coronary stenting and in particular stents of second generation which have made "untreatable" dissection treatable. 2) Presently the indication for emergency CABG has been mainly due to procedural mechanical complications not solvable by transcatheter therapeutics.

P959 Do coronary stents improve clinical outcomes? A retrospective study comparing stent device utilization and adverse outcomes

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We compared outcomes in two groups of patients who had single and multivessel revascularization (n = 6.671) during 1997 as follows: 1) those who had PTCA (n = 3.097), and 2) those who received stents (n = 3.574) in all treated vessels. Consecutive patients from 32 hospitals in 16 states were studied. Stent patients were significantly less likely to have emergency CABG (p = 0.001) or die during the initial procedure (p = 0.034), but they were more likely than PTCA patients to be treated for hematoma (p = 0.002) and bradycardia (p = 0.004). Further analysis focusing only on stent patients indicated that those patients with adverse outcomes used more devices (including stents) and had smaller stent diameters. Among patients with any adverse events in the 6 months after their initial procedure, the following statistically significant findings were revealed: 1) the total number of devices used were greater in patients who died, underwent CABG, or had an MI, 2) the total number of stents used were greater in patients who underwent CABG or had an MI, 3) the total length of stents used were greater in patients who underwent CABG or had an MI, and 4) the diameter of the stent(s) used were smaller in patients who underwent CABG.

Parameter	No Adverse Outcome	Any Adverse Outcome	p
Total Device Count	6.17 ± 2.38	6.76 ± 2.81	>0.001
Stent Count (only)	1.37 ± 0.71	1.46 ± 0.78	0.014
Total Stent Length	22.50 ± 15.13	25.33 ± 15.13	>0.001
Stent Diameter	3.41 ± 0.41	0.17% ± 4.09	0.005

Our results suggest that device use does, in fact, have an impact on long-term clinical outcomes and that the relationship between device use and adverse outcomes needs additional study.

P960 Mid-term clinical and angiographic outcomes of the España and Portugal NIR stent registry (ESPORT-NIR)

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Introduction: Coronary stenting has played a major role on coronary angioplasty outcomes. Despite the great development of new types of stents, there is little information about their clinical performance. To assess the efficacy and safety of NIR stent in the treatment of coronary lesions, we undertook a prospective multicenter registry (ESpaña and PORTugal NIR stent registry).

Metods: From Aug 97 to Oct 98, 1004 pts (1136 lesions) were recruited by 50 centers. Inclusion criteria were de novo lesion or first restenosis after balloon angioplasty located in native vessels of ≥2.75 mm reference diameter. Patients with left main disease, recent myocardial infarction (MI), and left ventricular ejection fraction (LVEF) < 25% were excluded. All significant lesions had to be treated with a NIR stent. Primary end-points were major adverse cardiac events (MACE) at 7 months. Angiographic restenosis rate was evaluated from 213 randomly selected patients (237 lesions. Quantitative coronary angiographic analysis was performed in a central core lab by expert technician not involved in the study.

Results: Patients mean age was 61 years, 82% were male, 17% had diabetes. The target lesion was located in the LAD (47%), RCA (32%), LCX (21%). Mean LVEF was 59%. Indication for revascularization was unstable angina in 64%. Clinical success was 99% (angiographic success without in-hospital events). Angiografic restenosis (>50%) rate was 17.3% (12.5%–22.1%). Ranking scale of MACE are summarised below.

	Death	MI	TVR	MACE
1st month	2/1004; (0.2%)	8/1004; (0.8%)	5/1004; (0.5%)	15/1004; (1.5%)
7th month	9/996; (0.9%)	12/996; (1.2%)	66/996; (6.6%)	87/996; (8.7%)

Conclusion: In the wide clinical and anatomical setting of the population included in these registry, NIR stent implantation resulted in a highly effective procedure with a good midterm clinical and angiographic outcome.

P961 Clinical and angiographic results from the Austrian Multilink Duet Stent Registry (AMULET)

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A prospective multicenter registry was conducted to determine the safety and efficacy of coronary stenting with a new, flexible, balloon-expandable, radiopaque stainless steel stent (ACS Multilink Duet™) and its delivery system.

Methods: The immediate clinical and angiographic results and 30-day follow-up outcomes from 272 pts (62 ± 11 y, 73% male) with 322 Multilink Duet stents in 299 lesions (1.1 stent/lesion) are analyzed. Thirty percent of pts had unstable angina, and 26% had a recent myocardial infarction. Vessel distribution was LAD in 113 (38%), LCx in 52 (17%), RCA in 126 (42%), and SVG in 8 (3%) target lesions, 251 (84%) of which were de novo, 18 (6%) restenotic lesions, and 30 (10%) chronic total occlusions. Lesion morphology was type A in 69 (23%), B1 in 110 (37%), B2 in 69 (23%), and C in 51 (17%) lesions. Median lesion length was 8.08 mm (range 0 to 46.8). Stent indication was elective (68%), suboptimal PTCA (31%), or bailout (1%). Balloon pressure was 13.3 ± 2.3 atm, and the balloon to artery ratio (by QCA) was 1.09 ± 0.12.

Results: Stent deployment was successful in 99% of lesions, with delivery failure in 3 (1%) lesions due to inability to cross the lesion with the stent. Core-laboratory QCA results are summarized in the table below:

	MLD (mm)	Reference (mm)	% Diameter Stenosis
Pre	0.94 ± 0.50	2.79 ± 0.45	66.9 ± 24.6
Post	2.70 ± 0.40	3.02 ± 0.36	10.7 ± 7.6

Acute gain (MLD pre-MLD post) was 1.77 ± 0.56 mm, relative gain (acute gain/reference diameter) 0.64 ± 0.20. Vessel size < 2.75 mm was found in 49% of treated lesions. In-hospital and 30-day clinical follow-up is available in 248 (91%) pts so far, with stent thrombosis in 2 (0.8%) pts and intercurrent re-angio (without re-PTCA) in 3 (1.2%), revealing a 30-day event-free survival of 98%.

Conclusions: Coronary implantation of the Multilink Duet™ stent was associated with a high procedural success rate. Immediate and 30-day outcomes are very promising, despite relatively unfavorable baseline patient demographics and angiographic lesion characteristics.

P962 Cerebral protection for carotid angioplasty and stenting: first clinical experience with new techniques

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Purpose: To study feasibility, safety, indications of cerebral protection during carotid angioplasty with stenting.

Methods: Study of 247 carotid angioplasties performed in 229 high-risk patients with appearance of 11 cerebral embolizations (4.5%) (TIA: 4, minor strokes: 4, major strokes: 3). No death. 90 procedures were performed with cerebral protection. We tried to determine the time of occurrence of neurological accident, to assess its origin and risk factors (age of the patient, severity of the lesion, angiographic and echographic aspect), and the ways to prevent them. 2 main types of stents were used: the Palmaz and the Wallstent stents. 3 cerebral protection devices were used: Theron's technique (n = 47), the PercuSurge GuardWire™ technique (n = 35), and a new technique we developed (n) 8). Angioplasty + stenting were performed under cerebral protection and the dilated area was aspirated and cleaned.

Results: Embolic particles may be created at any time of the procedure. Patients' selection, medication (aspirin, ticlopidin), and the technique itself may reduce embolic risks. The stent is not as sufficient protection. With Theron's technique: neurological complications: 4/47. No complication with the 2 other devices. Advantages and disadvantages of these techniques of cerebral protection will be discussed.

Conclusion: Cerebral embolization remains the major problem of carotid angioplasty. Cerebral protection techniques should reduce its frequency. The 2 new techniques seem easy to use, safe and efficient, and should probably be developed in the near future to enlarge carotid angioplasty indications and render the procedure safer, and an alternative to surgery. Larger studies are expected.

P963 Early symptom-limited treadmill stress testing after intracoronary stenting

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Background: Due to concerns of subacute stent thrombosis, early exercise testing is rarely performed following intracoronary (i.c.) stenting. To assess the safety and feasibility of early exercise testing following i.c. stenting, we conducted a prospective trial randomizing patients (pts) to early treadmill stress testing after i.c. stenting or discharge without stress testing.

Methods: A total of 280 pts (232 males, 48 females) undergoing i.c. stenting at the University Hospital of Bern without contraindications to stress testing, were randomly assigned to one of two groups. Pts in group 1 underwent a symptom-limited exercise test the day after stent implantation, whereas pts in group 2 were discharged without prior stress testing. The clinical endpoints were subacute stent thrombosis and vascular access complications. Follow up was done by telephone contact 14 days after the procedure and was complete in all pts.

Results: The two goups were comparable and there was no statistically significant differerence in baseline characteristics or endpoints.

	Group 1 (stress test)	Group 2 (no stress test)	Total
No. of pts	139	141	280
Age (years ± SD)	61 ± 10	61 ± 11	61 ± 11
No. of stents (mean ± SD)	1.3 ± 0.5	1.3 ± 0.3	1.3 ± 0.7
Totall stent length (mm ± SD)	21 ± 12	19 ± 10	20 ± 12
Multivessel PTCA	41 (29%)	32 (23%)	73 (26%)
GP IIb/IIIa antagonist	19 (14%)	13 (9%)	32 (11%)
Subacute stent thrombosis	2 (1.4%)	3 (2.1%)	5 (1.8%)
Vascular access complications	2 (1.4%)	2 (1.4%)	4 (1.4%)

Conclusion: Early symptom-limited stress testing following i.c. stenting is sate and feasible in a general patient population without evidence of an increased incidence of subacute stent thrombosis or complications at the access site.

P964 Differences in restenosis rate in arterial segments with hinge motion points: comparison of different stent designs

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Arterial hinge points, defined as coronary segments with angle change > 15° between systole and diastole, have been associated with increased restenosis rate, with independence of the degree of straightening introduced by the stent. It is unclear whether stent desing influences restenosis at hinge points. With this aim, baseline artery angulation, hinge, and their modification by stenting were measured in segments treated with 3 stent designs: Multilink (MLK) n = 107, Bard-XT (XT) n = 71 and Palmaz Schatz n = 121. All patients had angiographic follow-up at 6 months. According to standard definitions of angulation and hinge motion MLK, XT and PS were placed on segments with angle > 45° in 20%, 48% and 33% cases respectively. Arterial angulation was reduced in 3.1 ± 15° by MLK, 8° ± 18 by XT and 11° ± 10° by PS. Relative risk (RR) for restenosis in the presence of each morphologic criterion and p values are shown below.

Morphology	MLK (n = 107)		XT (n = 71)		PS (n = 121)	
	RR	p	RR	p	RR	p
Baseline angle > 45°	0.15	NS	2.32	NS	0.87	NS
Angle change > 15°	0.28	NS	1.75	NS	0.72	NS
Baseline hinge	0.63	NS	2.68	p = 0.03	3.37	p < 0.01
Hinge change > 15°	2.66	NS	2.12	NS	2.42	NS

Conclusions: Stent design influences restenosis rate in coronary segments with hinge motion. Continuous, multicellular designs may be the design of choice in this situation.

P965 Antrin photoangioplasty: results of a phase I trial of a novel therapeutic modality in patients with lower extremity arterial atherosclerosis

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Lutetium Texaphyrin (Antrin) is a photesensitizing expanded porphyrin that is avidly taken up by atheromatous plaque. The safety, tolerability, and preliminary efficacy of Antrin photoangioplasty (PA) was assessed in a Phase I dose-ranging clinical trial in patients with claudication due to atherosclerotic stenosis of the iliac or superficial femoral arteries. Antrin was given IV over 5 min at doses of 1, 2, 3, 4, or 5 mg/kg. Photoillumination with laser-generated far-red light at 732 nm was performed using an optical fiber with a 3 cm diffusion tip centered over the target lesion at fluence rates of 425, 531, 664, or 830 mW/cm. Pharmacokinetics were assessed with timed plasma sampling. Quantitative angiography and intravascular ultrasound (IVUS) of the target lesions were performed at baseline and 28 days after treatment. Doses of drug and light were escalated in cohorts of 3 pts. In the absence of dose-limiting toxicity, drug or light doses were increased in subsequent cohorts. To date, 34 pts have been enrolled, and follow-up angiography and IVUS have been completed and analyzed in 23. In 15 (65%) of these 23 pts, there was >10% improvement in MLD or cross-sectional area by quantitative angiography and IVUS, respectively. There have been no major symptomatic, angiographic, or biochemical adverse effects of Antrin PA.

Conclusions: These preliminary results strongly suggest that Antrin photoangioplasty is a novel, safe, well-tolerated, nontraumatic, and effective treatment for atherosclerotic obstruction of the iliac and superficial femoral arteries. The results of the completed trial will be presented.

P966 Influence on stent design in restenosis rate: randomized comparison between the ACS multilink stent and the new AVE-stent (GFX)

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Background: Several new designs have been developed to improve reliability, flexibility and visibility. It is not known, however, whether the specific stent design affects reduction of restenosis rate. We have been evaluated the angiographic and clinical outcomes of the AVE-Stent (GFX) and the Multilink stent (ACS).

Methods: Consecutive patients with new and restenotic lesions underwent stent implantation under IVUS guidance were randomly assigned to either GFX (n = 51) or ACS (n = 50) from Jan. 1998. Restenosis was defined as a > 50% diameter stenosis at follow-up.

Results: Stable angina was 72% and acute coronary syndrome was 28%. Baseline and clinical characteristics were similar between the 2 groups. QCA showed similar reference vessel diameter (GFX; 3.15 ± 0.58 vs ACS; 3.14 ± 0.46 mm), pre-procedural MLD (0.45 ± 0.39 vs 0.50 ± 0.38 mm), post-procedural MLD (2.94 ± 0.52 vs 2.94 ± 0.44 mm), pre-procedural%DS (85 ± 12 vs 82 ± 12%), post-procedural%DS (8 ± 12 vs 7 ± 10%), and acute gain (2.49 ± 0.56 vs 2.37 ± 0.48 mm) (all p = NS). Delivery failure was 0%. Patients were treated with ASA (243 mg/day) and Cilostazol (200 mg/day). Acute and subacute closure occurred in 1 patient in GFX group and 1 patient in ACS group. Until Feb. 1999, early FU QCA was available on the first 68 patients. FU MLD was larger in ACS group than in GFX group (2.50 ± 0.61 vs 2.12 ± 0.81 mm, p = 0.03). Late loss was larger in GFX group than in ACS group (0.99 ± 0.78 vs 0.50 ± 0.39, p = 0.001). Restenosis rate was higher in GFX group than in ACS group (8/32; 25% vs 1/36; 3%, p = 0.01).

Conclusion: We demonstrate that post angiographic results with GFX are comparable to ACS. Stent design, however, affects intimal hyperplasia and restenosis rate.

P967 Magic5I study: a prospective multi-center study to evaluate the safety and influence of 5 different stent lengths of the Magic Wallstent on the occurrence of restenosis

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The purpose of this study was to evaluate the safety and efficacy of 5 different lengths of the self-expanding Magic Wallstent in native coronary lesions up to 45 mm in length, in terms of freedom from MACE and angiographic restenosis at 6 months. Also influence of actual stent length on outcome would be studied. Between 17 Sept 1997 and 23 Oct 1998, 277 pts with 312 lesions were included, 36 treated by MiniMagic[Mini] (10 mm), 67 by Extra-short[ES] (15 mm), 74 by short[S] (24 mm), 59 by medium[M] (32 mm), 49 by long[L] (48 mm) and 27 by a combination of these stents or other stents. Data collection and analysis was carried out at an independent core-laboratory. Mean age was 61 years, 79% of pts were male, 42% had prior MI, 14% were diabetic. Indication for stenting was unstable angina in 49%. Target vessel was LAD in 31%, CFX in 15% and RCA in 53%. Lesion type was 82 or C in 70%. Stenting was successful (reduction of stenosis to <20% by on-line quantitative angiography) in 98.6%. Mean vessel diameter was 3.02 ± 0.53 mm, lesion length (LL) 11.9 ± 9.07 mm, minimal luminal diameter pre 0.92 ± 0.38 mm, increasing to 2.62 ± 0.32 mm post, giving a mean diameter stenosis post of 17 ± 6%. In-hospital MACE occurred in 5.7% (0.8% q, 3.0% non-q MI and 1.9% re-PTCA). Post-stent therapy was aspirin and ticlopidine 250 mg daily for 1 month. There were no major bleeding events. Mean hospital stay was 1.7 days. At this time, 264 pts (96%) have completed 6 month clinical follow up and 25.4% have experienced MACE (1.9% death, 1.1% q and 3.8% non-q MI, 1.1% CABG and 17.4% re-PTCA (of whom 53% during routine follow up angiography). In single stent procedures a Mini was implanted in 28 pts (mean LL = 7.80 mm), ES in 47 pts (mean LL 9.29 mm), S in 57 pts (mean LL = 13.45 mm), M in 49 pts (mean LL = 24.0 mm) and L in 41 pts (mean LL = 33.36 mm). Event free survival at 6 months was respectively 86%, 83%, 83%, 71% and 66% (Fisher exact, p = 0.014). Angiographic follow up will be completed April 1999.

Conclusion: The Magic Wallstent may be safely implanted with excellent acute and in-hospital results in patients with unstable as well as stable angina, in lesions from 4.44 mm to 54.27 mm in length and vessels from 1.84 mm to 4.27 mm in diameter. At 6 months, infarct free survival was 97% and survival free of all MACE was 74.6%. MACE were more frequent in pts with longer stents, partly related to more adverse lesion characteristics.

P968 A randomised comparison of the handcrimped Palmaz-Schatz and NIR stents: the DANSTENT study

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Background: The Palmaz-Schatz (PS) is the only stent that has been shown to be superior to balloon angioplasty with regard to clinical outcome and development of restenosis in larger trials.

Methods: The DANSTENT study is a randomised, multicenter trial comparing the procedural, clinical and angiographic outcome of implantation of the PS 153 and the 16 mm NIR stents in de novo coronary artery lesions. All stents were handcrimped onto the balloons and deployed at high pressures in 232 patients, 73% men, aged 59 (40–82) years with predominantly stable (80%) angina pectoris.

Results: Approximately 10% of the patients had diabetes, 24% hypertension and 75% were current or previous smokers. CCS class 1–2 and 3–4 stable angina pectoris were recorded in 55% and 25%, respectively, while 13% had unstable angina and 7% silent ischemia. Thirty percent of the patients had multivessel disease, and 78% of the lesions were type B and C (47% located in LAD). Deployment success was 98% and 100% for the PS and NIR stent, respectively, at similar mean pressures, 15.1 and 15.7 atm (NS).

	PS	NIR	P
Pre-PTCA, n = 232			
Reference diameter, mm	3.02 (0.58)	3.09 (0.57)	NS
Minimal luminal diameter, mm	0.94 (0.45)	0.87 (0.50)	NS
Diameter stenosis, %	68.4 (14.0)	71.4 (15.4)	NS
Post-PTCA, n = 232			
Reference diameter, mm	3.35 (0.54)	3.38 (0.51)	NS
Minimal luminal diameter, mm	2.88 (0.47)	3.01 (0.49)	0.07
Diameter stenosis, %	14.3 (5.8)	11.3 (5.7)	0.01
Follow-up (6 months), n = 150			
MACE (death, AMI, TLR), %	15.5	17.7	NS

Conclusion: Although deployed at the same pressure the immediate minimal luminal diameter in coronary artery lesions treated with a PS 153 stent tended to be smaller and the residual stenosis was slightly but significantly more pronounced. This difference does not seem to affect the clinical outcome. Core lab quantitative coronary angiography at 6 months will be available in approximately 90% of the patients.

P969 The STOP study: a randomized multicenter Israeli study for Stents in Total Occlusion and restenosis Prevention – final report

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Background: Several studies have noted an increase in restenosis and re-occlusion rates in-patients undergoing balloon angioplasty for chronic total occlusion. To assess whether stent implantation decreases restenosis rates, we organized a multi-center randomized study to assess the benefit of additional coronary stenting in chronic (≥10 days) occluded coronary arteries.

Methods: After obtaining optimal PTCA results, patients were randomized either to no further treatment or additional stent implantation. The AVE Microstent was used in all patients and all were expected to undergo 6-month angiographic follow-up to assess restenosis.

Results: Ninety-six patients have been enrolled in this study. The mean age was 59.3 ± 10.3 years and 16 were females. Forty-eight patients were randomized to the stent arm, receiving 51 stents (lengths 18–39 mm) with no procedure related major complications. Sixty-nine patients (72%) were catheterized at 6 months. Restenosis rate in the PTCA group was 71% with MLD of 1.01 ± 0.79 mm compared to 42.1% in the stent group with MLD of 1.63 ± 1.02 mm (p = 0.03).

Reocclusion occurred in 7.9% in the stent group compared to 16.1% in the PTCA group. Interestingly, in 90% of the patients, restenosis occurred exactly at the point of total obstruction (within 5 mm).

Conclusion: Coronary stenting can significantly decrease the rate of restenosis and reocclusion in total occlusions. Care should be taken to implant short stents at the occlusion site.

P970 Randomized comparison of four different stent designs in 1,000 stenoses

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Background: Primary success rate, incidence of early complications (myocardial infarctions (MI), CABG, death, stent thrombosis) and long term results may be influenced by stent design.

Methods: In a prospective randomized trial four different stent designs (Micro II, AVE; Sito, Sitomed; Pura vario (PuVa), Devon Medical; Inflow Inflow Dynamics) were compared in 1000 stenoses of 926 patients with respect to primary success rate, incidence of complications and angiographical long term results after 6 months. A total of 1345 stents were implanted. Increase of %-stenosis was analyzed by quantitative coronary angiography (QCA) after stent implantation and at follow up.

Results:

	Micro	Sito	PuVa	Inflow	p-value
Primary success rate	98.9	98.1	96.7	95.2	0.08
Stent loss rate	0	0.7	0	1.8	0.04
Multiple stents	21.1	23.4	28.9	26.7	0.21
Stent thrombosis	0	1.1	1.5	1.1	0.47
MI, CABG	0	0.7	1.1	1.8	0.26
Death	0.5	0.7	2.6	2.2	0.19
Δ% stenosis [median]	33.2	29.1	29.5	27.1	0.40
restenosis rate	27.2	30.3	33.3	29.6	0.64

Conclusion: Irrespective of design, a very high rate of primary success with few early complications was achieved with all stents employed in this study. Although there was a tendency to less restenosis and less complications with the sine wave design (AVE Micro II), the difference was not significant. Thus the design of these 4 stents has no influence on procedural success rate, early complications and long term results.

P971 Can we use only one stent design in order to treat all types of coronary stenosis? In-hospital and 6-month results

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The aim of this study was to evaluate the polyvalence of the DUET coronary stent in real practice.

Methods: we have prospectively evaluated the safety and efficacy of 400 DUET coronary stent which were consecutively implanted in 263 pts (61 ± 13 years, 28% women) including 381 lesions. All pts received ticlopidin and aspirin.

Results: clinical indications were acute coronary syndrome in 69% (unstable angina and myocardial infarction), stable angina in 19% and silent ischemia in 12% of pts. Revascularization was complete in 67% of pts. Lesions were type B/C in 68%, collateral branches were included in stent cells in 31%, bifurcation lesions were treated in 9.2% and ostial lesion in 12.8% of cases. The mean lenght of stent was 17.9 ± 6.1 mm, the mean diameter was 3.25 ± 0.31 mm and the mean inflation was 12 ± 2 atm. Technical success rate was 99.2%. Major adverse cardiac event occurred in 2.2% of pts (2 death in the setting of acute MI and 4 non Q-wave MI). There was no stent-related death, Q-wave MI, CABG or repeated PTCA. At 30 days there was one episode of stent thrombosis (0.38% of pts). Clinical 6-month follow-up was complete for the first 114 pts (173 stents) recurrence of angina and/or a positive stress test occurred in 13 pts (11.4%), 11 were treated by repeated PTCA and 2 by CABG.

Conclusion: a specific design give to the DUET coronary stent a polyvalence which allow, in real practice, to treat all types of coronary lesions with safety and efficacy.

P972 Clinical and angiographic outcome after implantation of the new coronary C1-stent in patients with coronary heart disease

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Introduction: The purpose of this study was to randomly compare the effect of low (8–10 atm) and high (14–16 atm) pressure implantation of C1-stents in 150 patients with single- or multivessel disease. In addition we planned to perform directional coronary atherectomy (DCA) of each in-stent restenosis (ISR) to compare tissue characteristics of the different lesions.

Methods and Results: QCA was performed using the Cardiovascular Measurement System, Medis, NL. Unpaired t-test was used for statistical evaluation. Until now, follow-up angiography was available in 84 pts. treated with high (HPI, n = 42) or low (LPI, n = 42) pressure stent implantation. Risk factors and angiographic parameters of the treated lesions were equally distributed in the two groups. Angiographic re-evaluation was performed 6 months after the intervention. In the total study population 20 pts. (23.8%) had ISR, 13 (31%) in the LPI group and 7 (16.7%) in the HPI group (p = 0.059). Acute results and in-hospital complications were the same in both groups.

	Low pressure	High pressure
Minimal luminal diameter before stent (mm)	0.66 ± 0.71	0.77 ± 0.63
Minimal luminal diameter at follow-up (mm)	1.79 ± 1.06	2.00 ± 0.79
Acute gain (mm)	2.39 ± 0.63	2.50 ± 0.78
Late lumen loss (mm)	1.33 ± 0.92	1.09 ± 0.86

(All values are given in number ± standard variation), all differences were not significant.

Conclusion: Implantation of the new C1-stent is safe and results in an excellent angiographic and clinical outcome. High pressure implantation is recommended.

P973 NIR stenting registry: retrospective observation on immediate results and clinical follow-up in 709 patients

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Background and Objectives: The NIR stent is an expandable cellular coronary prosthesis with high flexibility and excellent trackability. The very low crossing profile, associated to the high flexibility, makes this stent suitable for complex and distal lesions. The aim of this study was to evaluate the feasibility, safety and long term (clinical follow-up) efficacy of elective and/or urgent deployment of the NIR stent in a broad patient group with coronary artery disease.

Method: Between June 1996 and May 1997, n. 986 NIR STENTS were implanted in 781 vessels (de novo or restenotic lesions in native vessels, saphenous vein grafts and internal mammary conduits) of 709 consecutive patients (498 men, 211 women) undergoing coronary angioplasty in two Villa Maria Group Catheterization Laboratories.

Results: Procedural angiographic success was achieved in 98.4% of all the lesions treated, ranging from 100% success rate in type A lesion to 97.6% in type C lesions (overall procedural success 98.4%). Major cardiac complications (MACE) were considered from PTCA/stenting time to the patient discharge. The in-hospital MACE were limited and occurred in 15 patients: urgent CABG 0.8%, death 0.7%, sub-acute stent thrombosis 0.5% (overall in-hospital MACE rate 2.1%). Clinical follow-up data were obtained at 8.6 ± 2.8 months in 645 (92.4%) of the eligible patients. The event free survival rate was 88.3%. The late MACE rate evaluation showed death 1.2%, AMI 0.6%, TVR 9.8% (overall late MACE rate 11.7%).

Conclusion: The NIR stent performances in this broad patient population were excellent, showing very high procedural success rate both in normal and complex coronary anatomy. On the basis of the previous data, we can define NIR stent a safe multifunctional device suitable both for easy and complex situations. The clinical late results are very promising in term of event free survivals and late MACE.

P974 Multicenter evaluation of the ACS RX MULTI-LINK DUET™ coronary stent system in native de novo coronary lesions: the DUET study

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The DUET Study is a multi-center prospective efficacy and safety evaluation of the ACS MULTI-LINK™ coronary stainless steel, balloon expandable stent.

Aim: Primary objectives were to determine the one-month incidence of MACE (Major adverse cardiac events). The secondary objectives were the acute success rate, the restenosis and reocclusion rates (assessed by QCA) at six months and the occurrence of MACE in hospital and at six months.

Methods: 210 patients were enrolled between February and June 1998 in 18 European centers. Successful stent placement was achieved in 209 patients. All patients were treated with ticlopidine 250 mg/day for one month and with aspirin ≥100 mg/day. To allow the investigators to gain familiarity with the stent system, the first one to three patients per center formed a separate lead-in population leaving an intention-to-treat population of 157 patients.

Results: 79% of the intention-to-treat population was male, 28% had unstable angina, 69% had stable angina, 44% had a previous MI, 15% had a previous PTCA, and 3% had an history of stroke. The target vessel was 39.7% LAD, 20.6% LCX and 39.7% RCA. All of the intention-to-treat patients but one were effectively stented (17 required multiple stenting). Minimal lumen diameter (MLD) post-procedure was 2.61 ± 0.33 mm, with a residual diameter of stenosis of 16%. Preliminary follow-up data showed a MLD of 1.88 ± 0.55 mm with a residual diameter stenosis of 36%. The binary interpolated restenosis rate (≥50% residual stenosis) was 14.7%. Mean in hospital stay was 3 ± 4 days. Up to discharge 3.8% of the patients experienced any MACE (all MI). In addition there was one incidence of subacute occlusion. Up to one month two additional patients underwent revascularisation, resulting in a MACE-free population of 94.9%. 86% of the patients were angina free at one month. Final six-month angiographic and clinical data will be available by April 1999.

P975 Determinants and Implications of late expansion in coronary wallstents: an intravascular ultrasound study

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The self-expandable nature of the Wallstent (WS) has been shown to result in late Stent expansion (LE) and a greater neointimal growth. However, the determinants and final implications of LE have not been established. Accordingly, we have reviewed all our native coronary WS implanted in our Unit in which an intravascular ultrasound (IVUS) study with automatic pullback was available both at baseline, at the end of the procedure and at follow-up (FU). Each WS was divided in cross-sections at 2 mm intervals, which were considered independently and carefully matched at each situation, using both the aorto-ostial junction and fixed landmarks. IVUS dimensions as well as plaque and procedural data were included in the analysis. A total of 11 WS in 11 patients were studied (5 LAD, 2 LCX, 4 RC), with diameters from 4 to 5.5 mm (mean = 4.5), and lengths from 17 to 33 mm (mean = 23 mm), allowing for a total of 166 cross-sections to be compared. Multiple linear regression analysis was performed.

At FU, LE was present in 93% of the sections analysed, with a mean of 2.0 $mm^2 \pm 1.9$ (post-implantation Stent area 7.1 ± 1.2 and FU Stent area 9.1 ± 2.1; $p < 0.001$), and a corresponding decrease in the total Stent length from 29 ± 9 to 27 ± 8 mm, $p < 0.001$. LE was greater in non calcified segments. LE was larger in the proximal portion with a stepwise decrease to the mid and distal thirds, and was positively and independently associated with Stent oversizing. Neointimal proliferation at FU was positively associated with LE ($r = 0.63$; $p < 0.001$), even after adjusting for plaque area, minimal area or area gain. Late loss in luminal area, however, showed an inverse relation to LE (β [adjusted] = −0.3, 95% CI: −0.451/−0.15).

Conclusions: LE is a common phenomenon after WS, especially in non-calcified segments, and is mainly determined by Stent oversizing. Despite the fact that it is associated with greater neointimal proliferation it seems to have a net beneficial effect on luminal loss.

P976 Arterial wall stretch due to stent implantation: an additional predictor for major adverse cardiac events

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Stent deployment on tortuous vessel straightens the artery, and consequent arterial wall stretch may contribute to major adverse cardiac events (MACE).

Methods. Clinical (age, sex, coronary risk factors, unstable angina, restenotic, type C and LAD lesions) and angiographic data (stent diameter, maximal stent-balloon pressure, balloon/artery ratio, stenosis length, acute lumen gain /ALG/, late lumen loss /LLL/; pre-, post-stent and follow-up /FUP/ minimal lumen diameter /MLD/, reference diameter, %diameter stenosis /%DS/ and vessel angulation /determined as the angle defined by the tangents of proximal and distal parts of the stenosis or stents/) on 404 patients with single stent implantation were analysed to multivariate nominal logistic regression analysis for prediction of MACE. The predictive accuracy, sensitivity and specificity values and cut-off points of the continuous variables were determined by using receiver operating characteristics curves.

Results The best predictive accuracies and sensitivities/specificities of factors indicating MACE were found for MLD-FUP ≤ 1.7 mm (0.9305, 86.6%), post-stent MLD ≤ 2.63 mm (0.773, 77.2%), %DS-FUP ≥ 42.2% (0.9432, 87.1%), ALG ≤ 1.523 mm (0.6280, 60.9%), LLL ≥ 0.99 mm (0.7680, 69.4%), pre-stent vessel angulation ≥ 33.5° (0.6797, 68.2%) and post-stent changes in vessel angulation ≥ 9.1° (0.6279, 62.2%). Multivariate analysis demonstrated post-stent MLD, MLD at FUP, %DS, acute lumen gain, late lumen loss, pre-stent vessel angulation and post-stent changes in vessel anqulation as significant predictors for MACE (table).

	p (multivariate)	Odds ratio	95% CI (odds ratio)
Post-stent MLD	0.0376	2.116	1.242–3.605
MLD-FUP	0.0021	20.286	10.447–39.394
%DS-FUP	0.005	41.795	19.57–89.258
Acute lumen gain	0.0402	1.743	1.026–2.963
Late lumen loss	0.0064	8.186	4.483–14.95
Pre-stent vessel angulation	0.0327	1.721	1.013–2.925
Post-stent changes in vessel angulation	0.0319	1.774	1.043–3.017

Conclusions. Permanent arterial stretch due to changes in vessel angulation after stent implantation contributes significantly to the occurrence of MACE, and this finding may have an impact on the future stent design.

P977 Value of signal-averaged electrocardiogram to predict the state of patency of the infarct related artery

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After myocardium infarct (MI) the presence of ventricular late potentials determines a major risk of ventricular arrhythmias, and it has been documented that an effective thrombolysis limits its development. This low amplitude and high frequency signals presents in the last 40 mseg. of the QRS are generated in small areas of myocardium that had different electrophysiological properties than the surrounding tissue. The changes in the electrical conditions are related with the state of permeability of the responsible artery after a MI and could be an important prognostic factor. In our study we trayed to evaluate the test for the determination of late potentials as a method to predict the state of patency of the infarct relatect artery.

In 106 patients with acute MI, three determinations of late potentials where performed with time domain averaging technique and with the filters of 25, 40 and 80–250 Hz, at 24, 72 and 144 hours of the beginning of the symptoms. In all patients coronarigraphy was done, that let to classify them in two groups. Group I includes patients with TIMI 0–1 (obstruction completes or minimum flow in the responsible artery), group II includes patients with TIMI 2–3 (open artery with filling complete and rapid).

The group I had a longer filtered QRS and duration of the terminal potential under 40 uV and lower root mean square voltage of the last 40 msec with all the filters employed. This correlation was stronger with the later studies.

The signal-averaged electrocardiogram has the ability to predict whose patients had a patent vessel post MI and it could be used to predict the thromboysis therapy success.

P978 Reuse of intracoronary ultrasound catheters in the age of cost containment: safety and efficiency study

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Reuse of medical devices labeled for single use, such as electrophysiology, angioplasty and diagnostic catheters, is known to be performed in numerous institutions. However, potential reuse of intracoronary ultrasound (ICUS) catheters is still controversial. Thus, purpose of the study was to evaluate whether reuse of ICUS catheters is feasible, safe and efficient.

Methods: 15 new ICUS catheters (3.5F, 20 MHz, mechanically rotating) were applied in consecutive pts for up to 3 times each, comparing results of brand-new devices with reused ones. On angiography all pts had nonocclusive coronary lesions of simple morphology. Following the use, ICUS catheters were decontaminated in ultrasound chamber, rinsed, dried by compressed air and sterilized with ethylene oxide. Prior to reuse, physical testing and quality assurance was performed. Informed consent for catheter reuse was provided from all pts.

Results: By described reuse strategy, 41 pts could be successfully studied overall, applying 15 new ICUS catheters (2.7 pts/catheter). For the new devices successful positioning at desired vessel site was achieved in 15/15 pts; acquired image quality was classified as optimal in 15/15 pts. For the first reuse 14/15 catheters were selected, since 1 failed to pass mechanical performance testing; successful positioning was in 14/14 pts; image quality was optimal in 13/14 pts and suboptimal in 1/14 due to the moderate image degradation (particular catheter was withdrawn from subsequent use). For the second reuse successful positioning was in 12/13 pts; image quality was optimal in 12/12 pts. Unsuccessful vessel negotiation in 1 case was due to decreased ICUS shaft pushability, requiring introduction of new device. There were no acute procedure related complications in all studies. None of pts developed fever, chills or hypotension following the procedure.

We conclude that, by meticulous cleaning, sterilization and testing, ICUS catheters can be safely reused in patients with noncomplex coronary lesions, retaining proper imaging characteristics. For communities with limited resources such approach may further expand utilization of this high tech procedure.

EXPERIMENTAL ISCHAEMIA AND REPERFUSION

P979 Acute myocardial infarction: regulation of protein kinase C in the non-ischaemic area of the infarcted heart

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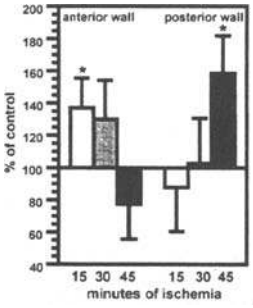
It is not known if regional myocardial infarction may modulate cell signaling in the non-ischemic area of the infarcted heart. Such mechanisms in the remote area might contribute to remodelling processes involving proliferation and hypertrophy. Protein Kinase C (PKC), a central enzyme in cell signaling which mediates hypertrophy, has been shown to be activated and subjected to an increased subtype-selective expression in the ischemic zone after acute myocardial infarction.

To address the question if regional infarction may promote an enhanced expression of PKC also in the remote area, the mRNA expression of one of the dominant isoforms of PKC, PKC-ε was investigated at various times (15, 30, 45 min) after LAD ligation in rat hearts in situ and compared to sham-operated controls. Quantification was performed using quantitative RT-PCR with internal and external standards.

Results: In the ischemic zone (anterior wall, fig.), a rapid increase of PKC-ε mRNA already after 15 and 30 minutes of ischemia was observed (n = 7, *p < 0.05, fig.). An even more pronounced increase of mRNA for PKC-ε was characterized in the non-ischemic zone of the infarcted heart. In contrast to the ischemic zone, this increase occurred significantly later (after 45 min, fig.).



Conclusions: These data characterize for the first time a subtype-specific regulation of PKC expression in the remote zone of the infarcted heart, suggesting a modulation of cell signaling even at a distance to the infarcted area which may contribute to remodelling processes.

P980 Differential gene regulation in early myocardial infarction: analysis of complex expression patterns using PCR-select cDNA-subtraction

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Until recently the analysis of gene regulation in myocardial infarction was focused on a limited number of gene products. However, it is generally accepted that ischemia induces complex patterns of gene expression involving more than one signaling pathway. We tested the new method of PCR-select cDNA-subtraction in an animal model of myocardial infarction to assess the potential of in vivo analysis of differential gene expression.

Methods: In 3 male Wistar-Kyoto rats (250 g) the proximal LAD was ligated to induce an anterior myocardial infarction (MI). Three age and sex-matched sham-operated animals served as controls (C). Sixty minutes after coronary artery ligation the heart was removed and samples from the non-infarcted posterior left ventricular wall (PW) and from the same area of sham-hearts were snap-frozen. Messenger RNA was isolated from pooled MI- and C-tissue and reverse transcribed into cDNA. MI- and C-cDNAs were marked with different cDNA-adapters. After two hybridisation steps and PCRs differentially expressed sequences were amplified, sequenced, and identified using the NIH-Gene Bank.

Results: In the non-infarcted PW 53 differentially regulated genes have been identifed so far -24 were upregulated, 29 downregulated. In addition to sequences of proteins of the JAK-Stat-pathway, heat shock related protein, myosin light chain, and the adenin nucleotide translocator other proteins with so far unknown functional significance during ischemia have been identified: i.e. Annexin and zinc-finger proteins.

In conclusion, the new method of PCR-select c-DNA subtraction permits the in vivo analysis of complex pathogenic gene expression patterns and has the potential to identify new unkown co-regulated proteins.

P981 The inhibition of the extracellular-regulated kinases by PD 098.059 creates a complete cancellation of the ischaemic preconditioning-induced cardiac protection

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There is a protective role of the the extracellular-regulated-kinases (ERK) on ischemic preconditioning (IP), which is indicated through our previous results. We studied the influence of ERK inhibitor PD 098.059 in IP, to test the hypothesis.

Methods: The experiments were carried out in 11 anesthetized, ventilated, open chested, male castrated pigs using the specific MEK1/2-inhibitor (PD 50 μM in KHB and DMSO 1 μl/ml). An intramyocardial infusion (20 μl/min), via three pairs of needles, injected the substance in the risk area (RA) during 15 min. The experimental design included 2 cycles of 10 min LAD occlusion and 10 min reperfusion as IP and followed by a 40 min occlusion/60 min reperfusion cycle, as Index ischemia. In each experiment a parallel infusion of the solvent was performed as a control. In an additional control group with no drug application the infarct size was determined. Biopsies of the area of infusion were taken after the second reperfusion. With western-blot analysis the phosphorylation of the ERK and Elk-1 was ascertained and with in-gel-phosphorylation (IGP) the activity of the ERK was tested.

Results: No infarcts were detected in the control group with the experimental design of IP using 40 min index ischemia. In the area of the PD-infusion significant wedge-shaped infarcts could be seen. In the rest of the RA no infarcts occurred, even in the area of solvent infusion. The western-blot analysis showed a decrease of the phosphorylation of ERK as well as their substrate Elk-1 after PD infusion. The result of IGP showed, that PD inhibited the ERK-1 activity (49.9 ± 6.5%) and ERK-2 (56.2 ± 4.3%) refer to DMSO as control.

Conclusion: Our experiments demonstrate that the use of the MEK1/2-inhibitor PD 098,059 results in a blockade of IP in vivo. These datas prove the important role of the ERK in IP.

P982 Ebselen protects the heart against ischaemia-reperfusion injury in rabbits

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Ebselen is a selenoorganic compound that has exhibited multifunctional actions such as antioxidant capacity and anti-inflammatory effects. We previously reported the cardioprotective effects of this agent in canine ischemia-reperfusion injury but the treatment was started before coronary occlusion (Am J Physiol 267: H2342, 1994). In the present study, we evaluated the effects of ebselen on infarct size using a rabbit coronary artery occlusion-reperfusion model of myocardial infarction when treated immediately before coronary reperfusion.

Methods: In male Japanese white rabbits (n = 29), the branch of left coronary artery was occluded for 30 minutes and was reperfused for 48 hours. Rabbits were randomized for treatment with ebselen (n = 19) or its vehicle (n = 10); ebselen was administered 5 minutes before coronary reperfusion (1 mg/kg bolus + 1 mg/kg iv for 60 minutes, n = 10, Ebselen-L; 2 mg/kg bolus + 4 mg/kg iv for 60 minutes, n = 9, Ebselen-H). Infarct size was assessed by a dual staining method using triphenyltetrazolium chloride and Evans blue dye.

Results: Plasma selenium level during coronary reperfusion was increased in ebselen-treated groups dose-dependently. Infarct size did not differ significantly between the control (482 ± 6.8%) and the Ebselen-L (36.6 ± 8.2%). However, the infarct size in the Ebselen-H (22.0 ± 3.9%) was significantly smaller ($p < 0.05$) than the control. The anatomic area at risk did not differ significantly among the three groups. There were no differences in hemodynamic parameters among the three groups during coronary occlusion and reperfusion for 1 hour.

In conclusion, ebselen treated immediately before coronary reperfusion significantly reduced myocardial ischemia-reperfusion injury in a dose-dependent manner in rabbits.

P983 Specific relocation of the S100A1 Ca^{2+}-binding protein during cardiopulmonary bypass

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Background: Myocardial ischemia during cardiopulmonary bypass terminated by reperfusion generally leads to damage of the cardiomyocytes induced by transient cytosolic Ca^{2+}-overload. Recently, much attention has been paid to the role of heart-specific Ca^{2+}-binding proteins in the pathogenesis of myocardial ischemia-reperfusion injury. S100A1 is a heart specific EF-hand Ca^{2+}-binding protein which is directly involved in a variety of Ca^{2+}-mediated functions in muscle cells.

Aim and Methods: The aim of our study was to investigate the ultrastructural localization of S100A1 in the human heart under normal (baseline) conditions and after prolonged ischemia and reperfusion of the myocardium. We utilized confocal laser scanning microscopy to study cardiac biopsies from patients undergoing cardiopulmonary bypass.

Results: In control tissue samples obtained from patients before initiation of the extracorporal circulation S100A1 was localized to the cytoplasm of cardiomyocytes where it appears in strong association with actin contractile filaments. Prolonged ischemia of the heart (30 min) induced specific relocation of S100A1 to the cell membrane and extracellular space. However, this relocation was reversible after prolonged reperfusion (>30 min) of the heart.

Conclusion: Our data suggest that S100A1 is directly involved in the transient perioperative myocardial damage conferred by cardioplegia during corrective heart surgery in humans. Given its role in the contractile function of muscle cells, this S100 protein could be an important "intracellular link" in ischemia-reperfusion injury of the heart.

P984 Ischaemia-induced Stat-1 expression modulates apoptosis in cardiac cell

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Loss of cardiac myocytes by programmed cell death (apoptosis) is an important mechanism in the development of cardiac failure during injury due to ischaemia/reperfusion and myocardial infarction. Siganal transducer and activator of transcription-1 (STAT-1) is a transcription factor that is activated by interferon-γ (IFN-γ) via the Janus kinases (JAKs). STAT-1 has recently been implicated in playing a role in apoptosis. In the present study we assessed the role of STAT-1 in ischaemia/reperfusion-induced apoptosis.

Methods: Primary cardiomyocytes were isolated from 2-day old neonatal rats and subjected to simulated ischaemia in media buffer consisting of 137 mM NaCl, 3.58 mM Kcl, 0.49 mM $MgCl_2$, 0.9 mM $CaCl_2$. 2 H_2O, 4 mM HEPES supplemented with 0.75 sodium dithionite, 10 mM deoxyglucose, 20 mM lactate and 12 mM hydrogen ion (pH 6.5) concentration to inhibit glycolysis and placed in an atmospheric chamber of 5% CO_2 and 95% argon at 37°C for 4 hours. The ischaemic buffer was removed and cells were place back with minimal media and cells were returned to 37 o C. 21% O_2 and 5% CO_2. Cells were harvested and analysed by Western blotting for STAT-1. Experiments were also performed in which cell death was assessed in cardiac cells that were transiently transfected with an expression vector to over-express STAT-1. We also analysed a target gene for STAT-1, caspase 1 that may be involved in promoting apoptosis. Ex-vivo ischeamia/reperfusion studies were performed on isolated rat hearts using the Langerdoff perfusion apparatus and sections were analysed by immunofluorescence for both TUNEL labeling to assess apoptosis and STAT-1 immuno-staining.

Results: Exposure of cardiac cells to hypoxia/ischaemia results in apoptosis and is accompanied by phosphorylation and increased expression of STAT-1. To determine whether the increase in STAT-1 expression in cardiac myocytes was sufficient to induce apoptosis, cardiac cells were induced to over-express STAT-1 by transfection with a constitutive STAT-1 expression vector and then exposed to hypoxia. STAT-1 transfected cells were more susceptible to hypoxic-induced apoptosis than cells transfected with a control plasmid lacking the STAT-1 cDNA.. Expression of caspase-1, a cysteine protease enzyme involved in the final effector arm of the cell death pathway is also increased in response to hypoxia. IFN-γ which is known to to activate the STAT-1 pathway, also increases the expression of caspase-1 and also transactivated a caspase-1 reporter constract in cardiac myocytes. Moreover, IFN-γ-induced apoptosis was inhibited by yVAD-CHO, an inhibitor of the caspase-1 protease. Finally, ischaemia/hypoxia reperfusion also induces STAT-1 and caspase-1 expression in ventricular myocytes ex-vivo. Immunofluorescent staining also demonstrated an increase in STAT-1 positive staining in cardiac myocyte cells which also parallelled the incraese in TUNEL positive staining in response to ischaemia/reperfusion injury.

Conclusion: These results suggest that STAT-1 might play a critical role in the regulation of ischaemia/hypoxia-induced apoptosis via a caspase-1 activation dependent pathway in cardiac cells.

P985 Sodium-hydrogen exchange inhibition provides cardioprotection, attenuates neutrophil activity, but does not effect platelet aggregation *in vitro* or *in vivo*

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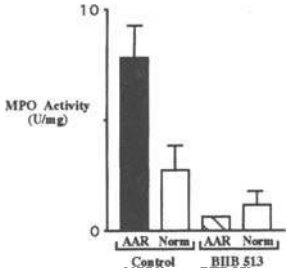
Background: Numerous studies have demonstrated the cardioprotective efficacy of sodium-hydrogen exchange inhibition. Earlier studies using less specific inhibitors of NHE-1 suggested both anti-platelet and anti-neutrophil activity. To data the effect of NHE-1 inhibition on platelet and neutrophil activity in vitro has been limited and in vivo has not been reported.

Methods: Using a canine model of ischemia-reperfusion injury and platelet mediated cyclic flow the selective NHE-1 inhibitor BIIB 513 was used to determine the *in vitro* and *in vivo* effects on ischemia-reperfusion injury as well as platelet and neutrophil activity.

Results: *In vitro* up to 1 mM of BIIB 513 did not attenuate collagen, ADP, or thrombin induced platelet aggregation. *In vivo,* up to 9 mg/kg (3× the previously determined cardioprotective dose) did not attenuate platelet mediated cyclic flow. In contrast, both PMA- and PAF-induced neutrophil oxidative burst were attenuated by 1 μM BIIB 513. Furthermore, *in vivo* administration of 3 mg/kg of BIIB 513 not only significantly decreasedmyocardial infarct size but also significantly attenuated neutrophil accumulation within the myocardium-at-risk during ischemia, as measured by MPO activity.



Conclusions: NHE-1 inhibition affords cardioprotection not only via direct cardiomyocyte protection but also via attenuation of neutrophil activity. However, NHE-1 inhibition does not inhibit platelet aggregation *in vitro* or *in vivo* and thus would not be expected to interact with currently employed antiplatelet agents.

P986 Cardioprotection by ischaemic preconditioning is disturbed in the remodeled heart after myocardial infarction

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Studies using normal myocardium have indicated a crucial role of protein kinase C (PKC) during ischemic insult in the mechanism of ischemic preconditioning (PC). However, intracellular signals to PKC and activity of this kinase are modified in the process of ventricular remodeling after myocardial infarction (MI). Therefore, we tested whether the PC mechanism is unchanged in the remodeled ventricular myocardium.

Methods: Using echocardiography, we confirmed that ventricular hypertrophy and dilation reach near maximal levels at 2–3 weeks after coronary ligation (COL) in the rabbit. Based on these results, the rabbit heart was excised 2 weeks after COL or sham operation, perfused with Krebs buffer and subjected to 30-min global ischemia (I)/2 h-reperfusion (R) to induce acute MI in vitro. The heart received either no pretreatment, PC with 2 cycles of 5-min I/5-min R, angiotensin II (AT-II, 100 nM), or diazoxide (100 μM), an opener of mitochondrial KATP channels (mito-KATP). The drugs were infused for 10-min before the global ischemia. Infarct size was determined by tetrazolium staining and expressed as a% of the left ventricle (%I/LV). The area of old MI induced by COL was excluded from infarct size measurement.

Results: Infarct size in the sham-operated hearts with no pretreatment (%I/LV = 47.9 ± 11.2) did not differ from that in the remodeled hearts with no pretreatment (%I/LV = 48.5 ± 6.8). Although PC and pharmacological PC with AT-II limited infarct size in sham-operated hearts (%I/LV = 9.2 ± 3.4 and 25.3 ± 4.5,respectively), they failed to protect the remodeled myocardium from infarction (%I/LV = 53.4 ± 0.8 and 46.0 ± 4.4,respectively). An opener of mito-KATP, which is a probable effector of PC, reduced infarct size in both sham-operated and remodeled hearts (%I/LV = 13.3 ± 3.3 and 11.7 ± 4.2,respectively).

Conclusion: The endogenous protective mechanism of PC is lost during ventricular remodeling after MI. This dysfunction in PC might be due to failure of signals elicited by PKC-linked receptors during PC to reach mito-KATP in the remodeled myocardium.

P987 Female gender and hypertension independently reduce tolerance to ischaemia-reperfusion injury post-myocardial infarction

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Background: Females (F) and hypertension (HTN) have both been associated with increased mortality following myocardial infarction (MI). We have shown that in F, relative to males (M), HTN increased compensatory left ventricular hypertrophy (LVH) post-MI. Increased LVH might decrease tolerance to ischemia-reperfusion (Isch+Reper) injury and thus contribute to worse prognosis in F and HTN patients post-MI. We therefore examined if gender and HTN influence susceptibility to Isch+Reper injury post-MI.

Methods: Male (M) and F salt-sensitive (SS) and salt-resistant (SR) Dahl rats underwent coronary ligation. Post-MI, 4 wks of high salt diet resulted in similar levels of HTN in MSS and FSS rats (>170 mmHg), with no HTN (NHTN) in MSR and FSR rats. Isolated, red-cell perfused, isovolumically beating hearts underwent an Isch-Reper protocol consisting of 30 min low-flow Isch (15% of baseline flow) followed by 30 min Reper (100% baseline flow). Four post-MI groups were examine in this study: M+NHTN (n = 12), M+HTN (n = 8), F+NHTN (n = 11), F+HTN (n = 12).

Results: Infarct size was similar in all four groups (46–48% of LV). HTN increased heart weight/tibia length similarly by 20% in M+F ($p < 0.05$ vs NHTN). With identical coronary flow, lactate production, and oxygen consumption, F gender independently resulted in increased diastolic dysfunction during Isch versus M (39 ± 2 vs 32 ± 2 mmHg, $p < 0.05$), but not during Reper (16 ± 1 vs 14 ± 2 mmHg, p = ns). HTN, however, when compared to NHTN, caused worse diastolic dysfunction during Isch (40 ± 3 vs 32 ± 1 mmHg, $p < 0.01$) and Reper (18 ± 2 vs 12 ± 1 mmHg, $p < 0.01$), independent of gender. All four groups had similar percent recovery of developed pressure at the end of Reper.

Conclusion: Both female gender and hypertension independently increase susceptibility to Isch-Reper injury in post-MI hearts and may adversely affect prognosis following myocardial infarction.

P988 Time-dependent expression of cardiac bradykinin receptors in experimental left ventricular myocardial infarction

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An increase in cardiac bradykinin (BK) might be a mechanism to protect the heart during acute myocardial infarction (MI). To characterise the regulation of myocardial B1 and B2 receptors during MI, we studied the expression of both BK receptors in the left ventricle (LV) 6 h, 24 h and 6 days after left coronary ligation. Experiments were performed in male Spraque Dawley rats and compared with sham operated animals (n = 5, each group). After total RNA extraction, the myocardial expression of B1 and B2 receptors was analysed by a RNase-protection assay, using specific probes from the coding regions of both receptor genes and the GAPDH gene (as a house-keeping gene). Under basal conditions the B2 receptor – but no B1-receptor expression was detectable, although GAPDH, as an internal control, was detectable in all groups. Rats with MI were normotensive and showed an impaired left ventricular function. After MI no B1-receptor expression was detectable to any investigated time points. In contrast, we revealed a 3-fold increase of the B2-receptor expression 6 h after induction of MI. After 24 h and 6 days this upregulation was 10 fold increased compared to sham operated rats. Our data clearly show that the described increase in BK after MI is accompanied with a rapidly upregulation of the B2-receptor expression, which stays stable for at least 1 week. In contrast, the B1-receptor axis of the kallikrein-kinin system seems not to be involved under this pathophysiological circumstance.

P989 Myocardial infarction mediated by endothelin receptor signalling in hypercholesterolemic mice

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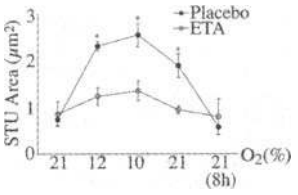
Endothelin (ET), a powerful vasocontrictor, is present in unstable coronary plaques and increases in patients with acute myocardial infarction (AMI). We tested the hypothesis that ET-mediated vasoconstriction precipitate AMI in a mouse atherosclerotic model.

Methods: 57 anesthetized apoE° LDL receptor° (E°/LDLR°) mice and 15 C57Bl6 control mice, aged >7 months, were subjected to acute hypoxia, as vasoconstrictor stimulus, by reducing oxygen (O_2) to 16, 14, 12 and 10%, (2' each step), followed by reoxygenation. E°/LDLR° mice were randomized to receiving placebo (Placebo, n = 30) or an endothelin receptor A antagonist (ETA, n = 17) just before hypoxia. STU area changes on the electrocardiogram (ECG) were considered as signs of ischemia. AMI was ascertained by serum Troponin T measurement, 14 days later, at autopsy.

Results: A total of 31/57 E°/LDLR° mice (54%) developed ischemic ECG changes. STU area changes were significantly greater in Placebo than in ETA group (figure, *$p < 0.01$).



Troponin T was higher in Placebo than in ETA group ($p < 0.5$). ECG and Troponin T were normal in controls.

Conclusion: E°/LDLR° mice develop coronary atherosclerosis and myocardial infarction. Hypoxic stress causes endothelin mediated acute myocardial infarction in atherosclerotic mice.

P990 Cariporide, a new selective Na^+/H^+-exchange inhibitor, improves postischaemic recovery by attenuating Ca^{2+}-overload and prolonging acidosis upon reperfusion

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Na^+/H^+-exchange inhibition improves mechanical recovery after ischemia. Despite an ongoing trial with Cariporide in patients with acute coronary syndrome (GUARDIAN trial), the mechanism of action remains speculative. Since Na^+/H^+-exchange is activated upon reperfusion, it has been hypothesized that its inhibition reduces Na^+- and (via Na^+/Ca^{2+} exchange) Ca^{2+}-overload. Attenuated Ca^{2+}-overload and prolonged acidosis are known to be cardioprotective.

Methods: To test this hypothesis, developed (DevP) and diastolic pressure (P_{dias}) were measured in isovolumic Langendorff rat hearts subjected to 30 min of ischemia and 30 min of reperfusion (T = 37°C) without (*Untreated*) or with 1 μM *Cariporide* (= HOE642) (*HOE*) added to the perfusate 30 min prior to ischemia. Intracellular $[Ca^{2+}]_i$ or pH_i were measured with aequorin or ^{31}P-NMR spectroscopy, respectively (n = 2 × 12).

Results (*$p < 0.05$): *Cariporide* did not affect mechanical function, Ca^{2+}-transients or pH_i under normoxic conditions. Mechanical recovery was substantially improved in *HOE* compared to *Untreated:* DevP (% of preischemic values) 92 ± 3 vs. 49 ± 7*, P_{dias} = 16 ± 3 vs. 46 ± 5* mmHg. No difference was found for ischemic contracture. $[Ca^{2+}]_i$ at end ischemia was significantly lower in *HOE:* 1.04 ± 0.06 vs. 1.84 ± 0.02* μM. $[Ca^{2+}]_i$ peaked in the first 30 sec of reperfusion and was significantly attenuated in *HOE:* 2.0 ± 0.3 vs. 3.2 ± 0.3* μM. pH_i was not different at end-ischemia (≈6.1). After reperfusion, pH_i was similar at 30 sec (≈6.5) and 60 sec (≈6.85) and ≥7 min (≈7.01) but acidosis was prolonged from 2 to 6 min in *HOE* compared to Untreated (e.g. 6.7 ± 0.05 vs. 7.3 ± 0.05* at 5 min).

Conclusion: The Na^+/Ca^{2+}-exchange inhibitor *Cariporide* improves postischemic recovery by reducing Ca^{2+} overload during ischemia and in the first minute of reperfusion and by prolonging acidosis in the following 5 minutes of reperfusion.

P991 Protection by mitochondrial ATP-sensitive potassium channel opener diazoxide of globally ischaemic cold-stored hearts

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There is increasing evidence that the cardioprotective effects of ischemic preconditioning are mediated by an opening of mitochondrial ATP-sensitive potassium channels (K_{ATP}). The objective of this study was to assess whether the K_{ATP} opener diazoxide could produce the protection of isolated hearts subjected to prolonged ischemic cold storage simulating the situation of cardiac allografts.

Methods: 34 isolated buffer-perfused rat hearts were arrested with and stored in Celsior (a new heart preservation solution) for 10 hr at 4°C. Reperfusion was then initiated for 2 hr. In the first group, hearts served as controls. In group 2, diazoxide was tested as a pharmacological preconditioning agent. After baseline functional assessment, hearts were subjected to a 15-min infusion of diazoxide (Hyperstat®, 30 μmol/l), followed by a 5-min washout period before arrest. In group 3, diazoxide was given as an additive to Celsior (100 μmol/l) and hearts were thus exposed to the drug during both arrest and storage. End points included recovery of left ventricular (LV) systolic and diastolic function (including pressure-volume (P-V) curves assessed by linear regression analysis of the end-diastolic pressure data to calculate a slope), total release of creatine kinase (CK) over the first 45 min of reperfusion, endothelium-dependent coronary vasorelaxation to 5-hydroxytryptamine ($5{\cdot}10^{-6}$ mol/l) under constant perfusion pressure conditions or to acetylcholine (10^{-6} mol/l) under constant flow conditions and myocardial water content.

Results: Baseline functional parameters were not different among the three groups. Main reperfusion data (mean ± SEM) are summarised below:

Group	Slope of P-V curve (mm Hg/ml)	LV max + dP/dt (mm Hg/s)	CK release (IU/g dry weight)	Water content (%)
1 (n = 12)	1212 ± 32	1061 ± 59	1013 ± 138	83.22 ± 0.26
2 (n = 12)	943 ± 55*	1068 ± 59	782 ± 55	81.86 ± 0.27*
3 (n = 10)	989 ± 86*	1577 ± 73**	780 ± 107	82.22 ± 0.23*

*$p < 0.05$ vs group 1; **$p < 0.01$ vs groups 1 and 2

Conversely, the endothelium-dependent coronary vasorelaxation to 5-hydroxytryptamine or acetylcholine was not different among the three groups.

Conclusion: Diazoxide-induced opening of mitochondrial K_{ATP} is an effective means of improving myocardial recovery after an extended period of cold global ischemia. The clinical relevance of these data stems from the availability of diazoxide for human use.

P992 Expression and protective effects of urocortin in cardiac myocytes

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Urocortin (Ucn) is a member of a family of peptides which includes hypothalamic corticotropin releasing hormone (CRH). We have previously shown that Ucn, but not CRH, is expressed in primary cultures of neonatal rat cardiac myocytes. In this study, we have assessed the role of cardiac Ucn in cell death induced by simulated ischaemia.

Methods: Neonatal rat cardiac myocytes were cultured in an atmosphere of 95% argon, 5% CO_2 for 6 hours. Ucn expression was assessed by PCR. Necrotic and apoptotic cell death was assessed in the absence and presence of Ucn and CRH. Four hour ischaemia-preconditioned medium was tested, both in the absence and presence of α helical CRH. Expression of transcription factors in control and ischaemic myocytes was evaluated by Western blotting. A fragment of the Ucn promoter containing an NF-IL6 consensus element ligated into a luciferase vector was transfected into cardiac myocytes, the cells exposed to ischaemia and luciferase activity measured on a luminometer.

Results: Ucn expression is increased by ischaemia and exogenous Ucn is roughly 10 × more potent than CRH in reducing both necrotic and apoptotic death induced by ischaemia, consistent with the higher affinity for Ucn of the type 2 CRH receptor expressed in the heart. The cardioprotective effects of ischaemia-conditioned media are also abrogated by the Ucn antagonist α helical CRH. For example, after 6 hours simulated ischaemia, 72% of cells were trypan blue positive; in the presence of ischaemia conditioned medium this fell to 44% but reverted to 70% with the Ucn antagonist. Ischaemia also produced a 10 fold increase in expression of the transcription factor, NF-IL6. Reporter activity of a Ucn promoter construct containing an NF-IL6. consensus site was doubled by ischaemia.

Conclusion: These data suggest that ischaemia increases expression and release of Ucn, an endogenous cardioprotrective agent.

P993 Effect of ischaemic preconditioning on mitochondrial function in perfused hearts after prolonged ischaemia

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The protective effect of ischemic preconditioning against myocardial ischemia may partially come from the improved energy metabolism. The aim of this study was to examine the protective effects of preconditioning on the physiological parameters of cardiac muscle, functional characteristics of mitochondrial respiratory chain and oxygen radical production by cardiac mitochondria.

Methods: Isolated perfused rat hearts were either subjected or not subjected to preconditioning before 30 min of global ischemia and 30 min of reperfusion. Preconditioning was achieved with four cycles of 5 min of ischemia followed by 5 min of reperfusion. In both groups, mitochondria were isolated from the myocardial tissue after initial perfusion, 30 min of ischemia or 30 min of reperfusion. The rate of superoxide radical production was determined from the EPR spectra of 4,5-dihydroxy-1,3-benzene-disulfonic acid (Tiron), an oxygen free radical scavenger.

Results: An ischemic contracture appeared earlier in preconditioned group, but its level by the end of prolonged ischemia, as well as after 30 min of reperfusion, was significantly lower than in control group. In control group, the product of developed pressure and heart rate was restored only to 16 ± 10% of its initial value, while in preconditioned group this parameter was restored to 73 ± 5%. Preconditioning protected the mitochondrial membranes during prolonged ischemia. In preconditioned group, the respiratory control of mitochondria isolated from the postischemic myocardial tissue remained as good as 2.3 ± 0.1 even after 30 min of ischemia. At the same time, the prolonged ischemia induced entire respiratory impairment in the control group. However, the mitochondrial oxygen consumption was essentially higher (148 ± 8%) in control group than in preconditioned group. After 30 min of ischemia, the rate of superoxide radical generation was higher in mitochondria isolated from the hearts of both groups, but it was significantly lower in mitochondria isolated after prolonged ischemia from the preconditioned hearts. The rate of superoxide radical production by the mitochondria in preconditioned group was equal to 56 ± 7% of its value in control group.

Conclusion: The results suggest that preconditioning preserves the normal mitochondrial function and reduces the rate of oxygen radical production by cardiac mitochondria after prolonged ischemia. It may play an important role in improvement of postischemic contractile function and energy metabolism.

P994 Extracellular leakage of annexin V and inhibitory effects of propranolol in myocardial ischaemia followed by reperfusion

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Background: Annexin V (AnV) is a calcium-dependent phospholipid-binding protein present in the myocardium. It is a new biochemical marker of myocardial injury. The purpose of this study is to evaluate the nature of AnV in myocardial ischemia followed by reperfusion, and the effects of propranolol to AnV.

Methods: In this experiment, 40 isolated rat hearts perfused by Langendorff's method were prepared. Thirty min of reperfusion was performed following global ischemia (GI) of 3 min, 10 min and 30 min in each eight rat hearts. Of 10^{-6} M propranolol was administered at 1 min before GI of 10 min and 30 min in each eight rat hearts. Haemodynamic parameters were obtained. We measured AnV concentration in perfusate by ELISA, and examined AnV localization in the reperfused heart by immunohistochemistry.

Results: Among various indices of cardiac fuction, LV developed pressure and coronary flow deteriorated after reperfusion following both 10 min and 30 min GI. LV diastolic pressure increased after reperfusion following 30 min GI. However, in reperfused isolated rat hearts with propranolol, cardiac performance was improved compared with that without propranolol.

AnV concentration in perfusate of before-GI was 0.6 ± 0.3 ng/ml. It did not increase after reperfusion following 3 min GI, but increased after reperfusion following 10 min GI. When GI lasted for 30 min, AnV concentration increased to 20.0 ± 3.4 ng/ml immediately after reperfusion, compared with before-GI level ($p < 0.0001$). Pretreatment with propranolol was effective for inhibiting the increase of AnV concentration immediately after reperfusion following 30 min GI (3.8 ± 0.6 ng/ml, $p < 0.0001$). Immunohistological examination revealed a significant staining of AnV in the cell membrane and intracellular space after 30 min reperfusion following 10 min GI, and the intracellular aggregation of AnV after 30 min reperfusion following 30 min GI. Propranolol inhibited both extracellular leakage and intracellular aggregation of AnV.

In conclusion, AnV leakage occurs by a reperfusion following GI, and propranolol inhibits the AnV leakage and the deterioration of cardiac function after reperfusion in this experimental setting.

P995 Ischaemic preconditioning preserves VEGF mRNA expression in rat infarcted myocardium

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Background: Ischemic preconditioning reduces infarct size following acute myocardial infarction (AMI). We have demonstrated that serum vascular endothelial growth factor (VEGF) concentration was greater in patients with AMI who had preinfarction angina than those who didn't have. However, exact mechanism of this phenomenon is unclear. In the present study, we investigated the effect of ischemic preconditioning on VEGF mRNA expression in rat left ventricle following AMI. Methods and Results: We used 12 male SD rats aged 8 weeks. We performed the operation of ischemic preconditioning (4 series of 5 min-ischemia and 30 min-reperfusion, IP operation) in 3 rats (group R), the operation of left coronary artery ligation for 5 hours in 3 rats (group M), the operation of left coronary artery ligation for 3 hours after the IP operation in 3 rats (group RM), and sham operation in 3 rats (group S). After the operation, the cardiac tissue was harvested and separated at the point of ligation into two portions; apical portion including the infarcted area and basal portion not including infarct. Northern blot analysis was performed to quantificate the levels of VEGF mRNA, and immunohistochemical examination was performed to detect the distribution of VEGF protein in each portion. The VEGF mRNA levels of the apical portions were significantly higher in group RM (237.6 ± 22.1% expression compared with group S), not in group R (109.6 ± 4.5%) and group M (102.9 ± 4.3%), than in group S (100%) ($p < 0.0001$). The VEGF mRNA levels of the apical portions were significantly greater in group RM than in group R or group M ($p < 0.0001$). The VEGF mRNA levels of the basal portions were similar among the 4 groups. The levels of VEGF mRNA in group RM were significantly higher in the apical portions than in the basal portions (103.7 ± 9.2%) ($p < 0.05$). In group R, group M, and group S, the VEGF mRNA levels in the apical portions were not different from those in the basal portions. Immunohistochemical examination revealed that VEGF protein was not detected in group S. VEGF protein was expressed in endocardial myocytes of the apical portion in group R, myocytes in the non-infarcted area in group M, and myocytes in the infarcted area in group RM.

Conclusions: Ischemic preconditioning may preserve the expression of VEGF mRNA in the infarcted myocardium following AMI.

P996 Serine protease inhibitor (Aprotinin®) attenuates myocardial necrosis and apoptosis following ischaemia and long-term reperfusion in rats

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Although early coronary reperfusion of the ischemic myocardium is a desired therapeutic goal, evidence indicates that reperfusion itself contributes to additional myocardial injury. This has been in part attributed to neutrophil released mediators like oxygen derived radicals and proteases.

The cardioprotective effects of the serine protease inhibitor Aprotinin (APR) were examined in a murine model of myocardial ischemia and long-term reperfusion (i.e., 20 min. + 24 hours). Aprotinin (20.000 U/kg) administered 5 min. prior to reperfusion significantly attenuated myocardial injury compared to vehicle treated rats (79 ± 18 vs 890 ± 65 CK difference, $p < 0.01$). 5000 U/kg of APR resulted only in partial inhibition of reperfusion injury. Further, cardiac myeloperoxidase (MPO) activity, a marker of neutrophil accumulation was significantly reduced following Aprotinin treatment (0.34 ± 0.2 vs 1.34 ± 0.15, MPO difference, $p < 0.05$). Histological analysis of ischemic-reperfused myocardium of vehicle treated animals demonstrated increased neutrophil infiltration compared to the protease inhibitor treated rats (68 ± 15 vs 24 ± 8 PMN/mm^2, $p < 0.05$). Further, induction of apoptosis following myocardial ischemia and reperfusion could be significantly reduced following APR administration.

Thus, inhibition of neutrophil released proteases with Aprotinin appears to be an effective mean to preserve ischemic myocardium from reperfusion injury even following 24 hours of reperfusion. The cardioprotective effect appears to be at least in part due to reduced PMN infiltration with subsequent diminished myocardial necrosis.

P997 Soluble L-selectin levels decrease following dipyridamole administration in patients with ischaemic heart disease but not with syndrome X

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Background. Activation of leukocytes during myocardial ischaemia contributes to the development of ischaemic myocardial injury. Increased leukocyte adhesion to endothelium as a result of myocardial ischaemia occurs via adhesion molecules and is known to be involved in the "no-reflow" phenomenon with impairment of coronary capillary flow. L-selectin, an adhesion molecule expressed by neutrophils, is known to contribute to increased leukocyte-endothelial adhesion during ischaemia.

Aim. The purpose of this study was to evaluate whether myocardial ischaemia produced during administration of dipyridamole results in release of soluble adhesion molecule L-selectin (sL-selectin) in patients with ischaemic heart disease (IHD) and with syndrome X (defined as ischaemic- like chest pain, positive exercise ECG and angiographically normal coronary arteries).

Methods. Plasma samples were obtained from 7 patients with syndrome X and 7 age-matched subjects with IHD before and 7 min. after i.v. administration of dipyridamole (0.56–0.84 mg/kg). Soluble L-selectin levels were measured by a sensitive ELISA assay.

Results. Dipyridamole decreased plasma levels of sL-selectin in patients with IHD from 1381 ± 246 to 999 ± 137 ng/ml ($p < 0.02$, mean ± SEM) but had no effect on sL-selection levels in patients with syndrome X (846 ± 13 and 966 ± 105 ng/ml, respectively).

Conclusion. Dipyridamole induced myocardial ischaemia results in a decrease of plasma levels of sL-selectin in patients with IHD but not in subjects with syndrome X. We speculate, that the decrease in sL-selectin levels as a result of dipyridamole infusion may be related to stimulation of expression of cellular L-selectin counter-receptors with subsequent "trapping" of soluble L-selectin. High basal concentrations of sL-selectin in patients with IHD may be a result of systemic leukocyte activation.

P998 Vulnerability of the aged rat heart to ischaemia and reperfusion

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Myocardial aging is associated with contractile dysfunction and higher sensitivity to ischemia. However, the respective part of ischemia (I) and reperfusion (R) in the post-ischemic recovery of the aged heart remains unclear. Isolated hearts from 4 and 24 month old rats were subjected to paced low flow ischemia (60 min at 15% of initial coronary flow (CF); 4 mo-I and 24 mo-I groups) or to no-paced low flow ischemia (45 min at 15% CF) followed by 30 min of reperfusion (4 mo-IR and 24 mo-IR groups). Active tension (AT) and coronary resistance (CR) were recorded at baseline and after 1, 5 and 15 min of paced low flow ischemia, and AT and CF were recorded at baseline and after 15 and 30 min of reperfusion.

Results: mean ± SEM (in % of baseline value). $^*p < 0.05$ vs 4 mo groups.

	AT I 1 min	AT I 5 min	CR I 5 min	CR I 15 min
4 mo-I (n = 10)	74 ± 5	52 ± 6	157 ± 28	248 ± 62
24 mo-I (n = 11)	49 ± 5*	36 ± 4*	424 ± 101*	521 ± 95*

At the end of no-paced ischemia, CR and cardiac work (AT*heart rate product; 27 ± 3 vs 32 ± 3% of baseline value respectively) were similar in 4 mo-IR and 24 mo-IR groups.

	AT R15 min	AT R30 min	CF R15 min	CF R30 min
4 mo-IR (n = 9)	78 ± 6	73 ± 5	78 ± 10	71 ± 7
24 mo-IR (n = 8)	57 ± 7*	45 ± 7*	52 ± 9*	43 ± 9*

Conclusion: Myocardial function and vascular tone are impaired in senescent heart as soon as the first 15 min of ischemia, indicating a higher sensitivity to paced low flow ischemia during aging. After no-paced ischemia, which induces the same decline in cardiac work in both groups, the myocardial reperfusion however induces lower recovery of myocardial function and coronary flow in senescent hearts. These results indicate specific sensitivity of aged heart to reperfusion.

P999 Urodilatin limits acute reperfusion injury in the isolated rat heart

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Hypercontracture is an important mechanism of myocyte injury during reperfusion. cGMP modulates the sensitivity of contractile myofilaments to Ca^{2+}, and increasing its concentration during the last minutes of anoxia prevents reoxygenation-induced hypercontracture in isolated cardiomyocytes. The purpose of this study was to determine whether stimulation of particulate guanylyl cyclase with the natriuretic peptide urodilatin, given at the time of reperfusion, reduces myocardial necrosis in the intact rat heart submitted to transient ischemia. Isolated rat hearts (n = 53) were submitted to either 40 or 60 min of non-flow ischemia and 2 hours of reperfusion, and allocated to receive either no drug (Control) or urodilatin 0.05 μmol/L during the first 15 min of reperfusion. A marked reduction in cGMP release was observed in control hearts during reperfusion after 40 or 60 min of ischemia (21 $\pm$ 6% and 11 $\pm$ 6% of preischemic values respectively). Urodilatin increased cGMP release to levels close to pre-ischemic values (135 $\pm$ 23% of preischemic values at 15 min of reperfusion after 40 min of ischemia and 92 $\pm$ 17% after 60 min ($p < 0.001$ respect to controls). This increase in cGMP was associated to a markedly improved contractile recovery after 40 min of ischemia ($p = 0.0309$), and attenuated reperfusion-induced increase in left ventricular end-diastolic pressure ($p = 0.0139$), LDH release ($p = 0.0263$), and contraction band necrosis ($p = 0.0179$) after 60 min of ischemia. Stimulation of a separate set of hearts with different concentrations of urodilatin demonstrated a sharp correlation ($r2 = 0.96$) between myocardial cGMP content and release.

These results indicate that reduced cGMP concentration may impair myocyte survival during reperfusion. Modulation of particulate guanylyl cyclase activity appears as a new therapeutic strategy to prevent immediate lethal reperfusion injury.

STABLE ANGINA: CLINICAL PRESENTATION, EVALUATION AND TREATMENT

P1000 Variability of angina symptoms: correlates and consequences

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Objective: To describe the variability associated with reported angina symptoms from one occasion to another, and to examine the effect of this variability on ischaemic heart disease outcome.

Methods: 7108 middle-aged men completed two chest pain questionnaires five years apart: the first (Q1) in 1978–80 and the second (Q5) in 1983–85. At each time point men were classified into one of four groups: definite angina (WHO angina meeting all criteria), possible angina (exertional chest pain without all other criteria), non-exertional chest pain or no chest pain. All men were followed up from Q5 to December 1995 (10.5–13 years) for major ischaemic heart disease events (fatal and non-fatal).

Results: Although age-specific angina prevalences were similar at Q1 and Q5, there was considerable variability in response. A minority (39%) of the 310 men with definite angina at Q1 reported definite angina at Q5, with 22% reporting possible angina, 11% reporting non-exertional chest pain and 29% reporting no chest pain. Of the 211 men with possible angina at Q1, 25% reported definite angina at Q5. Indicators of severe disease such as evidence of previous myocardial infarction, recall of a CHD diagnosis, and an abnormal ECG at screening were much more common in men who reported angina (definite or possible) at both Q1 and Q5 than those with angina on one occasion only. Persistence of angina was also strongly associated with subsequent ischaemic heart disease outcome. Compared to men without angina on either occasion, the age-adjusted relative hazard (95% CI) of a major ischaemic heart disease event from the time of Q5 was 1.5 (1.1, 2.2) for angina at Q1 only, 2.6 (2.1, 3.2) for angina at Q5 only and 3.4 (2.8, 4.3) for angina on both occasions. Persistent possible angina was associated with as poor a prognosis as persistent definite angina.

Conclusion: Angina symptoms elicited by questionnaire in population studies show substantial variability from one occasion to another. Persistence of reporting of symptoms is an important indicator of disease severity and prognosis.

P1001 European Survey on Circadian Variation of Angina Pectoris (ESCVA) – wake-time adjusted morning risk

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A circadian variation has been observed for acute coronary syndromes (myocardial infarction, sudden cardiac death, myocardial ischaemia) with a peak during the morning and a trough during the night. The previous reports, however, were based primarily on selected patients in clinical studies. The present study has been designed to determine the timing of attacks of angina pectoris in an out-of-hospital setting, the association of wake time and possible external triggers with angina attacks, and the influence of cardiac medication.

Methods: The ESCVA Study (European Survey on Circadian Variation of Angina Pectoris) is a multicenter international cross-sectional survey of patients in general medical practice of 7 European countries. Inclusion criteria are stable angina pectoris for at least three months, average frequency of two or more attacks per week, and treatment with on demand nitrates. Standardised self-administered questionnaires are provided to all consecutive patients of the participating physicians.

Results: From January to July 1998, 1,087 patients (61% male, 64 $\pm$ 9 years, 39% female, 67 $\pm$ 10 years) have been enrolled in 196 centers. A total of 3,453 angina pectoris attacks were reported, on average 3.2 per patient per week (range 0–48). The occurrence of angina pectoris attacks demonstrates a significant circadian variation ($p < 0.001$) with a primary morning peak from 9:00 to 12:00 (relative risk 3.0 compared to other times of day) and a secondary afternoon peak from 15:00 to 18:00. 50% of all attacks occurred within 6 hours after awakening. 75% of all patients reported possible external triggers of angina such as physical activity or anger.

Conclusions: A multicenter survey in general medical practice demonstrates marked wake time related circadian variation in angina pectoris attacks. To improve preventive strategies, type, dosage and particularly timing of cardiac medication are important, as may be behavioural approaches.

P1002 Diastolic and systolic function as predictors of exercise capacity in patients with stable angina

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Background: Data regarding relationships between exercise capacity and left ventricular systolic and diastolic function are conflicting. We therefore examined such relationships in patients with stable angina pectoris, participating in the Angina Prognosis Study In Stockholm (APSIS).

Methods: Measurements of left ventricular (LV) systolic and diastolic function at rest were examined as predictors of maximum exercise capacity in 675 patients with stable angina. Diastolic function was assessed by early (E) to late (A) mitral flow ratio (E/A-ratio) in 365 patients.

Results: In univariate analyses, maximum exercise time was more significantly related to patients height, E/A-ratios and left ventricular fractional shortening (FS) in men. E/A ratios among women were more closely related to exercise capacity. In contrast, FS was significantly related to exercise capacity in men ($r = 0.26$, $p < 0.001$), but not in women ($r = 0.05$, ns). In multivariate analyses, female sex ($p < 0.001$), height ($p < 0.001$) and E/A ratio ($p < 0.001$) all made independent contributions to exercise capacity.

Conclusion: Maximum exercise capacity of patients with stable angina is more closely related to indices of diastolic function than systolic function, especially among women. Exercise testing and evaluation of cardiac function with echocardiography and Doppler may be regarded as complementary procedures in patients with stable angina pectoris.

P1003 Prognostic implications of ambulatory ischaemia and relationships to ischaemia on exercise in patients with chronic stable angina pectoris: a report from APSIS

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Aim: To assess the prognostic significance of ambulatory ischaemia, alone and in relation to ischaemia on exercise in patients with chronic stable angina pectoris, and to evaluate effects of treatment with metoprolol or verapamil.

Material, methods: We investigated 673 (302 men) out of 809 patients taking part in the Angina Prognosis Study In Stockholm (APSIS), who had satisfactory 24 h ambulatory ECG registrations and exercise tests at baseline.

Results: During a median follow-up of 40 months, 29 patients died of cardiovascular causes (CV death), and 27 suffered a non-fatal myocardial infarction (MI). Patients suffering CV death had more episodes with signs of ischaemia (5 vs 1; $p < 0.01$), and a longer median duration of ST-segment depression (23 vs 2 min; $p < 0.01$). There were no differences for patients with non-fatal MI. In a multivariate Cox model, including sex, previous MI, history of hypertension and diabetes, the duration of ST-segment depression showed an independent prognostic impact. When assessed together with results from exercise testing, ambulatory ischaemia carried additional prognostic information only among those patients with ST-segment depression $\geq$2 mm on exercise. Treatment significantly reduced signs of ambulatory ischaemia. However, when the treatment given and treatment effects on ischaemia were added to the Cox model, no significant impact on prognosis was found.

Conclusion: Ischaemia detected during ambulatory monitoring in patients with stable angina pectoris showed independent prognostic importance regarding CV death, but not the combined end-point of CV death+MI. Ischaemia on exercise testing and ambularoty monitoring are to some extent complimentary, but only in patients with marked ST-segment depression on exercise. One clinical implication of this finding is that when the exercise test is negative, little additional information is obtained from the ambulatory monitoring. Treatment reduced signs of ischaemia, but the short-term treatment effects did not influence the prognosis.

P1004 Value of continuous ambulatory pulmonary artery pressure monitoring in comparison to ECG holter monitoring in detecting ischaemia

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In group of 19 patients (pts) with angiographically proven coronary artery disease, 9 hours continuous pulmonary artery diastolic pressure (PADP) monitoring was performed by means of Gealtec (type 7 MPR) system concomitantly with Holter ST monitoring. All pts revealed ST depression of at least 1 mm together with pathological PADP increase >13 mm Hg (resting values within normal range) while exercised in supine cycloergometrer. All patients continue their normal daily activity and additionally were put to two tests – counting and interview in front of TV camera. Changes in PADP, ST deviation and HR in response to stress were compared. Excluding exercise test period, total number of 45 ST episodes and 68 episodes of pathological PADP increasing were recorded. In 13 pts both ST segment and PADP changes were found: 38 episodes of concomitant ST and PADP changes, 23 episodes of exclusive PADP and 5 solitude ST segment changes. Only in 1 pt ST segment changes run without PADP increase. On contrary, 4 of 5 pts revealed at least one episode of PADP increase without accompanying ST changes. In 31 of 38 episodes of concomitant PADP and ST changes, the former preceded ST changes by 64 ± 42 seconds. During interview 7 (36.7%) pts revealed PADP increase, in 6 cases associated with both pain and ST changes and in 1 case with pain only. During counting only in 3 of 6 pts PADP increase was accompanied by ST segment changes. During exercise stress test maximal increase of PADP was almost by 10 mm Hg higher and ST depression 0.25 mm dipper then that during the rest of ambulatory monitoring.

Conclusions: Ambulatory monitoring of pulmonary artery diastolic pressure detects ischemia more frequently then Holter ST monitoring. Pathological increase of pulmonary artery diastolic pressure precedes ST segment changes by about one minute.

P1005 Does exercise-induced severe ischaemia result in elevation of plasma troponin T level in patients with chronic coronary artery disease?

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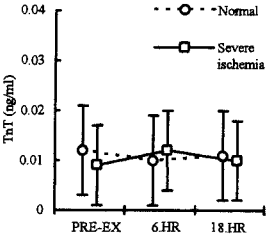
It has been reported that a loss of cell-membrane integrity during severe ischemia results in elevation of plasma troponin T (TnT) in unstable angina. We investigated whether TnT is released into circulation during exercise-induced severe ischemia in patients (pts) with chronic coronary artery disease (CAD).

Methods: 212 pts with angiographically documented CAD and 54 normal subjects underwent exercise Tl-201 SPECT imaging. Blood samples were obtained before, 6 and 18 hours after exercise for TnT measurements. SPECT images were divided into 20 segments. Pts with $\geq$5 redistribution defects were considered to have severe ischemia.

Results: 48 pts had severe ischemia on SPECT images. The mean TnT were 0.009 ± 0.010, 0.012 ± 0.009, 0.010 ± 0.010 ng/ml in pts with severe ischemia and 0.012 ± 0.009, 0.010 ± 0.009, 0.011 ± 0.010 ng/ml in normal subjects before, 6 and 18 hours after exercise, respectively. There was no significant difference between the 2 groups and also in pre-, post-exercise TnTs in each group. All TnTs were normal (<0.1 ng/ml). Additionally, There was no significant difference with respect to TnT levels among pts with increased lung uptake and transient left ventricular dilatation which are indicators of severe ischemia and those without.



Conclusion: Exercise-induced severe ischemia does not result in elevation of plasma TnT level in patients with chronic CAD.

P1006 Aspirin reduces transient ischaemia in stable angina by reducing increased cytokine plasma levels and platelet activation

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Macrophage colony stimulating factor (MCSF) causes macrophage/monocyte activation and thus release of vasoactive substances, interleukins 1b (IL1b) and 6 (IL6), platelet chemoattractants and tissue factor. We investigated whether platelet activation, thrombin generation or high cytokine levels are related to transient ischaemia in stable angina (SA) and whether reduction of the above factors by aspirin is associated with reduction of ischaemia.

Methods: We measured prothrombin fragments (PF1 + 2, nmole/l), MCSF, IL1b, IL6 (pg/ml) plasma levels and 24 h urine excretion of 11 dehydrothromboxane B2 (DTXB2, ng/mg creatinine) in 60 patients with SA and in 24 matched controls. Samples and urine collections were obtained at the end of a 48 h Holter (HM). Patients had angiographically documented disease. Fourty had ischaemia at HM and were randomly treated with ASA 300 mg, o.d. or placebo for 3 weeks in a double blind, cross-over trial.

Results: PF1 + 2, MCSF, and IL6 were increased in patients compared to controls (table). MCSF and IL1b increased according to the number of diseased (1–2–3) vessels ($p < 0.05$). Patients with ischaemia on HM had higher MCSF and DTXB2 but similar PF1 + 2 levels compared to those without (MCSF: 1124 ± 651 vs 528 ± 417, DTXB2: 4.2 ± 3.2 vs 2.3 ± 1.9, $p < 0.05$). MCSF was related to DTXB2 before and after aspirin administration ($r = 0.47$ and $r = 0.50$, $p < 0.01$). Aspirin reduced cytokine levels, PF1 + 2, DTXB2, the number and duration of ischaemic episodes (IE) at HM.

	SA	ASA	Controls	p
MCSF	1076 ± 613	950 ± 567	479 ± 287	<0.05
IL6	4.2 ± 1.3	3.5 ± 0.8	2.0 ± 0.9	<0.05
PF1 + 2	2.26 ± 1.8	1.73 ± 1.2	0.93 ± 0.5	<0.01
DTXB2	4.4 ± 2.8	2.2 ± 2.1	3 ± 3.3	<0.05
IE (no)	8.9 ± 1.1	6.6 ± 1.1		<0.01

Conclusion: Daily life ischaemia in patients with SA is related to increased platelet activation induced by high cytokine levels and not to thrombin generation and is reduced by aspirin possibly due to the antiplatelet and antiinflammatory effect of the drug.

P1007 Aspirin reduces procoagulant activity and thrombin generation in patients with stable angina

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Cytokines, C-reactive protein (CRP) and antiphospholipid antibodies (aPL) demonstrate significant procoagulant activity. aPL also induce thrombocytopenia. We investigated whether these factors are a) related to platelet activation and thrombin generation b) reduced by aspirin in stable angina.

Methods: We measured a) prothrombin fragments (PF1 + 2, nmole/l) b) IgG, IgM, IgA-aPL titers (Units) c) macrophage colony stimulating factor (MCSF), interleukin 1b (IL1b) and 6 (IL6) (pg/ml) and CRP (mg/l) plasma levels d) 24 h urine excretion of 11-dehydrothromboxaneB2 (DHTXB2, ng/mg creatinine) in 60 patients with stable angina (SA) and in 24 controls. Patients had angiographically documented disease and were randomly treated with aspirin (ASA) 300 mg, o.d. or placebo for 3 weeks in a double blind, cross-over trial.

Results MCSF, IL6, CRP, IgA-aPL and PF1 + 2 were increased in patients compared to controls (table, $p < 0.01$). IgA-aPL was inversely related to patelet count and DHTXB2 ($r = -0.39$ and $r = -0.32$, $p < 0.01$). Conversely, MCSF was related to DHTXB2 ($r = 0.40$, $p < 0.01$) No relation between aPL and CRP or cytokine levels was found. MCSF was related to IL1b and CRP ($r = 0.40$ and $r = 0.40$ $p < 0.05$). MCSF, IL6, CRP, IgA, IgG-aPL, DHTXB2 and PF1 + 2, levels were significanly decreased by ASA (table)

	Placebo	ASA	p	Controls	p
MCSF	991 (459–1476)	843 (501–1357)	<0.05	370 (265–770)	<0.01
IL6	3.9 (3.2–4.6)	2.9 (2.5–3.4)	<0.01	1.7 (1.3–2.5)	<0.01
CRP	1.4 (0.54–4.05)	1.0 (0.5–3.1)	<0.05	0.23 (0.17–1.4)	<0.05
IgA-aPL	3.4 (2.6–5.4)	2.9 (1.8–5.1)	<0.01	2.4 (1.5–3)	<0.01
DHTXB2	3.3 (2.3–5.4)	1.3 (0.8–3.1)	<0.01	2.9 (1.6.8–3)	NS
PF1 + 2	1.5 (1.1–2.7)	1.2 (1.1–1.8)	<0.01	0.82 (0.65–0.97)	<0.01

Conclusion: Elevated cytokine, CRP and aPL levels suggest an increased inflammatory and procoagulant activity that may partly explain the presence of increased thrombin generation in SA. Increased platelet activation is related to high MCSF levels whereas low platelet activity is associated with high aPL titers. Reduction of the above factors by ASA may represent an additional mechanism of its therapeutic action in coronary artery disease.

P1008 Long-term anti-ischaemic effects of spinal cord stimulation: a 48-hour ambulatory electrocardiogramme monitoring study

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Spinal cord stimulation (SCS) has anlgesic properties and may be used to treat the anginal pain in patients with refractory angina not candidates to myocardial revascularization. Some studies shoved also antiischemic effects. The aim of this study was to evaluate the long term persistence of the antiischemic effect of SCS.

Methods: Fifteen patients (9 male, 6 female, mean age 76 ± 8 yrs, range 58–90) treated with SCS for a mean follow up of 39 ± 27 months (range 9–92) with severe refractory angina pectoris (Canadian Class III-IV, optimal pharmacologic therapy not candidates to myocardial revascularization) were included in the study. Eleven patients had a previous myocardial infarction, 5 previous CABG, the mean EF was 0.54 ± 0.07 (range 0.36–0.65). All patients underwent a 48 hrs ambulatory electrocardiogram monitoring and were randomly assigned to 24 hrs without SCS (OFF period) and 24 HRS with SCS (ON period): The following parametners were evaluated: mean HR (bpm), number of ischemic episodes, total duration of ischemic episodes (min), total ischemic burden (mV.min).

Results: The Canadian Class improved during the follow up from a median value of 4.0 before SCS to 2.0 after implant ($p < 0.05$). The HR detected during ambulatory electrocardiogram monitoring was similar during the OFF period and the ON period (mean value 62.3 ± 4 and 63.1 ± 6 bpm, respectively). The number of episodes of ischemia decreased from a median value of 6 (range 0–29) during the OFF period to a median value of 3 (range 0–24) during the ON period ($p < 0.05$). The total duration of ischemia decreased from a median value of 29 min (range 0–186) during the OFF period to a median value of 16 min (range 0–123) during the ON period ($p < 0.05$). Total ischemic burden decreased from a median value of 2.5 mV.min (range 0–19.5) during the OFF period to a median value of 0.8 mV.min (range 0–13) during the ON period (p NS).

Conclusion: This study showes that SCS has antiischemic properties persisting over time.

P1009 Nitric oxide synthase inhibition improves coronary microcirculatory function in patients with coronary artery disease

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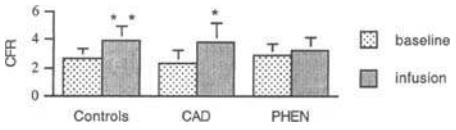
Nitric oxide (NO) release in response to shear stress modulates coronary artery diameter. However, its impact on the coronary microcirculation and coronary flow reserve (CFR) particularly in patients with coronary artery disease (CAD) is unclear.

Methods: Myocardial blood flow (MBF, ml/min/g) at rest (R) and during iv adenosine (Ado; 0.14 mg/kg/min) was measured in 21 healthy males and 7 CAD patients using positron emission tomography and oxygen-15 labeled water. CFR was calculated as Ado-/R-MBF. Both measurements were repeated 15 minutes later during iv infusion of: 10 mg/kg NG-Monomethyl-L-arginine (L-NMMA) in 13 controls and 7 CAD patients; phenylephrine (PHEN) to increase blood pressure as with L-NMMA in 8 controls.

Results: Hemodynamics were similar in all groups at baseline. Mean arterial pressure (MAP) increased (+10%) and hear rate decreased (−10%) in all controls an patients (both $p < 0.05$) during the respective infusion. CFR increased significantly vs. baseline in controls (+59%, ** $p < 0.001$) and CAD (+56%, *$p < 0.05$) with L-NMMA but not with phenylephrine.



Conclusions: L-NMMA increases CFR, an this is not explained by the increase in MAP. Although the mechanisms remain unclear, this study proves that a further reserve is available on top of that achieved with standard doses of Ado in controls and in CAD patients.

P1010 Lesser inotropic reserve in response to dobutamine than to calcium in short-term hibernating myocardium

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We have previously shown in a porcine model of short-term hibernation that the β-adrenoceptor density during 90 min ischemia (I) remains unchanged and that the myocardium responds to dobutamine (Dob) and calcium (Ca) with an increase in contractile function. The increase in contractile function to Dob during I, however, is attenuated compared to normoperfusion (NP). It is not clear, whether this attenuated response to Dob is a consequence of alterations in the signal transduction pathway downstream of the β-adrenoceptor – as demonstrated to occur in heart failure – or a result of alterations in calcium handling of the myofibrils. We therefore compared the extent of inotropic reserve during Dob and Ca in 5 enflurane-anesthetized pigs, both during NP and I. During NP, Dob and Ca were infused into the cannulated LAD at increasing doses until an anterior wall work index (WI, mm·mmHg, sonomicrometry and micromanometry) did not increase further. To induce I, coronary inflow was reduced for 90 min to decrease WI from 343 ± 107 (SD) to 172 ± 44 mm·mmHg. Transmural blood flow (microspheres) was decreased from 0.69 ± 0.32 to 0.40 ± 0.19 ml/min/g. Dob and Ca infusions were repeated at 80–90 min I. The maximal increase of WI (ΔWI_{max}) during Ca was higher than during Dob, both during NP and I. Moreover, ΔWI_{max} with Dob, but not with Ca was lower during I than during NP. The doses of Dob (ng/ml blood) and Ca (mg/ml blood) at which ΔWI_{max} was recruited were not different during NP and I.

	Normoperfusion		Ischemia	
	ΔWI_{max}	dose	ΔWI_{max}	dose
Dob	92 ± 22*	187 ± 60	50 ± 27*#	192 ± 76
Ca	150 ± 48	261 ± 43	136 ± 39	270 ± 26

*: $p < 0.05$ vs Ca; #: $p < 0.05$ vs Normoperfusion; 2-way ANOVA

Since the β-adrenoceptor density and the Ca-mediated increase in WI remain unchanged, these results suggest an alteration in the signal transduction pathway between the β-adrenoceptor and the myofibrils in short-term hibernating myocardium.

P1011 Acute myocardial ischaemia lessens the potential protection afforded by ischaemic preconditioning

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Background: Acute myocardial ischaemia is known to sensitize adenylate cyclase through a receptor-independent mechanism, which may lead to cell damage via activation of cAMP-dependent protein kinase (PKA). HYPOTHESIS: There is both a deleterious and a protective role of the trigger ischaemia in preconditioning (PC). The detrimental effects are mediated through activation of cAMP-dependent protein kinase (PKA).

Methods: Using the isolated rat heart, control hearts were subject to an ischaemia/reperfusion protocol of 30 min global normothermic ischaemia and 30 min reperfusion (index I/R). PC hearts were subjected to one episode of 10 min global normothermic ischaemia ending 10 min prior to the I/R phase. The work was repeated in the presence of 2 μM H89, the specific PKA antagonist (uM Ki values PKA = 0.048, PKC = 31.7). PC + H89 hearts were perfused with the antagonist for 3 min and antagonist perfusion stopped at the commencement of the PC ischaemia. After 5 min drug-free perfusion hearts were subjected to the index I/R. Control + H89 hearts were perfused with the antagonist for 3 min then subjected to 15 min drug-free perfusion followed by the index I/R protocol. The functional recovery after the index I/R was measured in all groups.

Results: See table.

PKA inhibition enhances PC

Expt	% Functional recovery (rate-pressure product)
Control	14.8 (2.9)*
Control + H89	36.7 (2.1)
PC	44.8 (4.3)
PC + H89	60.0 (3.0)*

* $P < 0.05$ v PC/Control + H89

Conclusion: PKA activation contributes to I/R damage. The ischaemic stimulus of PC affords protection and paradoxically limits this protection through PKA activation.

P1012 Conditioning myocardium via mechanical transmyocardial channeling provides protection for ischaemia

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Background: Transmyocardial revascularization (TMR) has emerged as a promising modality for the treatment of chronic refractory myocardial ischemia. Recently we described a new non-laser means of TMR in which transmural myocardial channels are created via mechanical coring and vacuum tissue extraction. In this study we tested the hypothesis that the process of mechanical transmyocardial channel formation (TMC) followed by sixty day healing will lead to an altered myocardial substrate better able to support function in the setting of acute ischemic challenge.

Methods: In 12 pigs (female, 30 kg.) left thoracotomy was performed and the heart was exposed. In 6/12 pigs channels (1 mm, 5 mm inter-channel spacing, 31 ± 2/pig) were created mechanically in the left ventricular anterior wall (AW), from the level of the second diagonal to the apex (TMC group). 6/12 pigs, w/o TMC, served as controls (non-TMC group). All animals were allowed to recover. Sixty days post-TMC the LAD was ligated at the level of the second diagonal in all 12 pigs. ST elevation V4-V6 (mm.), heart rhythm, regional wall motion (2D Echo-AW segments, scoring: 1 NML, 2 hypokinetic, 3 akinetic, 4 dyskinetic, 5 aneurysmal) and microsphere retention ((blood inflow index) spheres/g tissue) were assessed at 60 min post LAD occlusion and were compared to non-TMC controls.

Results: ST elevation V4-V6 was reduced with TMC pre-channeling versus control (1.8 ± 2.0 vs 5.9 ± 2.0, p = 0.017). The # of VFib episodes (0.63 ± 0.7 vs 1.9 ± 1.0, p = 0.03) was significantly less for TMC than non-TMC control. Regional AW motion was more preserved in the TMC group versus control (1.4 ± 0.7 vs 2.25 ± 0.5 p = 0.02). Microsphere retention was increased with TMC versus control (1229 ± 678 vs 51 ± 27, $p < 0.001$).

Conclusion: Mechanical transmyocardial channeling combined with a sixty period of myocardial healing provides significant protection to the left ventricular myocardium in the setting of acute ischemic challenge. Conditioning the myocardium via the process of TMC and subsequent healing may be a useful adjunct therapeutic approach for the treatment of advanced ischemia not amenable to conventional therapies.

P1013 Correlation between heart rate variability and segmental left ventricular motion in patients with coronary artery disease before and after successful PTCA

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Heart rate variability (HRV) is a noninvasive index of the neural activity of the heart. HRV is frequently reduced in patients (pts) with coronary artery disease. We evaluated the correlation between parameters of HRV and segmental left ventricular motion in pts with coronary artery disease before and after successful percutaneous transluminal coronary angioplasty (PTCA). 152 pts (114 men, 38 women age range 40–68) underwent 24 hour Holter monitoring and echocardiographic examination before and 2 weeks after PTCA. Echocardiographic segmental left ventricular (LV) motion, parameters of time domain (SDNN, SDANN, SD, RMS-SD, p-NN50) and of frequency domain (LF band, HF band) were analysed.

All the pts were divided into Three groups before PTCA: 59 with normal segmental LV motion (group I), 51 with hypokinetic segments (group II), and 42 with akinetic segments (group III). All the parameters of time domain were similar in pts in group I and II, while HF band were lower in group II than in group I. In group III the parameters of HRV were significantly ($p > 0.01$) lower than in group I. The improvement of segmental LV motion after PTCA was observed in group II and III. All analysed parameters of HRV were not significantly changed in group I and II, although in group III following parameters significantly ($p > 0.01$) increased after PTCA: SDNN from 112.01 ± 17.0 to 140.02 ± 10.5, SDANN from 98.2 ± 17.2 to 126.1 ± 13.2, pNN50 from 5.8 ± 2.8 to 10.3 ± 4.3, LF band from 902.4 ± 473.2 msec^2/Hz to 1326.4 ± 519.4 msec^2/Hz, HF band from 392.4 ± 200.4 msec^2/Hz to 918.2 ± 491.1 msec^2/MHz.

Conclusion: HRV is correlated with left ventricular function. Abnormal segmental LV motion, especially akinetic segments, influense on diminished HRV parameters. The reversal of left ventricular dysfunction by successful PTCA improved heart rate variability.

P1014 Assessment of resting myocardial perfusion using sonovue myocardial contrast echocardiography using triggered pulse inversion harmonic imaging: a comparison to SPECT sestamibi imaging

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Background: We have previously shown in experimental studies that Pulse Inversion Detection is a sensitive technique for detection of microbubbles in the myocardium. We examined the efficiency of Pulse Inversion Harmonic (PIH) imaging for clinical myocardial contrast echocardiography (MCE).

Methods: 12 pts with a clinically indicated nuclear sestamibi scan and an adequate quality TTE identifying a resting wall motion abnormality (RWMA) were included in the study. The single view in which the wall motion abnormality was most evident was used for MCE using end-systolic triggered (1:1 and 1:4 cardiac cycle) PIH imaging (min 3 frames per trigger) on an ATL 5000 HDI machine. Each pt received a 3.0-ml bolus of IV SonoVue. The transmit focus was placed in the distal field and the mechanical index varied between 0.9 and 1.3 (average 1.1). MCE and nuclear images were interpreted independently for myocardial perfusion using identical regional scoring system. Data were analyzed for agreement between nuclear and MCE for 1) presence or absence of perfusion abnormalities, and 2) regional concordance in a given view.

Results: The apical 4 chamber (AP4C) view and the parasternal short-axis view, at the level of the papillary muscle (SAX-PM) were selected for imaging in 8 and 4 pts respectively. All pts had at least one abnormally perfused region on nuclear imaging. There was 100% agreement in the AP4C view and 95% agreement in SAX-PM view between SonoVueä PIH MCE imaging and nuclear sestamibi for the presence or absence of perfusion abnormalities. Regional concordance in the AP4C view was: apex 100%, mid septum 89%, basal septum 78%, mid lat wall 85%, basal lat wall 74%. In the SAX-PM view regional concordance was: ant septum 96%, ant wall 92%, ant lat wall 88%, post lat wall 78%, inf wall 88%, inf septum 94%.

Conclusion: SonoVue MCE when combined with triggered Pulse Inversion Harmonic Imaging shows excellent concordance to nuclear imaging for delineation of resting myocardial perfusion patterns in patients with resting wall motion abnormalities.

P1015 Preinfarction angina as a prognostic factor of new coronary events in patients after first acute coronary syndrome: one year follow-up

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The effect of preinfarction angina on prognosis after first acute coronary syndrome [ACS] is unclear. The aim of the study was to assess the role of preinfarction angina [PA] as the prognostic factor of new coronary events [NCE]: sudden cardiac death [SCD], unstable angina [UA] and myocardial infarction [MI] in patients after first ACS. Study population consisted of 234 patients [pts]; mean age 48.7 yrs [range 42–76 yrs]; male-167, with first ACS. PA was defined as chronic stable angina present for more than 1 month before ACS. At discharge patients were divided into two groups according to the presense or absence PA. Group I – 133 pts with ACS and PA, Group II – 101 pts with ACS and without PA. Before discharge in all patients left ventricular function [assessed as ejection fraction [EF]] was evaluated using Echo-2D and Doppler method. During two years follow-up frequency of new coronary events: sudden cardiac death [SCD], unstable angina [UA], infarction [MI] and total cardiac mortality [CM] were assessed.

Results:

	Group I [PA+] n = 133 pts	Group II [PA–] n = 101 pts	p
Mean EF [%]	45	54	<0.001
SCD [%]	7.5	4.9	<0.05
MI [%]	17.3	10.9	<0.001
UA [%]	28.5	13.8	<0.001
CM [%]	11.3	8.9	<0.01

Conclusions: New coronary events during two year follow-up occurred more often in patients with preinfarction angina. Angina before acute coronary syndrome – PA – seems to suggest more extensive coronary artery disease.

P1016 External counterpulsation increases capillary density during experimental myocardial infarction

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The mechanism(s) by which enhanced external counterpulsation (EECP) improves myocardial perfusion and relieves angina in coronary disease has been postulated to be due to recruitment or development of collaterals. An experimental acute dog infarction (MI) model was used to test this hypothesis.

Method: Acute MI was induced in 14 dogs [6 controls (C) and 8 EECP treated] by ligating the apical branch of the LAD. The EECP group was treated immediately after occlusion for 80 minutes, and again for 60 minutes prior to sacrifice of both groups at 6 hours. Frozen sections of myocardium were prepared using Bell's alkaline phosphatase and sectioned at 75 micron thickness. Capillary density (CD-capillaries/cm^2) and diameter (μm) were measured in both groups in infarct and non-infarct zones at three levels: subendocardium, intramyocardial, subepicardium. Statistical analysis was performed using the unpaired t test with a significance level of $p < 0.05$.

Results: Significant increases in CD were observed after EECP in the infarct zone (table). However, there were no significant differences in CD after EECP treatment in the non-infarct zone (average 6,066 ± 1,003 in C versus 6,659 ± 715 in EECP) and no differences in capillary diameters in either infarct or non-infarct zones (average 6.58 ± 0.20 μm in C versus 6.65 ± 0.24 μm in EECP).

Infarct Zone	Control	EECP	Significance
Subendocardial	4,578 ± 501	5,938 ± 502	p < 0.01
Intramyocardial	5,312 ± 916	7,138 ± 972	p < 0.01
Subepicardial	4,990 ± 686	6,586 ± 916	p < 0.01

These results demonstrate that CD in areas of acute MI can be significantly increased after EECP treatment. This finding may provide some insights into the mode of action for the use of EECP during acute and chronic ischemia.

P1017 Does exercise-induced hypotension necessarily predict adverse outcomes in patients with coronary artery disease?

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Purpose: Exertional hypotension (EH) is generally thought to portend severe CAD and/or myocardial ischemia and is an indication, as per AHA guidelines, for coronary angiography. The predictive utility of this criterion, however, has not been examined in an ambulatory outpatient population.

Methods: We studied 591 consecutive patients (mean age 67 yrs, 85% males) undergoing ETT in a cohort of patients with known CAD. EH was defined according to AHA criteria: EKG evidence of ischemia along with A) a sustained decrease of >10 mm Hg OR B) flat blood pressure response (<130 mm Hg) at peak exercise. Primary endpoints were MI or death.

Results: We found EH in 195 subjects (33%). There were no significant differences in baseline characteristics between those with and without EH. In a multivariate regression model, triple anti-anginal therapy (nitrates, B-blockers and Ca-antagonists) was the most significant factor associated with presence of EH. Rates of subsequent revascularization were equal in the two groups. During a mean f/u of 37 months, event rates were as follows: EH group [196 subjects, 21 (11%) MI, 10 (5%) death], non-EH group [395 subjects, 35 (9%) MI, 22 (5.7%) death). The differences were not significant ($p > 0.2$ for both). In univariate analysis, EH was not statistically associated with primary endpoints [hazard ratio = 1.3, 95% CI = 0.8–2.0, p = 0.3]. In multivariate Cox regression model, after adjusting for potential confounders, EH remained non-significant (HR 1.36, 95% CI 0.8–2.3, p 0.3)

Conclusions: We conclude that EH, as defined by AHA criteria, is not a significant predictor of worse outcomes in subjects with chronic CAD. EH is multifactorial and decisions regarding its management need to be individualized.

P1018 Increase of spatio-temporal beat-to-beat variability in coronary heart disease patients using magnetocardiography

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Magnetocardiographic (MCG) mapping provides an excellent tool to investigate the beat-to-beat variability (BBV) of electric heart activity. By solving the inverse problem the current source can be localized and consequently, the spatio-temporal BBV can be carried out. For patients with coronary heart disease (CHD) we expect an enhancement of BBV for the time instants of the heart cycle which correspond to disturbed electrical polarization in diseased regions of myocardium.

Method: The MCG-mapping (49-channel gradiometer in a shielded environment) was performed in 33 patients with angiographically documented CHD (16 post-myocardial infarction (PMI) patients and 17 patients with sustained ventricular arrhythmias (VA)) and in 19 healthy controls. Acquisition time amounted to 100 s at a sampling rate of 1 kHz. In the frame of our turbulence analysis the moving current dipole model was used to determine the time dependent location and strength of the current source. To measure spatio-temporal BBV we introduced a parameter, electrical Circulation (EC), which expresses a correlated shift of electrical activity in the time and space domain for consecutive heart beats.

Results: EC was significantly enhanced in the last phase of QRS-complex for all CHD patients compared to values for healthy controls. The investigated patient groups could be distinguished by means of the EC value within the T-wave, normalized on the amplitude of the current dipole vector. We achieved the following values: 2.2 ± 2.1, 6.2 ± 3.6 and 11.4 ± 3.4, for healthy controls, PMI patients and VA patients, respectively ($p < 0.005$ for all groups).

Conclusion: Significantly increased Circulation throughout the final part of the QRS-complex was observed in all CHD patients which can be correlated to the arrhythmogenic substrate. Additionally, an enhancement of Circulation within the repolarization provides a useful risk parameter for malignant cardiac arrhythmias.

REPERFUSION STRATEGIES

P1019 The influence of female gender on PTCA results and clinical outcome in the "Prague" study: national multicenter randomized study on patients with acute myocardial infarction presenting to community hospital

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Several studies have shown unfavorable short-term outcome of women with respect to men after acute MI, even after adjusting for age. We assessed the influence of female gender on the short-term (30 days) prognosis after MI in randomized trial focused on evaluation of the best reperfusion strategy for patients with AMI admitted to the community hospital without cath-lab.

A total 255 patients were included (179 men, 76 women) and randomized to one of the following treatment: thrombolysis (TL) in the community hospital (group A, 70 patients), TL during transport to PTCA (group B, 71 patients) and direct transport to primary angioplasty (group C, 69 patients). All patients received aspirin and heparin, there were no death or VF during transport. Combined end-point at 30 days was death, re-MI and stroke.

Results:

	Group A		Group B		Group C	
	male	female	male	female	male	female
Mean age [years]	61	64	62	65	60	64
Door/reperfusion [min.]	115	115	120	128	98	105
PTCA success [%]	-	-	96	94	91	90
TIMI 2 + 3 pre [%]	-	-	48	39	28	33
TIMI 2 + 3 post [%]	-	-	96	95	94	95
30 d mortality [%]	12	21	15	13	7	13
30 d re-MI [%]	14	14	8	8	2	0
30 d urg. revasc. [%]	16	11	8	8	7	0
Comb. end-point [%]	25	29	19	21	8	13

Conclusions: Intermediate results of ongoing study shows a trend to benefit from transport to primary PTCA in the combined end point as well as in 30 days re-MI and urgent revascularization procedures. There were no significant differences between males and females in our study.

P1020 Thrombolisis versus PTCA in patients with recent acute myocardial infarction: exercise stress echocardiographic study

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Background: Intravenous thrombolitic therapy reduces mortality in patients (pts) with acute myocardial infarction (MI). More recently, catheter-based reperfusion for achieving infarct vessel patency and reducing the incidence of death or non-fatal MI has been introduced.

Objective: The aim of this study was to assess the left ventricular function during exercise stress echocardiography (EST-Echo) in pts who underwent primary percutaneous coronary angioplasty (PTCA) and in those who received fibrinolytic therapy.

Methods and patients: EST-Echo was performed in 146 pts 5 ± 3 days post MI. Medical therapy was not discontinued at the time of the test. The study population was divided into two groups: group 1 (G1) included 62 pts (51 Males, age 57 ± 10 yrs) who underwent PTCA at hospital admission and group 2 (G2) 84 (71 Males, age 58 ± 10 yrs) pts who received traditional thrombolytic therapy (rTPA).

Results: In basal conditions left ventricular ejection fraction (LV-EF), end-diastolic volume (LV-EDV), and end-systolic volume (LV-ESV) were similar between the two groups (G1: 49 ± 6, 141 ± 46 and 71 ± 29 respectively; G2: 48 ± 12, 142 ± 51 and 74 ± 42 respectively). Myocardial ischemia was induced by EST-Echo in 10/62 (16%) pts of G1 and in 34/84 (40.5%) of G2 ($p = 0.001$). In pts with ischemia during exercise, LV-EF, LV-EDV and LV-ESV were unchanged in comparison to baseline. In pts without ischemia during EST-Echo LV-EF increased in response to exercise (from 49 ± 6 to 54 ± 8 in G1, $p = 0.0002$; from 50 ± 14 to 58 ± 22 in G2, $p = 0.001$), the LV-EDV did not change from baseline whereas the LV-ESV decreased (from 66 ± 29 to 60 ± 28 in G1, $p = 0.02$; from 70 ± 43 to 68 ± 44 in G2, p = ns).

Conclusion: The echocardiographic parameters on baseline were similar between the two groups. The left ventricular function in response to effort, in both subgroups with and without ischemia during EST-Echo, did not differ between pts who underwent PTCA and pharmacological reperfusion. By contrary, this finding supports that the incidence of exercise-induced ischemia was significantly lower in pts who underwent PTCA than in those who received thrombolytic therapy.

P1021 Emergency revascularization and hybrid approaches in cardiogenic shock

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Acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) is still associated with a high mortality rate. Previous studies suggest that immediate revascularization with primary percutaneous angioplasty (PTCA), bypass surgery (CABG) or both can improve prognosis in this setting.

Methods: Between May 1996 and January 1999 36 patients (32 male), mean age 60 ± 10 years (44–80), were referred to our cath-lab with the diagnosis of CS complicating AMI. Intraaortic balloon counterpulsation (IABP) was used as adjunctive hemodynamic support in 89%. PTCA of the culprit lesion was always attempted if coronary anatomy was suitable, and multivessel PTCA was performed whenever there was no hemodynamic improvement. Left-main stenosis and non-suitable lesions for PTCA were considered an indication for surgery, as well as associated mechanical complications.

Results: 27 patients (32 lesions) were successfully revascularized with PTCA, and seven of them were immediately transferred to the operating room for CABG (hybrid revascularization in 3 patients) or repair of a mechanical complication (3 mechanical valves in mitral position and a left ventricle free-wall patch). Five patients underwent emergency CABG without previous PTCA, because left-main or multivessel disease made surgical revascularization a better option. Only four patients were not eligible for any kind of revascularization. Successful PTCA was achieved in 89% of lesions, and coronary stenting was performed in 84% of them. Mean time of IABP was 39 ± 32 hours, and no severe complications were related with counterpulsation. Survival rate at 30 days was 72%.

Conclusions: Successful direct early revascularization and hybrid surgical approaches in patients with AMI complicated by CS significantly reduce in-hospital mortality. Coronary stenting and IABP support may also contribute to this improved survival rate.

P1022 Serial coronary flow reserve in the successfully recanalized coronary artery and non-infarct artery in patients with acute myocardial infarction: the role of collateral circulation

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Coronary flow reserve (CFR) in the infarct related artery (IRA) immediately after successful revascularization is frequently increased although not normalized in patients with acute myocardial infarction (MI). In addition, CFR in the normal contralateral vessel (non-IRA) is decreased immediately after successful revascularization. To assess the time course and the role of collateral circulation, 24 consecutive patients with acute myocardial infarction were studied. In all normal TIMI 3 flow was established after stent implantation. Distal coronary flow reserve was monitored in the infarct and non-infarct coronary artery immediately after stent implantation and after 24 hours. Patients were divided into 2 groups according to the presence (Rentrop 2 and 3) or absence (Rentrop 0–2) of collateral circulation.

		t = 0	t = 24
CFR (non-IRA)	Total group	2.01 ± 0.71	2.35 ± 0.79*
	R 0–2	2.25 ± 0.76	2.45 ± 0.81*
	R 2–3	1.59 ± 0.63	2.55 ± 0.84#
CFR (IRA)	Total group	1.41 ± 0.62	1.93 ± 0.69*
	R 0–2	1.42 ± 0.65	2.11 ± 0.70*
	R 2–3	1.45 ± 0.72	1.88 ± 0.81*

* $p < 0.05$ compared to t = 0, # $p < 0.05$ compared increase IRA R 2–3

Conclusion: both IRA and non-IRA have impaired CFR immediately after successful recanalization in patients with acute MI, which is significantly increased after 24 hours. In addition, the increase in CFR of the non-infarct IRA giving collateral circulation is significantly higher as compared to non-infarct IRA without collateral flow.

P1023 Heparinized stents in acute myocardial infarction: first results from the BESSAMI (Berlin Stent Study In Acute Myocardial Infarction) trial

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BESSAMI is an ongoing single center prospective randomized trial to assess the combined complication rate of reintervention, CABG, reinfarction and death after primary PTCA alone versus IVUS-guided implantation of heparinized Wiktor-i stents in acute myocardial infarction (AMI).

Inclusion citeria are clinically and angiographically confirmed AMI with a vessel size of >2.5 mm. Excluded are patients with severe 3-vessel disease and urgent need of CABG. So far 52 consecutive patients are included. Patients with dissection after initial recanalization by PTCA as evidenced by flouroscopy and/or IVUS and/or TIMI-flow < 3 were randomized to group A (with stent; n = 26) or group B (without stent; n = 23). If no dissection was obvious and TIMI 3 reestablished, patients were allocated to group C (control; n = 3). All patients were treated with ticlopidine 500 mg/die for 4 weeks.

Results: There were no major differences in the baseline characteristics (see table). The procedural details are also given in the table.

	Group A (n = 26)	Group B (n = 23)	Group C (n = 3)
Sex	female 5 (22%)	female 7 (27%)	female 2 (66%)
Age	61 ± 4.9	62 ± 2.7	59 ± 10.7
3 vessel disease	5 (22%)	7 (27%)	0 (0%)
1 vessel disease	8 (35%)	11 (42%)	1 (33%)
Dissection after PTCA	21 (81%)	18 (78%)	0 (0%)
% Stenosis after PTCA#	49.1 ± 9.1	45.9 ± 3.9	39.0 ± 11.0
% Stenosis after stent#	–	17.9 ± 5.3*	–

*p < 0.001 for reduction of residual stenosis; #measurements by IVUS

The combined endpoint was reached in 2/26 patients of group A (2x urgent CABG) and 14/23 in group B (12x stenting for imminent vessel closure, 2x urgent CABG, p < 0.02). No endpoint was observed in group C. There was no in-hospital-mortality in either group.

In conclusion: IVUS-guided implantation of heparinized Wiktor-i stents in AMI is a safe procedure assosiated with few complications.

P1024 Abciximab associated with primary angioplasty and stenting in acute myocardial infarction: the ADMIRAL study, 30-day results

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Primary angioplasty is a validated procedure in the treatment of acute myocardial infarction (ami) and intracoronary stenting has been proposed to improve both the immediate results and the restenosis rate. Through its effects on platelet aggregation and on the vitronectin receptor of abciximab might be effective in further reducing complications in ami patients undergoing stent implantation. ADMIRAL is a phase 3 multicenter double blind placebo controlled randomized trial in patients undergoing primary PTCA and intracoronary stent implantation. 300 adult patients with a clinical diagnosis evolving ami within the first 12 hours and referred for urgent primary PTCA were included after obtaining written informed consent. Patients were randomized in equal probability to one of the following treatment groups: placebo or abciximab 0.25 mg/kg bolus followed by a 0.125 mcg/kg/min 12-hour infusion. Treatment was administered either during the pre-hospital phase, in the emergency room or in the catheterization laboratory before sheath insertion. All patients received aspirin (6 months) and ticlopidine (1 month) for stent implantation. Unfractionnated heparin was administered according to EPILOG criteria. Angiographic images were obtained prior to and immediately after PTCA and stenting, 24 hour after the procedure and at 6 months. Clinical follow up at 24 hours, 30 days and 6 months was carried out in all patients. The primary objective was to evaluate the incidence of a combined endpoint including death, recurrent myocardial infarction and urgent revascularization in the 2 groups at 30 days post randomization. Baseline characteristic of patients included and randomized are the following: median age (61.3 ± 12.8 years), male (81.6%), median weight (76.7 ± 15.2 kilos), Killip class I (91.3%), Diabetes (42.7%), Hypertension (45.3%), Dyslipidemia (39.0%), Previous unstable angina (8.2%), Previous infarction (11.5%), Previous PTCA (8.3%), Previous CABG (1.5%), target vessels (RCA in 38.4%, LAD in 37.9%, LCx in 8.0%), AMI diagnosis (anterior in 40.1% and Inferior in 49.3%); Initial TIMI 3 Flow (16.9%). Median presentation delay is 184 ± 147 minutes, median time to treatment is 210 ± 141 minutes and median time to cath'lab is 237 ± 144 minutes. Abciximab bolus was administered in 100.0% and bolus plus infusion in 99.5%. Initial coronary angiograms were performed in 99.5%, PTCA in 93.1% and Stent implemented in 85.8%.

P1025 Primary coronary angioplasty vs. thrombolytic therapy for treatment of acute myocardial infarction (MI). Findings from the PCAT collaboration

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We combined the individual case findings from 10 randomised trials of percutaneous transluminal coronary angioplasty (PTCA) vs thrombolysis (2635 patients) to determine the effects of each treatment on 30-day and long-term outcomes and to evaluate any differences in treatment effect sizes in subsets of patients. PTCA was associated with a lower risk of death or non-fatal MI at 30 days (odds ratio 0.46, 95%CI 0.35–0.61) and at 6 months (odds ratio 0.55, 95%CI 0.43–0.7). There was a similar relative treatment effect for defined subgroups, including those based on gender, diabetes, prior MI, site of MI and age. The absolute risk, however, of death or MI at 30 days was higher for women than men (16.7% vs. 12.3% in the lytic group), for patients with diabetes than without (19.3% vs 12.0%) and for patients with a prior history of MI than without (22.7% vs 11.6%), with greater absolute treatment effects of PTCA therefore expected in the higher risk groups. For patients aged over 60 years, death or MI at 30 days was reduced from 17.1% in the lytic group to 9.3% in the PTCA group; while for patients less than 60 years, the rates were reduced from 8.7% to 4.5%.

Conclusions: The benefit associated with PTCA therapy at hospital discharge is maintained at 30 days and at 6 months. While some variability in treatment effect was noted across the trials, the relative treatment effect was similar among all risk subsets. However, the magnitude of absolute benefit was greatest in patients at greater risk, such as those with diabetes, women, those with prior MI and older patients.

P1026 Long-term outcome after emergency PTCA

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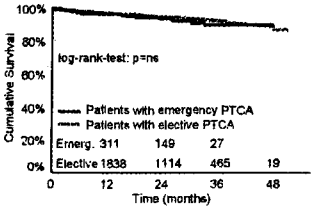
Whether performing PTCA in an emergency setting is detrimental to the long-term outcome has not yet been compared to elective PTCA.

The outcomes of all consecutive patients undergoing PTCA for AMI or unstable angina (target sample, n = 634) and of all patients with elective PTCA (control sample, n = 2684) during 1994–1996 were compared. In the target sample, 5.2% of patients were in cardiogenic shock. Among 30-day survivors, follow-up at 21.1 ± 11 (1–48) months of 94.0% of patients in the target sample, and at 24.8 ± 13 (1–53) months of 89.7% of patients in the control sample, respectively, was completed.

At follow-up 21/564 (3.72%) patients in the target sample and 117/2657 (4.40%) patients in the control sample had expired, p = ns. The rate of subsequent catheterizations (19.5% versus 20.9%, p = ns), interventions (27.0% versus 34.2%, p = ns), CABG surgery (20.9% versus 18.4%, p = ns), and left ventricular performance, functional status and drug intake at follow-up did not differ between samples. Differences were found with regard to repeat interventions that were performed earlier, and more frequently as emergency interventions themselves in the target sample, than in the control sample.



Performing PTCA as an emergency procedure is not detrimental to the long-term outcome of patients who survive the acute cardiac event. These results encourage all reasonable efforts to stabilize the emergency situation in order to enable patients survival unaffected from the acute coronary event.

P1027 Impact or reperfusion modality after acute myocardial infarction on reestablishing coronary blood flow

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Although thrombolysis (TH) and primary angioplasty (PA) are both effective in establishing reperfusion after acute myocardial infarction (AMI), various flow disturbances have been reported and seem to be related with adverse prognosis. In the present study we have examined the difference in the quality of coronary blood flow after AMI, in relation to the perfusion modality (either PA or TH).

Methods: 51 patients (pts) admitted for AMI within 3 hours from symptoms onset were randomized to TH (n = 25) and PA (n = 24). All pts underwent coronary angiography (CA) 90–120 min. after the beginning of TH or PA. Unsuccessful cases (TIMI grade flow < 2) were excluded and consequently 44 pts were randomized either to TH group (20 pts) or to PA group (24 pts). CA was repeated 18–36 hours later. The cTFC (corrected TIMI frame count) was used as coronary flow index and was measured in all (culprit or not) coronary arteries.

Results: cTFC values in culprit vessels, 90–120 min. after the beginning of TH or PA,. were significantly lower and near normal in PA group compared with those of TH group (27.4 ± 7.7 vs 39.8 ± 10, p < 0.001). After 18–36 hours cTFC values in TH groups, although decreased, still exceeded the normal ones (30.6 ± 7.9, p < 0.001). In addition, while in TH group cTFC was significantly higher (abnormal) in culprit arteries than normal ones (39.8 ± 10 vs 27 ± 8.1, p < 0.001), in PA group the above difference was not significant (27.4 ± 7.7 vs 25.7 ± 6.3, p = NS). In non culprit arteries cTFC 18–36 hours after reperfusion decreased in both groups. These variations, however, were insignificant in both the TH group (from 27 ± 8.1 to 23.7 ± 5.1, p = NS) and the PA one (from 25.7 ± 6.3 to 21 ± 3, p = NS).

In conclusion, in successfully reperfused coronary arteries after acute myocardial infarction, primary angioplasty reestablishes normal basal coronary flow faster as compared with thrombolysis.

P1028 "Open artery" theory: how will it affect the management of patients with myocardial infarction?

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Revascularization after myocardial infarction (MI) is conventionally reserved for patients with residual ischaemia. Given that normal flow in infarct related arteries (IRA) is an independent prognostic factor in these patients, possible verification that both early and late "opening" of occluded arteries is advantageous might have a dramatic effect on future management of such cases. The aim of this study was to estimate the consequences that acceptance of this theory would have in clinical practice

Methods: All patients hospitalized in our clinic with MI during a 2 month period (Feb–Mar 1998) underwent coronary angiography (CA) before discharge as well as a treadmill stress test which was repeated in 1 month. Subsequent treatment was based on conventional guidelines and only those with positive stress tests underwent myocardial revascularization.

Results: 49 patients with MI were studied. 11/49 underwent early revascularization because of contra-indication to or failure of thrombolysis (4) and post-infarct angina (7). CA in the remaining 38 revealed 3 vessel disease in 14, 2 vessel in 11 and 1 vessel in 13 patients. 17 patients had occluded infarct related arteries (2/17 also had 3 vessel disease). Revascularization would have been indicated in 29/38 patients based on the open artery theory of which 26/38 were anatomically suitable. Non invasive testing was positive for residual ischaemia in 15/38 of whom 13 were suitable for revascularization. Thus, based on the open artery theory 49/49 (100%) would have undergone CA (de facto, to determine occluded IRA) and 37/49 (76%) revascularization (to open IRA) whereas current indications (patients in need of early revascularization and those with residual ishaemia) call for 26/49 (53%) and 24/49 (49%) respectively (χ^2 test: p < 0.001 and p < 0.001).

Conclusion: Confirmation of the open artery theory would radically modify MI management strategies, which would become more invasive. Whether or not this novel approach will change the natural history of the disease remains to be seen.

ACUTE MYOCARDIAL INFARCTION: FROM BASICS TO PRACTICE

P1029 Estimation of apoptosis in acute myocardial infarction by Fas–Fas ligand system

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The presence of myocardial apoptosis in addition to overt necrosis after ischemia and reperfusion has been demonstrated in experimental and post-mortem studies of acute myocardial infarction (MI) using the methods of detecting DNA fragmentation. The methods, however, indicate overlap positivity with necrosis, and the time course of possible apoptosis following ischemia could not be assessed by the methods. Thus, evaluation of changes in Fas-Fas ligand system, which is the representative system of apoptosis-signaling receptor molecules and initiates the apoptotic death program, was attempted in MI.

Methods: A total of 13 patients with MI who underwent primary percutaneous transluminal coronary angioplasty (PTCA) were studied. They consisted of 7 anterior MI and 6 inferior MI, and 4 of them indicated the signs and symptoms of heart failure, but there was no in-hospital death. All of them underwent primary PTCA without thrombolytic therapy at 5 ± 1 hours after the onset. Left ventriculography and coronary angiography were repeated before discharge. Blood samples were obtained before and after PTCA, and before discharge. Plasma soluble Fas (sFas) and soluble Fas ligand (sFas-L) were measured by enzyme-linked immunosorbent assay (ELISA).

Results: Plasma level of sFas was 2.03 ± 0.34 ng/ml before PTCA, decreased to 1.65 ± 0.24 ng/ml after PTCA (p < 0.05) and increased to 2.80 ± 0.30 ng/ml before discharge (p < 0.02). Plasma sFas-L did not change significantly; 0.04 ± 0.02 ng/ml before PTCA, 0.03 ± 0.02 ng/ml after PTCA and 0.03 ± 0.01 ng/ml before discharge. There were no significant changes in left ventricular end-diastolic volume (from 154 ± 9 ml to 151 ± 7 ml) and ejection fraction (from 46 ± 3% to 49 ± 4%) from pre-PTCA to pre-discharge periods.

Conclusions: The underlying conditions prone to induce apoptosis in MI estimated by Fas-Fas ligand system appear to decrease transiently by primary PTCA and increase thereafter gradually, suggesting that apoptosis might be playing a role for a balance between myocardial repair and remodeling during the convalescent phase of MI.

P1030 Effects of acute or chronic nitric oxide synthesis inhibition on mortality, haemodynamics and remodelling in rats with myocardial infarction

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The role of endogenous nitric oxide (NO) post myocardial infarction (MI) is unclear. We studied the acute (3 hour to 3 weeks) or chronic (3 to 8 weeks) NO synthesis inhibition by L-NAME (L, 67 mg/L drinking water) on mortality, hemodynamics and left ventricular (LV) volume in rats with MI. Separate groups of rats were treated with hydralazine (H, 80 mg/L) plus L or placebo (P). Mortality were similar among various groups. After 3 or 8 weeks, mean arterial pressure (MAP, mmHg), LV end-diastolic pressure (LVEDP, mmHg), dP/dtmax (mmHg/s × 10^3) and cardiac index (ml/min/kg) were measured by Millar-tip catheter and electromagnetic flowmeter and total peripheral resistance index (mmHg/ml/kg) calculated. LV volume (Vol, ml/kg) was obtained by passive pressure-volume curves. Results for sham rats and rats with large MI (>35% of LV) are shown below:

	Sham + P	MI + P	MI + L	MI + L + H
		Acute		
N	13	11	17	20
MAP	113 ± 4	102 ± 3	94 ± 4*	88 ± 3*†
LVEDP	5.4 ± 1.0	15.6 ± 3.1*	25.2 ± 2.2*†	22.0 ± 2.1*†
DP/dtmax	16 ± 0.6	11 ± 0.8*	8 ± 0.5*†	7 ± 0.7*†
CI	327 ± 13	310 ± 18*	190 ± 17*†	260 ± 124*‡
TRPI	0.3 ± 0.0	0.3 ± 0.0	0.5 ± 0.1†	0.3 ± 0.1‡
Vol	1.6 ± 0.1	2.1 ± 0.1*	2.2 ± 0.1*	2.3 ± 0.1*
		Chronic		
N	11	6	19	22
MAP	112 ± 5	101 ± 2*	115 ± 3*†	102 ± 3‡
LVEDP	5.0 ± 1.0	14.4 ± 2.2*	17.3 ± 2.8*	13.0 ± 2.2*
DP/dtmax	15 ± 0.8	12 ± 0.5*	11 ± 0.7*	11 ± 0.7*
CI	310 ± 19	261 ± 12*	224 ± 14*†	280 ± 13‡
TRPI	0.3 ± 1.0	0.3 ± 0.0	0.4 ± 0.0†	0.3 ± 0.0‡
Vol	1.5 ± 0.1	2.4 ± 0.1*	2.5 ± 0.1*	2.5 ± 0.1*

(mean ± sem; *p < 0.05 vs. Sham; †p < 0.05 vs. MI + P; ‡p < 0.05 vs. MI + L)

Thus, acute NO inhibition post MI aggravated LV dysfunction (LVEDP, dP/dtmax, CI). Afterload normalization through H improved CI but had no effect on LV dysfunction (LVEDP, dP/dtmax). Chronic NO inhibition did not aggravate LV dysfunction. In the acute phase post MI, NO plays a role in LV function beyond afterload reduction in this model.

P1031 Differential effects of carvedilol on ischaemia-based or post-infarction ventricular remodelling in rats

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Remodeling after myocardial infarction (MI), and remodeling of non-infarcted but ischemic myocardium due to coronary stenosis would be pathophysiologically different. Thus, the effect of carvedilol on these two different states might be different. To clarify it, we compared the effects of carvedilol on remodeling in the chronic ischemic state by fixed coronary stenosis and that after MI by coronary ligation in rats.

Methods: Coronary stenosis was made by ligating proximal portion of the left coronary artery together with a thread, followed by thread removal. An inert vehicle [group (Gr)-1A, n = 15], carvedilol 10 mg/kg/day (Gr-2A, n = 15) was orally administered for 12 wks starting from 6 hrs after operation. The same treatments were performed (vehicle, Gr-1B, n = 12; carvedilol, Gr-2B, n = 12) in rats with coronary ligation. Remodeling was assessed at 12 wks by echocardiography.

Results: At 12 wks compared with 6 hrs after stenosis, LV end-diastolic (EDV) and end-systolic volumes (ESV) increased ($p < 0.01$) and ejection fraction (EF) decreased ($p < 0.05$) in both of Grs-1A and -1B, compared with baseline values before coronary stenosis or occlusion. However, in Gr-2A compared with -1A, EDV (367 ± 36 vs 464 ± 62 μL, $p < 0.05$) and ESV (74 ± 17 vs 143 ± 47 μL, $p < 0.05$) were smaller and EF (75 ± 3 vs 68 ± 5%, $p < 0.05$) was greater. Heart rates and systemic blood pressure in Grs-2A and -2B were lower ($p < 0.01$) compared with Grs-1A and -1B respectively. In Grs-1B and -2B, EDV and ESV were greater and EF was lower ($p < 0.01$, each) than Grs-1A and -2A. These values tended to be greater in Gr-2B than Gr-1B, but did not reach to significant differences.

Conclusion: Carvedilol exerted an anti-remodeling effect in rat hearts with fixed coronary stenosis, but was not effective in attenuating remodeling after MI. These results indicate that carvedilol attenuates remodeling of non-infarcted but ischemic myocardium due to coronary stenosis rather than that developed after MI.

P1032 Pre-myocardial infarction angina has an arrhythmo-suppressive effect on reperfusion therapy: substudy of a prospective randomized JIMI trial

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Background: It has not been concluded whether there is a relationship between pre-myocardial infarction angina pectoris (pre-MI AP) and reperfusion arrhythmia, although it has been reported that pre-MI AP has a beneficial effect in preserving left ventricular function. Moreover, determinants of reperfusion arrhythmias in patients with acute myocardial infarction (AMI) who have been successfully reperfused by reperfusion therapy are unknown.

Objective: To determine the predictive factors of reperfusion arrhythmias in patients with AMI who are successfully reperfused.

Methods: The Japanese Intervention Trial in Myocardial Infarction (JIMI) study (n = 123) is a prospective randomized trial that compares intracoronary thrombolysis with primary coronary balloon angioplasty. One hundred and ten consecutive patients with AMI who had been successfully reperfused in the JIMI study were studied. Multivariate logistic regression analysis was performed using ten clinical factors. Reperfusion arrhythmias were defined as all arrhythmias that occur within one hour after successful reperfusion therapy.

Results: 1) Reperfusion arrhythmias developed in 65 patients (59%). 2) Multivariate logistic regression analysis confirmed that inferior AMI and pre-MI AP were independently associated with reperfusion arrhythmia. 3) The odds ratio predicting reperfusion arrhythmias was 2.37 (95% CI; 1.06–5.31, p = 0.02) for inferior AMI. On the other hand, the odds ratio was minimal at 0.24 for pre-MI AP (95% CI; 0.09–0.65, p = 0.0036). 4) The method of reperfusion was not independently associated with reperfusion arrhythmias.

Conclusion: Pre-myocardial infarction angina pectoris suppresses reperfusion arrhythmia, while inferior AMI is an independent promoting factor for the arrhythmia.

P1033 Glucose-insulin-potassium infusion as adjunctive therapy to primary angioplasty for acute myocardial infarction

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Background: Treatment with Glucose-insulin-potassium (GIK) infusion during the acute phase of myocardial infarction (AMI) has been proposed to support the ischemic myocardium. Until now, GIK therapy has mainly been tested in the pre-thrombolytic era.

Methods: 238 patients (pts) with AMI and <75 years were included. They were allocated to receive GIK in addition to standard medication or only standard medication, prior to reperfusion therapy. GIK therapy consisted of 2 ml/kg/h glucose 20%, 4 ampuls of KCL and 20 units insulin per liter, given at admission for 6 h. Standard medication consisted of aspirin, heparin and nitroglycerin. Enzymatic infarct size was determined by measurements of LDHQ72, ejection fraction (EF) by radionuclide technique at day 4.

Results: The majority of pts were treated with primary angioplasty (91%), 3% underwent CABG and 6% were treated conservatively. GIK therapy was given in 124 pts, whereas 114 pts received only standard medical therapy. No difference was observed in hospital mortality, GIK pts: 5%, control pts; 4%, enzymatic infarct size; GIK pts 1214 IU (± 1125 IU), control pts: 1192 IU (± 914 IU) or EF; GIK pts 43%(± 11%), control pts 42% (± 11%).

Conclusions: No benefit of GIK therapy was observed in patients treated with primary angioplasty for AMI. Further studies are required with a higher dosage of GIK or with longer duration of treatment.

P1034 Protective effects of preinfarction angina are not evident in acute myocardial infarction treated by primary coronary angioplasty and stenting

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Preinfarction angina occurring shortly before the onset of acute myocardial infarction (MI) has been shown to have protective effects against ischemia, but the impact of primary percutaneous transluminal coronary angioplasty (PTCA) and stenting on this phenomenon is not known.

Methods: We studied 613 patients with transmural MI. Group I (n = 306) was treated by conventional medical therapies and coronary thrombolysis, and group 2 (n = 307) was treated by primary PTCA supported by stenting (success; 99%, stenting; 35%). Each group was subdivided into those with and without preinfarction angina within 24 hours before the onset of MI. There was no significant difference between the subgroups of groups 1 and 2 in clinical characteristics.

Results: In group 1, there were differences between patients with preinfarction angina (n = 84) and those without (n = 222) in in-hospital mortality (11% vs. 18%), pump failure (Killip classes 3 and 4) (11% vs. 21%, $p < 0.05$), left ventricular ejection fraction (LVEF) at discharge (52 ± 1% vs. 48 ± 1%; $p < 0.05$), and peak creatine kinase (CK, 2106 ± 179 U/L vs. 2764 ± 144 U/L, $p < 0.02$). In group 2, however, there was no significant difference between those with preinfarction angina (n = 82) and those without (n = 225) in mortality (6% vs. 6%), pump failure (12% vs. 12%), LVEF (50 ± 1% vs. 50 ± 1%), and peak CK (3285 ± 254 U/L vs. 3291 ± 151 U/L). Multivariate analysis indicated that preinfarction angina was an independent determinant of in-hospital death and pump failure in group 1, but not in group 2. Moreover, five year survial was significantly higher in those with preinfarction angina (85%) than in those without (74%, $p < 0.05$) in group 1, but there was no difference between those with and without angina in group 2 (88% vs. 88%).

Conclusions: We conclude that the protective effects of preinfarction angina in MI are not evident in those treated by primary PTCA and stenting, possibly because of the overwhelming protective effects of complete coronary recanalization provided by primary PTCA and stenting.

P1035 Effects of trimetazidine administration before thrombolysis in patients with anterior myocardial infarction: short-term and long-term results

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Reperfusion may prevent or reduce the development and extent of necrosis, but may also lead to an increase in reperfusion damage. Experimental studies performed in various animal models of myocardial ischemia have demonstrated the anti-ischemic properties of trimetazidine (TMZ) and have suggested that TMZ has antioxidant properties without any direct hemodynamic effects. Our study was aimed at investigating the effects of TMZ before thrombolysis in acute anterior myocardial infarction and included 81 patients, hospitalized within 4 h of the onset of symptoms. Patients were randomly (double blind) subdivided in two groups. The first group (40 patients, Group A, TMZ pretreatment) received 40 mg TMZ orally about 15 min before thrombolysis and subsequently 20 mg every 8 h. The second group (41 patients, Group B) received placebo before thrombolysis. Ventricular arrhythmias (VA) due to reperfusion were evaluated in the first 2 h. VA occurred in 15 of patients in group A versus 29 in group B ($p < 0.05$). CK peak normalization time was achieved after 55.7 ± 12.5 h in group A versus 61.2 ± 12.1 h in group B ($p = 0.048$). CK peak was 1772 ± 890 in group A vs 2285 ± 910 UI/l in group B ($p = 0.012$). In the follow-up (range 6–22 months), there were 4 deaths, two patients in each group. After 180 days from treatment, the TMZ group showed a smaller ESV than in placebo group (echocardiographic data), 46.2 ± 12 and 52.8 ± 13 m/m^2 respectively ($p = 0.037$). Our data suggest that TMZ probably reduces reperfusion damage and/or infarct size in patients with anterior AMI subjected to thrombolysis and affects the post AMI remodelling. Our data must be interpreted with caution because of the selection of patients. These findings require a much more extensive studies.

P1036 Low-dose continuous infusion of the synthetic glycolipid RC-552 provides sustained cardioprotection against infarction in dogs

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As has been demonstrated with the first generation glycolipid cardioprotectant monophosphoryl lipid A, a new cardioselective synthetic glycolipid (RC-552) can reduce infarction within 10 minutes of administration to dogs and pigs. Bolus plus infusion dosing protocols were evaluated in the canine infarct model to determine if the brief, acute protective effect observed with bolus dosing could be maintained for hours with drug infusion.

Methods: Forty-one dogs received either: 1) RC-552 (70 μg/kg bolus); 2) RC-552 (70 μg/kg bolus plus 40 μg/kg/hr × 5 hours); 3) RC-552 (35 μg/kg bolus plus 4 μg/kg/hr × 5 hours); 4) Injection Vehicle (high dose volume equivalent). Three hours after bolus dosing, dogs experienced 1 hour LAD occlusion followed by 3 hours reperfusion. Radiolabled microspheres were administered during ischemia and at 1 hour reperfusion to determine myocardial blood flow. Infarct size (IS) as a percent area at risk (AAR) was determined by triphenyltetrazolium chloride-Unisperse® counterstaining.

Results: As expected bolus only administration of RC-552 was not effective against infarction 3 hours after dosing. In contrast, administration of either a high or low dose drug infusion after the bolus resulted in similar (50%) reduction in infarct size 3 hours after bolus dosing.

Treatment Groups	IS (% AAR)	Midmyo Coll Flow** (mL/min/g)
Vehicle (high dose bolus + infusion volume)	22 ± 4	0.06 ± 0.02
RC-552 (70 μg/kg bolus)	22 ± 3	0.09 ± 0.02
RC-552 (70 μg/kg bolus + 40 μg/kg/hr × 5 hr)	11 ± 4*	0.13 ± 0.04
RC-552 (35 μg/kg bolus + 4 μg/kg/hr × 5 hr)	9 ± 4*	0.16 ± 0.06

Values are Mean ± SEM *$p < 0.05$ ANOVA **at 30 minutes ischemia, p = NS

Conclusion: Combination of drug infusion following bolus dosing with RC-552 reduced infarct size to ischemic challenge beginning 3 hours post bolus dose, while bolus dosing alone was ineffective. Clinical use of this dosing protocol should allow RC-552 administration immediately prior to and throughout cardiopulmonary bypass without immunostimulation or deleterious effects on peripheral hemodynamic function.

P1037 Early versus later use of ACE inhibitors in acute myocardial infarction: a meta analysis

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Background: Early use of ACE inhibitors in treatment of acute myocardial infarction (AMI) has remained controversial given inconsistent findings on appropriate left ventricular ejection fraction (LVEF) and systolic blood pressure (SBP) level. This meta analysis was conducted to determine indicators of therapeutic success with early (within 48 hours of chest pain onset) versus late use (72 hours) of ACE inhibitor therapy.

Methods: A meta analysis was conducted of all randomized placebo-controlled double-blind clinical trials published from January 1988 to June 1998 that assessed cardiovascular (CV) morbidity/mortality and tolerability in AMI patients who received ACE inhibitors within 24 to 72 hours of chest pain onset.

Results: Early use of ACE inhibitors reduced risk of CV-related mortality (RR 0.81, 95% CI 0.60, 1.02) and heart failure (RR 0.36; 95% CI 0.12, 0.60) regardless of baseline LVEF or SBP. Late use provided no additional benefit. Patients with anterior wall MIs were most likely to benefit from the survival advantage of early ACE inhibitor therapy ($p = 0.04$). Hypotension was significantly associated with anterior wall infarction ($p = 0.005$) and other medications with BP-lowering effects ($p = 0.02$), and was unrelated to start time or baseline SBP. Risk of renal dysfunction was lower with late (RR 0.36; 95% CI 0.09, 0.81) versus early use (RR 0.45; 95% CI 0.15, 1.05), and was significantly associated with anterior wall infarction ($p = 0.01$), elevated wall motion index ($p = 0.03$), and prior CV disease ($p = 0.02$).

Conclusion: Early use of ACE inhibitors within 48 hours of chest pain onset, particularly in anterior wall infarction, provides significant reduction in CV morbidity and mortality, independent of LVEF or SBP. Careful BP monitoring and titration of medications with BP-lowering effects can help avert hypotention. Careful monitoring of renal function in patients with prior CV morbidities is also warranted.

P1038 Paradoxical effects of smoking on the severity of myocardial infarction

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Background: The electrocardiogram remains the most useful tool for diagnosis of myocardial infarction and provides a simple means of monitoring the evolution of injury. Regional ST elevation occurs within seconds of coronary occlusion but early recanalisation accelerates its resolution and may protect against Q wave development.

Methods: Prospective analysis of 1399 patients with a first myocardial infarction in order to identify factors affecting the electrocardiographic evolution of injury.

Results: Smoking increased the odds of ST elevation (odds ratio (OR): 1.61; 95% confidence intervals (CI): 1.08–2.36) but reduced the odds of Q wave development (OR: 0.69; CI: 0.49–0.96). Prior aspirin therapy reduced the odds of ST elevation (OR: 0.57; CI: 0.35–0.94) and Q wave development (OR: 0.53; CI: 0.34–0.84). Admission within 2 hours of pain onset more than doubled the odds of ST elevation (OR: 2.44; CI: 1.65–3.59) but did not influence Q wave development. ST elevation and Q wave development were both associated with an adverse prognosis with estimated 6 month survival rates of 83.3% (81.0–85.6%) and 81.9% (79.5–84.3%), respectively, compared with 89.7% (84.9–94.5%) and 94.3% (91.4–97.2%) for patients without these ECG changes.

Conclusion: The thrombogenicity of the blood at the time of a plaque event may be a major determinant of infarct severity. Smoking, which increases thrombogenicity, has complex effects, increasing the likelihood of ST elevation while providing a substrate for successful thrombolysis which reduces the risk of Q wave development. The net effect, in prognostic terms, may be beneficial. Prior aspirin therapy, by reducing thrombogenicity, may reduce infarct severity, protecting against ST elevation and Q wave development more effectively than aspirin given after hospital arrival.

P1039 Early changes in neutrophil CD18 adhesion molecule expression predict infarct size in a rabbit model of myocardial infarction

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CD18 integrins mediate leukocyte adhesion to vascular endothelium following myocardial necrosis. We hypothesised that changes in the expression of these rapidly activated and readily measured adhesion receptors on circulating neutrophils (PMN) would reflect the extent of cardiac damage.

Methods: Myocardial infarction was induced in anaesthetized adult male New Zealand white rabbits (n = 8) using a standard protocol. After 45 min the heart was reperfused for 3 h and the absolute and relative infarct size were calculated. Whole blood was collected before the induction of ischaemia, after 20 and 45 min of ischemia, and after 20, 60 and 180 min of reperfusion. Samples were immediately incubated with anti-CD18 and anti-IgG1 control monoclonal antibodies. Cells were lyzed, stabilized and fixed, after which flow cytometry was used to assess PMN CD18 expression. Absolute and relative infarct size were correlated with absolute levels of, and changes in, CD18, using linear regression.

Results: Mean CD18 expression was 2.42 (SEM ± 0.20) at baseline (range 1.66–3.53) and increased to 4.43 (±0.34, range 3.44–6.20: $p < 0.01$) after 3 h reperfusion. Mean CD18 expression had increased to 3.07 (±0.29; $p < 0.05$) within 20 min of ischaemia. Absolute and relative infarct size did not correlate with absolute PMN CD18 expression at 3 h ($r = 0.12$ & 0.04 respectively). When corrected for baseline levels, the changes in CD18 expression were correlated with absolute and relative infarct size ($r = 0.85$ & 0.89 respectively, $p < 0.001$ for both)

Conclusions: In this model of myocardial infarction PMN CD18 expression increases rapidly following myocardial injury. It should be acknowledged, however, that a proportion of the observed increase may be due to surgical stress. Absolute and relative expression at 3 h does not correlate with infarct size. However, when changes in PMN CD18 expression are assessed, rather than absolute receptor levels, there is an excellent correlation with infarct size. Further work is required to assess whether this is replicated in humans.

P1040 Angiographic morphology in patients presenting with ST-segment elevation myocardial infarction in relation to prior angina history

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Background: Angiographic studies have shown that patients presenting with acute ST-segment elevation MI have a higher incidence of total coronary occlusions, one vessel disease and poorly developed collaterals. Patients with prior angina presenting with Q-wave MI may have different angiographic characteristics compared to those with recent onset of angina (<7 days) or no prior symptoms. We analyzed 108 consecutive acute MI patients with ST segment elevation divided into two groups: Group I included patients with either no prior symptoms or new onset of angina (n = 60). Group II included patients with prior stable or crescendo angina (n = 48).

Results: There were no significant differences between the two groups with regards to baseline clinical variables.

Angiographic characteristics	Group I (n = 60)	Group II (n = 48)	p
One vessel disease (%)}	56	12	<0.001
Three vessel disease (%)	2	30	<0.001
ACC/AHA B2/C lesions (%)	63/20	40/58	<0.001
Mod-heavy calcification (%)	6	62	<0.001
Lesion thrombus (%)	40	29	NS
TIMI flow 0–1 (%)	30	38	NS
Collaterals (%)	26	42	0.04
Peak CPK (U/L)	2458 ± 628	1199 ± 268	<0.01
Q-wave MI (%)	83	50	0.002

Conclusion: Patients with prior angina presenting with ST segment elevation had a higher incidence of multivessel disease, calcified lesions, ACC/AHA B2/C lesions, collaterals and lower incidence of Q-wave MI with lower peak CK values. The impact of these angiographic findings on long-term prognosis needs to be further evaluated.

P1041 Quality of life 4 years after myocardial infarction: are the physical and mental summary scales of the SF-12 as reliable and sensitive at measuring quality of life as those of the SF-36?

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The Short Form 36 (SF36) is a widely used quality of life (QOL) tool. The scoring system provides detailed scores for 8 different "domains" of health, plus two individual physical and mental component summary scores (PCS and MCS) and a global QOL score. While the SF36 has proved acceptable to patients, the SF12, a shorter tool derived from the SF36, could be more useful. The SF12 produces summary scores only but should retain the reliability and sensitivity of the SF36. We compared the two QOL tools in patients with coronary artery disease.

Method: 475 four-year survivors of a myocardial infarction, identified from a heart attack register, were mailed the SF36, the Rose angina and dyspnoea questionnaires and a demographic questionnaire.

Results: Of the 424 (89.1%) responders, 421 (99.3%) had answered the SF36. The PCS and MCS could be computed for both the SF36 and SF12 in 278 (66.0%) cases. The characteristics of responders and non-responders were similar. For both the SF36 and SF12 the correlation coefficients of each of the 8 domains to the two component summary scores were found to be in the expected range or higher. Reliability estimates calculated for the PCS36 and MCS36 were at least as good as those published for general populations. There was no significant difference between the SF12 and SF36 PCS or MCS scores when compared as a group ($P = 0.750$ and 0.123 respectively). The table shows that the PCS and MCS scores of the SF36 were capable of detecting the impact on quality of life of breathlessness of differing severity and that the SF12 was just as sensitive at identifying these differences. Similar results were observed when comparing severity or frequency of chest pain.

Table 1

Dyspnoea score	n	%	Comparison	SF-36 PCS	SF-12 PCS	SF-36 MCS	SF-12 MCS
0	111	39.9	0 v 1	<0.001	<0.001	0.451	0.166
1	54	19.4	1 v ≥2	<0.001	<0.001	0.016	0.002
>2	108	38.8	0 v ≥2	<0.001	<0.001	0.012	0.005

Conclusions: The SF12 is a reliable and sensitive substitute for the SF36 in determining differences in symptom-related QOL for patients with coronary artery disease where summary scores alone suffice. Response rates are likely to be higher when it is issued alone rather than embedded in the SF36.

P1042 Influence of angiotensin-converting enzyme gene polymorphism on plasma natriuretic peptide levels after reperfusion in patients with acute myocardial infarction

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Purpose: To investigate the relationship between the angiotensin-converting enzyme (ACE) gene polymorphism and the improvement of left ventricular (LV) function by measuring plasma A-type natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) levels after direct coronary angioplasty in the patients with acute myocardial infarction (AMI).

Methods: ACE gene polymorphism was determined in 29 patients with AMI who underwent successful direct angioplasty and had no significant restenosis three weeks after angioplasty. The patients were classified as having the 190 bp deletion homozygous genotype (Group D/D, n = 7), the 490 bp insertion homozygous genotype (Group I/I, n = 12) or the 490 bp insertion 190 bp deletion heterozygous genotype (Group I/D, n = 10). Plasma ANP and BNP levels immediately after reperfusion and three weeks after reperfusion, LV ejection fraction (EF) three weeks after reperfusion and peak serum creatine kinase (CK) values were compared between the three groups.

Results: There was a significant difference in age between the three groups (Group I/I: 48 ± 10, Group I/D: 71 ± 6, Group D/D: 65 ± 8 yr, $p < 0.01$ vs. Group I/I, respectively), while there was no significant difference in male gender (Group I/I: 50 (6/12), Group I/D: 50 (5/10), Group D/D: 57 (4/7)%, NS). Plasma ANP and BNP levels [pg/ml] in the three groups were as follows:

	Immediately after angioplasty		Three weeks after angioplasty	
	ANP	BNP	ANP	BNP
Group I/I	178 ± 111	22 ± 4	27 ± 12	35 ± 8
Group I/D	90 ± 26	224 ± 139*	20 ± 3	87 ± 30*
Group D/D	97 ± 24	299 ± 371*	42 ± 40	168 ± 177*

*$p < 0.01$ vs. Group I/I.

As shown, plasma BNP levels were significantly lower in Group I/I than in Group I/D and D/D after reperfusion. There was no significant difference in LVEF (Group I/I: 72 ± 2, Group I/D: 74 ± 3, Group D/D: 73 ± 9%, NS) and peak serum CK (Group I/I: 2074 ± 546, Group I/D: 2498 ± 1672, Group D/D: 1301 ± 513 U/l, NS).

Conclusion: The improvement of LV systolic function after successful reperfusion is greater in patients with AMI who have genetic insertion of ACE gene polymorphism.

P1043 Late progression of mild residual stenosis in culprit lesions after myocardial infarction

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Mid-term and long-term evolution of culprit lesions with mild coronary stenosis (<50%) after myocardial infarction (MI) and thrombolysis is not well known.

In a consecutive serie of 350 patients (p) with myocardial infarction treated with rtPA which were included in a serial angiographic study, we have found in a coronary angiogram performed before discharge (9 ± 5 days after MI) a culprit lesion with a non significative (<50%) residual stenosis in 65 p (19%) (mean: 31 ± 13%).

In this group of 65 p a second elective coronary angiogram was performed 11 ± 5 weeks after MI in 47 p (72%). A similar residual stenosis was documented in 42 p (90%). Only 5 p shown progression: 2 p (4%) developed reocclussion without reinfarction and 3 p (6%) had a stenosis 51–99%.

A third angiogram was done 40 ± 26 months after MI in 24/42 p with mild residual stenosis in the second angiogram, due to ischemic symptoms recurrence (18 p with severe angina and 6 p with a new MI in another territory). Progression was detected in 14/24 (58%) culprit lesions: 4 reocclussions and 10 severe stenosis.

To analyze the progression of coronary plaques we have divided the coronary tree in 15 segments. One segment in a p was eliminated from the analysis due to a previous balloon angioplasty. A progression over 70% stenosis was presented in 14/24 culprit lesion segments (58%) in contrast with only 29/335 non culprit lesion segments (9%) ($p < 0.001$).

In conclusion: Mild residual stenosis after myocardial infarction have a potencial evolution towards severe stenosis or reocclussion in a long-term follow-up.

P1044 Can heart rate identify patients at risk for ventricular remodelling after small to moderate myocardial infarction?

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Background: Neurohormonal activation largely depends on left ventricular dysfunction; moreover remodeling after myocardial infarction (MI) is related to MI size. Aim of the study: to evaluate the importance of heart rate variability (HRV), expression of autonomic unbalance, in predicting remodeling in pts with small to moderate MI.

Methods: We studied 140 pts with small to moderate size MI [wall motion index ≤ 1.79 measured at discharge (T1)]. The end-diastolic diameter (EDD, mm), end-diastolic volume (EDV, ml) and left ventricular ejection fraction (EF, %) were measured by 2D-echocardiogram (E) at T1 and every 3 months up to the end of a 12 month follow-up (T2). Time domain HRV indexes (SDNN, SDANN) were measured at T1 and T2 by 24 hour Holter monitoring. All pts were treated with β-blockers and ACE-inhibitors. Coronary angiography was performed in all pts within 1 month from MI.

Results: at T2 69 pts showed significant LV enlargment (G1) while the remaining 71 did not (G2). G1 and G2 pts did not differ in age, sex, site and size of MI and TIMI grade flow of the infarct related artery. Table shows the E results (*p < 0.001 T1 vs T2):

	EDD-T1	EDD-T2	EDV-T1	EDV-T2	EF-T1	EF-T2
G1	48 ± 0.4	52.8 ± 0.4*	115.8 ± 9	121.9 ± 9*	48.1 ± 5	44.9 ± 7*
G2	51.2 ± 0.7	48.2 ± 0.5*	116.7 ± 8	110.8 ± 5*	47.3 ± 4	51.1 ± 5*

At T1 HRV shows a significantly higher sympathetic activation in G1 than G2 (SDNN: 72 ± 13 vs 123 ± 8; p < 0.001. SDANN: 59 ± 12 vs 103 ± 12; p < 0.001).

Conclusions: 1) low HRV, expression of sympathetic activation, early predicts late development of ventricular remodeling; 2) further studies are necessary to investigate the influence of therapy on autonomic tone and ventricular remodeling in post MI pts.

P1045 Circulating platelet activation status in acute coronary syndromes: higher activation in unstable angina relative to myocardial infarction

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Background: Platelet-rich thrombus formation at fissured atherosclerotic plaques is a feature of both unstable angina and myocardial infarction. However, platelets are thought to play a more central role in the pathogenesis of unstable angina while fibrin deposition predominates the pathogenesis of myocardial infarction.

Aim: To determine the extent of systemic platelet activation in patients with acute coronary syndromes relative to healthy controls and to investigate if this differs between patients with unstable angina and myocardial infarction.

Method: Peripheral venous blood samples were obtained within the first 24 hours of onset of chest pain. Twelve patients with myocardial infarction and 14 with unstable angina admitted to the coronary care unit were included in the study. The diagnosis of unstable angina and myocardial infarction was confirmed on the basis of ECG changes, and CK levels. Blood samples were also obtained from 18 healthy control subjects. Platelets were stained with fluorochrome-conjugated monoclonal antibodies directed against CD42a (GpIb, a general platelet marker) and P-selectin (an activation-dependent marker). Flow cytometry was then used to quantify the degree of P-selectin expression only on cells (platelets) expressing the general marker. Data was acquired under logarithmic amplification with low flow to prevent coincidence in the laser beam. Circulating platelet activation status was thus determined as the percentage of cells staining for P-selectin.

Results: Platelet activation was significantly higher in patients with myocardial infarction (P-selectin positive platelets, Mean ± SEM = 5.1 ± 0.9%, P = 0.008) and unstable angina (9.1 ± 1.5%, P = 0.003) compared to the healthy control group (2.3 ± 0.5%). Unstable angina patients exhibited significantly higher platelet activation than myocardial infarction patients (P = 0.03).

Conclusion: Platelets are activated systemically in both acute myocardial infarction and unstable angina. The higher level of platelet activation in unstable angina compared to myocardial infarction suggests a more important role for platelet activation in such patients. This confirms the need for specific antiplatelet therapy in patients with unstable angina.

LIPIDS AND LIPID LOWERING: CLINICAL EFFECTS

P1046 Statins effects on plasma removal of chylomicrons and remnants in coronary artery disease: study with artificial emulsions

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Defects on the plasma removal of chylomicrons and remnants have been implicated in atherogenesis. Plasma removal of a chylomicron-like emulsion labeled with ^{14}C-Cholesteryl oleate (^{14}C-CO) and ^{3}H-Triolein (^{3}H-TO) was determined in 43 patients (mean age 56 ± 13) with coronary artery disease submitted to statin treatment. The ^{3}HTO and ^{14}C-CO kinetics evaluate respectively, lipolysis and removal of chylomicrons and remnants. Atorvastatin (A), (10 mg/day, n = 16), pravastatin (P), (40 mg/day, n = 13) or placebo (pl) (n = 14) were given for a 6-week treatment period. After a 12 hour fast, the emulsion was injected intravenously in a bolus and blood samples were collected in predetermined intervals during 60 minutes to determine the decaying curves and the fractional clearance rate (FCR) of the labels. There were similar reductions in total cholesterol (A = 24 ± 16%; P = 21 ± 11%, p = 0.0001 vs. baseline) and LDL cholesterol (A = 31 ± 19%; P = 25 ± 18%, p = 0.0001 vs. baseline), with statin treatment. The effects of statins on emulsion removal are shown in the table.

^{3}H-TO-FCR (min^{-1})	Atorvastatin	Pravastatin	Placebo
Baseline	0.029 ± 0.012	0.034 ± 0.026	0.029 ± 0.019
6 Weeks	0.037 ± 0.02	0.024 ± 0.017	0.019 ± 0.07
^{14}C-CO-FCR (min^{-1})	Atorvastatin	Pravastatin	Placebo
Baseline	0.008 ± 0.007	0.014 ± 0.014	0.016 ± 0.006
6 weeks	0.013 ± 0.013*	0.02 ± 0.018*	0.009 ± 0.008

Data = mean ± SD; *p = 0.01 vs. baseline vs.placebo ANOVA

There was a significant correlation between LDL cholesterol reduction and ^{14}CO-FCR increase (r = 0.5;p = 0.01). The ^{14}CO-FCR was increased in those patients in which the LDL cholesterol reduction was greater than 30%. There were no effects on lipolysis. Chylomicron-like emulsion removal was accelerated after both statins treatments, indicated by CO-FCR increase, and the acceleration was proportional to LDL cholesterol reduction. Improvement in chylomicron and remnants clearance may be an anti-atherogenic effect of statins.

P1047 Reduction of serum cholesterol concentration with a diet consisting of common foods enriched with plant sterols

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Plant sterols are natural components in edible vegetable oils and they have recently been used in the search for natural substances for hypercholesterolaemia. It has been also suggested that incorporation of calcium, magnesium and potassium to the diet may further enhance the cholesterol lowering effect of plant sterols. We explored the effects of a diet that included common food items such as bread, yoghurt and sausages enriched with non-esterified sitosterol and the above mentioned minerals on serum lipids.

Methods: 80 subjects with mild hypercholesterolaemia were included in this double-blind placebo-controlled parallel-group trial. Following the dietary stabilisation period and a 2-week placebo run-in phase patients fulfilling the randomisation criteria entered the 15-week double-blind diet period. Habitual dietary intakes during the trial were monitored using 3-day food diaries. Patients in the Enriched Diet Group (EDG) received a combination of bread, yoghurt and sausages enriched with plant sterols (75% b-sitosterol and 25% b-sitostanol) by 1.25, 2.5 and 5.0 g/day during the three 5-week periods, respectively. Patients randomised to the Placebo Group (PG) received matching placebo products. Compared with the baseline the net reductions in serum total cholesterol (TC) were 5% ($p < 0.05$), 6% ($p < 0.01$) and 6% ($p < 0.01$) during the three 5-week periods, respectively (trend test, $p = 0.0038$). The corresponding reductions in LDL cholesterol were 5% (n.s.), 7% ($p < 0.0.1$), and 7% ($p < 0.01$) (trend test $p = 0.0046$). The relative reduction in TC adjusted for changes in intake saturated fat in EDG compared with PG was 0.44 mmol/l ($p = 0.0016$), and that in LDL-C 0.42 mmol/l ($p = 0.0007$). There were no changes in serum HDL-C or triglycerides between the groups. The plant sterol concentrations determined from serum confirmed the dose increase, although the actual intakes were slightly (n.s.) lower than the prescribed ones. The initial plant sterol dose 1.25 g/day was as effective as higher doses in reducing TC or LDL-C.

In conclusion, plant sterol enriched diet combined with moderate changes in mineral composition of common foods will effectively reduce serum TC and LDL-C in hypercholesterolaemic subjects. Such a diet with a relatively low dose of plant sterols can be an important addition to the existing non-pharmacologic measures to lower high serum cholesterol.

P1048 Influence of lipid fractions on coronary flow reserve in asymptomatic males without coronary artery disease

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Coronary endothelial dysfunction has been reported in asymptomatic subjects with hypercholesterolemia. The aim of the present study was to evaluate the influence of total cholesterol and its subfractions on the coronary flow reserve (CFR), an index of the integrated function of the coronary circulation

Methods: Using oxygen-15 labeled water and positron emission tomography, myocardial blood flow (MBF, ml/min/g) was measured at rest and during iv adenosine (Ado, 0.14 mg/kg/g) in 80 asymptomatic males: group 1 ($n = 61$; age, 45 ± 7 years) had normal (≤ 6.5 mmol/l) and group 2 ($n = 19$; age, 48 ± 10 years) had elevated total cholesterol.

Results: Total cholesterol was 5.1 ± 0.8 and 7.2 ± 0.7 mmol/l in group 1 and 2 ($p < 0.001$), respectively; LDL was 3.2 ± 0.8 and 4.9 ± 0.7 mmol/l ($p < 0.001$), HDL was 1.1 ± 0.3 and 1.0 ± 0.4 (p = ns) and triglycerides were 1.8 ± 1.3 and 3.0 ± 1.8 mmol/l mmol/l ($p < 0.005$). Group 1 and 2 had comparable MBF-rest (0.87 ± 0.14 vs 0.84 ± 0.14), MBF-Ado (3.63 ± 1.02 vs 3.30 ± 0.86) and CFR (4.23 ± 1.29 vs 3.95 ± 0.93); p = ns for all 3 comparisons. A significant, but weak correlation was found between CFR and HDL in group 1 ($r = 0.29$, $p < 0.05$), but not in group 2. In contrast, a significant inverse correlation between LDL and CFR was found in group 2 ($r = -0.61$, $p < 0.05$), but not in group 1.

Conclusions: In contrast to previous reports we found no correlation between CFR and total cholesterol. This might be due to different selection criteria. However, LDL cholesterol subfraction correlated inversely with CFR in hypercholesterolemic subjects supporting a pathogenetic role for the LDL subfraction in microcirculatory dysfunction.

P1049 Lipoprotein a as an independent risk factor for coronary artery disease in patients with angina

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There are few studies using a multivariate analysis about predictor factors of coronary artery disease (CAD) in patients with angina. Seldom they include Lipoprotein a.

For that purpose, we have designed a case-control study including patients who underwent a coronary arteriography, collecting clinical variables and analytical parameters focusing on the lipid profile.

Methods: From a total population of 869 consecutive patients who underwent a coronary arteriography between April 1997 and Dec 1997, we included 188, with the following inclusion and exclusion criteria: age > 18, indication of invasive study because of unstable angina or stable angina with high risk criteria on non invasive tests. Exclusion: creatinine ≥ 2.5 mg/dl, hyperthyroidism, hepatopathy, and previous hypolipemiant treatment.

We collected the following clinical variables: age, gender, hyperlipidemie, hypertension, diabetes, tobacco, ancient AMI, and hematologic and biochemical parameters; total CHO, triglycerids, LDL, HDL, apolipoproteins A and B, lipoprotein a, platelets, fibrinogen and hemoglobine.

Blood samples were obtained before coronariography, and frozen to −40 degrees. A blind analysis was performed. We took the mean of three different measures on each sample.

Coronariography was performed by an independent physician, and lesions of any severity were considered. 144 patients had CAD, and 44 had no lesions.

Variables were analysed by SPSS 8.0, with t-Student test. We found significance for the following variables: ancient AMI, hypertension, diabetes, smoking, masculine gender, total cholesterol, LDL, LDL/HDL ratio, apolipoprotein b, fibrinogen and lipoprotein a.

Subsequently, a regression logistic test was performed, with a CI of 95%, and we obtained as independent risk factors for CAD: ancient AMI ($p = 0.0001$), masculine gender ($p = 0.0014$), ratio LDL/HDL ($p = 0.0042$), and lipoprotein a ($p = 0.010$). This last parameter had a Sens of 50% and a Spec 93.6%, with an OR = 14.66 (7.38–28.87) (CI Fisher), p corrected by Yates of 0.00001.

Conclusions: 1. In our study, in patients with angina, masculine gender, LDL/HDL ratio, and lipoprotein a > 30 mg/dl were the only independent risk factors for CAD.

2. The relative risk for CAD in patients with lipoprotein a > 30 mg/dl is 14 times that in subjects with low levels.

P1050 Hypertensive middle-aged men have exaggerated and prolonged rise of plasma triglyceride values postprandially similar to coronary artery disease and diabetes mellitus patients

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Objective: Previous studies have shown that patients with coronary artery disease (CAD) have an exaggerated rise and a delayed fall of plasma triglycerides (TG) after fat loading (FL). We designed this study since no data exist as regards the response to FL in patients (pts) with primary hypertension (HYP) compared to pts with CAD and non insulin dependent diabetes mellitus (DM)

Methods: A fat rich meal (83.5% fat, 1604 calories per m^2 body surface) was given to 21 pts with HYP without CAD, to 18 normotensive individuals without CAD and no risk factors (Controls), to 20 normotensive pts with proven CAD (CAD + No HYP) and 16 pts with DM without CAD or HYP, all with similar baseline TG values.

Results: Total and high density lipoprotein cholesterol did not change significantly in any group. The TG values increased % significantly 6 h after fat loading in HYP, CAD + NoHYP and DM pts compared to Controls ($137 \pm 79\%$ in HYP, $128 \pm 86\%$ in CAD + NoHYP pts, $91 \pm 67\%$ in DM, $76 \pm 54\%$ in Controls; $p = 0.001$, $p = 0.04$ and $p = 0.01$ respectively) and 8 h ($107 \pm 85\%$ in HYP, $81 \pm 66\%$ in CAD + NoHYP pts, $62 \pm 54\%$ in DM, $55 \pm 41\%$ in Controls; $p = 0.0003$, $p = 0.05$ and 0.004 respectively). The rise in TG values in HYP pts over that predicted from Controls was 82 mg/dl higher at 6 h ($p = 0.0009$) and 71 mg/dl ($p = 0.0008$) higher at 8 h than expected; in CAD + NoHYP pts the corresponding increases were 68 mg/dl at 6 h ($p < 0.05$) and 54 mg/dl ($p = 0.09$) at 8 h. In DM pts the corresponding increases were higher 63 mg/dl at 6 h, $p = 0.03$, and 50 mg/dl higher at 8 h than expected $p = 0.02$.

Conclusions: The study suggests that HYP and DM pts, have an exaggerated and prolonged rise of plasma triglyceride values after fat loading, similar to CAD + NoHYP pts compared to Controls.

P1051 Efficacy and safety of atorvastatin versus simvastatin in type II diabetes patients with coronary heart disease

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In type II diabetes, the atherogenic lipid trias contribute to the elevated risk of macrovascular disease. The Target Tangible study compared the effects of atorvastatin and simvastatin in a large cohort of coronary heart disease (CHD) patients in Germany. We conducted a subgroup analysis to assess the efficacy and safety of atorvastatin and simvastatin in patients with type II diabetes.

Methods: Patients with LDL-C levels ≥ 130 mg/dL (3.4 mmol/L) entered a 6-week washout. Those meeting the lipid entry criteria were randomized (2:1) to atorvastatin 10 mg or simvastatin 10 mg for 14 weeks. Dose was increased to 20 mg and 40 mg at weeks 5 and/or 10, respectively, if the target LDL-C level of <100 mg/dL (2.6 mmol/L) was not achieved. Primary endpoints were efficacy (responder rates) and safety (adverse events and laboratory measurements). Secondary endpoints were changes in lipid parameters including TGs.

Results: A total of 2856 patients met the lipid entry criteria; of whom 517 (18%) had diagnoses of type II diabetes. A greater percent of diabetic patients (67%) reached the goal than non-diabetic (61%). Significantly ($p < 0.001$) more patients achieved the LDL-C goal with atorvastatin (72% and 66% in diabetics and non-diabetics, respectively) than with simvastatin (57% and 52%). Furthermore, the median percent TG lowering on study completion was −29% on atorvastatin and −15% on simvastatin in diabetics vs −28% and −21%, respectively, in non-diabetics. There was no significant difference in adverse event rates between atorvastatin- and simvastatin-treated patients. Elevations of creatine kinase and liver enzymes > 3× ULN occurred in 0.4% and 0.2%, respectively, of diabetics and 0.3% and 0.1% of non-diabetics with no significant difference in these parameters between atorvastatin- and simvastatin-treated patients.

Conclusions: Benefits of statin treatment were significantly greater in diabetic than in non-diabetic patients. Atorvastatin was more effective than simvastatin in lowering LDL-C and TGs, and more type II diabetes patients reached LDL-C goals with atorvastatin than with simvastatin.

P1052 Cost-effectiveness of statin therapy against mild to moderate hypercholesterolemia in patients with coronary artery disease

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Background: The recent Lipoprotein and Coronary Atherosclerosis Study (LCAS) demonstrated that fluvastatin significantly slowed coronary artery disease (CAD) progression compared to placebo, with less need for revascularization procedures and fewer deaths over a 2-year follow-up period. This cost analysis was conducted to determine the long-term cost-effectiveness of fluvastatin based on these findings.

Methods: Wholesale drug costs and mean 1996 New York State Medicare/Medicaid charges were applied to drug and procedure rates reported in LCAS. The cost effectiveness of fluvastatin was assessed for lives saved (including all drug- and procedure-related charges), and myocardial (coronary angioplasty, coronary artery bypass grafting, coronary stent, atherectomy, or transcatheter revascularization) and all (myocardial revascularization, carotid endarterectomy, peripheral angioplasty, or peripheral bypass fraft) revascularization procedures avoided for up to 2 years.

Results: Fluvastatin resulted in per patient cost savings of from $621.19 to $836.39 for myocardial revascularization procedures avoided, and from $946.58 to $1274.51 for all rescularization procedures avoided. Moreover, fluvastatin provided cost savings of from $1568.11 to $2111.24 per life saved over a 2-year period.

Conclusion: Fluvastatin provides significant cost-effectiveness benefits in treatment of mild to moderate hypercholesterolemia in patients with CAD. These cost benefits are related to fewer deaths and fewer required revascularization procedures over a 2-year follow-up period.

P1053 Treatment of mixed hyperlipidaemia in coronary artery disease patients with fluvastatin and bezafibrate in monotherapy and combination

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Purpose: The Fluvastatin Alone and in Combination Treatment (FACT) study was designed (a) to compare the long-term effects of fluvastatin and bezafibrate in monotherapy and in combination on plasma lipids and serum fibrinogen in patients with coronary artery disease (CAD) and mixed hyperlipidaemia; (b) to assess the safety and tolerability of the fluvastatin and bezafibrate combination.

Methods: In this multicentre, double-blind, parallel group study 333 patients (age 56 ± 8 years, LDL- cholesterol 135–250 mg/dL and triglycerides 180–400 mg/dL) were randomised to receive fluvastatin (F) 40 mg or bezafibrate (B) 400 mg or fluvastatin 20 mg plus bezafibrate 400 mg or fluvastatin 40 mg plus bezafibrate 400 mg for 24 weeks.

Results: Baseline (Base) lipids and fibrinogen values (mean ± SD) and mean % change (Δ) are reported:

Parameter (mg/dL)	F 40 mg		B 400 mg		F 20 mg B 400 mg		F 40 mg B 400 mg	
	Base	% Δ	Base	% Δ	Base	% Δ	Base	% Δ
LDL-C	190 ± 35	−23†	179 ± 32	−8	187 ± 34	−23†	191 ± 36	−25†
Triglyceride	264 ± 65	−7	256 ± 65	−24†	254 ± 57	−35†	261 ± 73	−38†‡
HDL-C	39 ± 8	1	42 ± 10	16†	40 ± 8	21†	42 ± 9	21†
Fibrinogen	352 ± 83	−4	322 ± 51	−9†	339 ± 69	−14†	319 ± 57	−16†τ

†$p \leq 0.001$, τ$p < 0.01$, ‡$p < 0.05$

No clinically relevant hepatic or muscular laboratory abnormalities were reported. Adverse events did not occur more frequently with combination than with monotherapy.

Conclusion: The combination of fluvastatin 40 mg and bezafibrate 400 mg was significantly more effective in reducing both LDL-C and triglycerides than bezafibrate alone in CAD patients with mixed hyperlipidaemia.

P1054 Is the beneficial effect of lipid-intervention in coronary artery disease related to both lowering of triglycerides and of LDL cholesterol?

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It is well established that LDL-Cholesterol (LDL-C) promotes progression of coronary artery disease (CAD), and that lowering LDL-C will inhibit it. However, it is still a matter of debate wether lowering triglycerides (TG) also inhibits progression. This is what we studied.

Methods: The Coronary Intervention Study, CIS, is a multi-centre, randomized, double-blind, placebo-controlled study to investigate the *angiographic* effects of lipid-intervention on progression of CAD in 254 *young* men with hypercholesterolemia. LDL-C targeted treatment with up to 40 mg simvastatin or placebo o.d., and add-on medication (colestyramine), was pursued for a mean of 2.3 years and resulted in significant differences (Δ) of serum lipids between the treatment groups [e.g. ΔLDL-C = −5%, ΔTG = −6% by intention to treat analysis (ITT)].

Results: Two pre-defined primary end points had been chosen to assess for progression: the mean change in minimum lumen diameter ($MinLD_{1-2}$), and the visual global change score (GCS). These two parameters of progression developed differently between the treatment groups and in relation to treatment: the difference between the groups (Δ), amounted to 0.12 mm for the $\Delta MinLD_{1-2}$ ($p = 0.0000$), and to 0.61 for the ΔGCS ($p = 0.0001$), as determined in fully compliant patients by an analysis 'as treated' and, by ITT-analysis in all patients, Δ still amounted to 0.08 mm for the $\Delta minLD_{1-2}$ ($p = 0.0022$), and to 0.38 for the ΔGCS ($p = 0.02$). Upon multivariate analysis (ITT) of all patients in both treatment groups, TG and LDL-C turned out to be independently correlated to the quantitative criterion of progression, the $MinLD_{1-2}$, whereas HDL-C, VLDL-C, and APOA did not:

Multilinear Regression Analysis: $MinLD_{1-2} = -0.109 + 0.0003TG + 0.0008LDL\text{-}C$ [mg/dl]

N = 201	$r_{univariate}$	$r'_{multivariate}$	F-ratio***	$R_{multiple}$	Mean# ± SD
TG	0.228*	0.228	10.9	0.228	186 ± 105
LDL-C	0.226*	0.205	8.7	0.303	139 ± 42
VLDL-C	0.187*	−0.041	<4		31 ± 24
HDL-C	−0.129°	−0.037	<4		47 ± 10

*$P \leq 0.01$; °n.s.; ** > 4 indicates multivariate significance; r, r', R = correlations; # on treatment

Conclusion: In young men, under the conditions of the CIS, lipid intervention inhibited progression of CAD in a treatment related manner, and of the lipids studied, only TG and LDL-C determined progression independently.

P1055 Mutations in the human paraoxonase gene: frequencies, allelic linkages and association with coronary artery disease

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Objectives: We sought to investigate the frequencies and linkages of paraoxonase 1 (PON1) mutations and their association to the risk of coronary artery disease (CAD).

Background: Oxidative damage is a major cause of atherosclerosis. Since human paraoxonase is suggested to play a role in protection from LDL-oxidation, recent studies have dealt with the impact of hereditary PON1 gene polymorphisms as risk factors for CAD. The results from these studies are conflicting.

Methods: In a case-control study, 1000 Caucasian patients with angiographically confirmed CAD were recruited and matched by age and gender to 1000 controls. PON1 mutations in codons 55 and 192 were evaluated by PCR/RFLP and allocated to defined haplotypes *1 (55L/192Q), *2 (55L/192R), and *3 (55M/192Q).

Results: Frequency of PON1 genotypes without any mutation (PON1*1/*1, wild-type) in cases was 16.9% vs. 17.1% in controls. PON1*2/*2 showed a frequency of 6.6% vs. 7.3% ($p = 0.68$ compared to wild-type), and PON1*3/*3 occurred in 11.8% in cases vs. 10.3% among controls ($p = 0.40$). There was also no difference in the distribution of carriers heterozygous for *2 or *3 among cases and controls. A haplotype containing both mutations 55M and 192R was not observed. None of the investigated genotypes showed association with early manifestation, severity of disease, acute coronary syndromes, or myocardial infarction. Logistic regression analysis adjusting for age, gender, diabetes, hypertension, hypercholesterolemia, and smoking revealed no evidence of increased coronary risk associated with PON1 genotypes.

Conclusion: These results suggest that PON1 polymorphisms are not major genetic determinants of CAD.

P1056 Lipoprotein(a) and apo(a) isoforms are prognostic markers for women with coronary heart disease

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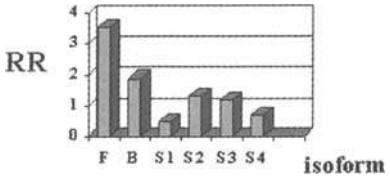
Lp(a) as a risk factor is controversial, and few studies have analyzed Lp(a) in relation to prognosis in established CHD. The Lp(a) level is genetically determined, and related to apo(a) isoforms. Low molecular weight isoforms are associated with high plasma levels. In this study lipoproteins, with focus on Lp(a) and apo(a) isoforms, was studied as prognostic markers for patients with CHD.

Subjects and methods: 964 patients (23% women) undergoing coronary angiography due to angina pectoris during 1985–1987. 814 of these had >50% stenosis of at least one vessel. Functional status, risk factors including serum-lipoproteins, Lp(a) and apo(a) isoforms was analyzed. Follow up regarding mortality and cause of death was done in 1998. Mean follow up time was 11.7 years.

Results: In univariate analysis death was related to age and cardiac function. Low HDL and apoA levels were related to increased risk. Surprisingly high cholesterol, LDL and apoB were associated with decreased risk for death. However, when only cardiovascular death was studied no association to cholesterol, LDL or apoB was seen. High Lp(a) was associated with increased risk only for women ($p < 0.02$).



Risk ratio for women in relation to apo(a) isoforms.

For women also the low molecular weight isoforms (F and B) were associated with increased risk for total as well as cardiovascular death. For men isoform F, but not B, was a risk marker.

Conclusion: For women with CHD high Lp(a) levels as well as low molecular weight apo(a) isoforms are associated with increased mortality. For men the results are inconsistent and not conclusive. The results are in accordance with earlier reported results from this study, where only female patients had higher Lp(a) levels compared with a random population sample.

P1057 Regression of atherosclerosis in patients with arterial occlusive disease in war time and post-war time in Sarajevo: a 6-year study

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It is well known that amelioration of multiple risk factors (MRF) can lead to regression of atheromatous plaques. During the war period, in the besieged city of Sarajevo, we have noticed a clear clinical improvement in the patients with previosly established diagnosis of arterial occlusive disease (AOD). They have prolonged their free walking distance (FWD) despite they were without any medication or medical treatment at all. The aim of this study was to asses potential regression of atherosclerosis by haemodynamic and Color Doppler measurements.

Methods: We followed a group of patients with arterial occlusive diseases (AOD) in Fontaine St. IIA (n = 53) and IIB (n = 76), which showed a clear clinical improvement of their vascular disease. We measured FWD and brachio-pedal index (BPI), as well as Color Doppler examination – pulsatility index (PI), resistive index (RI), average diameter of arterial lumen (ADAL), and regression of plaque (RP). The group was in high risk, with at least 4 out of 7 MRF. The study had three parts, Part I (1993–1994), Part II (1994–1996) and Part III 1996–1998).

Results: In Part I; we had improvement in FWD of 126.5% ($p < 0.001$), of BPI 36.9% and PI 26.4% ($p < 0.01$), and RI 9.2% ($p < 0.05$), of ADAL 11.2% ($p < 0.05$). Direct measurement of plaque regression (PR > 0.9 mm) was of no significance. In Part II; we had improvement of FWD of 58% ($p < 0.01$), of BPI 17.3% and PI 14.9% ($p < 0.05$), of RI 5.6% (NS), of ADAL 8.1% ($p < 0.05$), and RP non-significant. In Part III; improvement of FWD was just 8.5% (NS), of BPI 10.7% and PI 4.5% ($p = 0.02$), of RI −4.9%, and ADAL 1.9% (NS), and regression of plaque non-significant.

In conclusion: The results suggest that we have had initial clinical and flow improvement in Part I and II, which might be in correlation with complete change of life-style in war time (lack of food, body weight reduction, reduction of tobacco smoking). In Part III (post war period), we have improvement of life conditions, and FWD and haemodynamic parameters are going back to 1992.

P1058 Relation of serum C3 to fasting insulin and traditional risk factors in 1090 middle aged men

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Background: Serum C3, a powerful indicator of the risk of myocardial infarction (MI), is produced by activated macrophages, hepatocytes and adipocytes. C3 (the third complement component) is the precursor of C3a-des-Arg, the most potent stimulator of triglyceride synthesis and glucose transmembrane transport in the adipose tissue. C3 levels are known to correlate with body mass index (BMI), serum lipids, blood glucose and blood pressure. Aim of this study was to ascertain whether an association between C3 and fasting insulin, a recognized index of insulin resistance, may explain the above correlations.

Methods: The fasting serum levels of C3, insulin (INS), glucose (G), triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), as well as systolic (SBP) and diastolic (DBP) blood pressure, BMI, history of diabetes or hypertension, smoking habit, alcohol consumption, physical activity, previous MI and family history of MI (FH-MI) were assessed in 1090 unselected men, aged 55–64 years.

Results: In a logistic regression model including all the study variables, only C3 ($P = 0.011$), FH-MI ($P = 0.018$), ex-smoker status ($P = 0.020$), age ($P = 0.025$), G ($P = 0.028$) and HDL-C ($P = 0.051$, inverse relation) were significantly associated with previous MI ($N = 51$). In univariate analysis serum C3 (1.11 ± 0.18 (1 SD) g/l) was associated with all the variables assessed, except FH-MI and cigarette smoking. The strongest simple correlations were with INS (rho = 0.46), TG (rho = 0.35) and BMI (rho = 0.35). The relation of C3 to physical activity, alcohol consumption and HDL-C was of inverse type. In multiple linear regression (MLR), C3 was independently assbciated with INS ($r = 0.27$, $P < 0.0001$), TC ($r = 0.18$, $P < 0.0001$), BMI ($r = 0.13$, $P < 0.0001$), G ($r = 0.12$, $P = 0.0001$), SBP ($r = 0.10$, $P = 0.0007$), TG ($r = 0.09$, $P = 0.002$) and HDL-C ($r = -0.06$, $P = 0.048$). The overall R^2 was 0.31. In MLR, without C3 among the independent variables, INS correlated with BMI, TG, HDL-C (inversely), DBP and G. When C3 was included in the model, INS correlated with BMI, C3, TG and HDL-C only.

Conclusions: Serum C3 strongly correlates with INS, but this does not explain entirely any of the independent correlations between C3 and traditional risk factors. Rather, the relation of INS to some variables seems to be mediated by C3.

P1059 Elevated plasma lipid peroxides in acute myocardial infarction and stable angina

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The concept that oxidised low density lipoprotein (ox-LDL), not native LDL, plays a major role in atherogenesis is gaining support. The platelet-stimulating effect of ox-LDL may contribute to the pathomechanism of platelet hyper-reactivity observed in coronary artery disease (CAD). Lipid hydroperoxides in plasma are carried almost exclusively in LDL and reflect ox-LDL. Previously, elevated plasma ox-LDL was measured in patients with CAD after bypass surgery. As coronary bypass may contribute to generation of ox-LDL in the circulation, we measured plasma lipid hydroperoxides (ox-LDL) in acute myocardial infarction (AMI) and stable angina.

Methods and Results 24 patients with AMI and 29 patients with stable angina were compared with 21 age-matched controls. Lipids and lipoproteins were selectively removed from plasma by absorption to Liposorb® gel. Lipid hydroperoxide concentration in the washed gel was measured by a sensitive and specific triiodide spectrophotometric technique. Lipid hydroperoxide levels in patients with AMI and stable angina were significantly elevated (2.93 ± 0.21 μmol/L, p = 0.0218 and 3.18 ± 0.27 μmol/L, p = 0.066) compared to controls (2.28 ± 0.16 μmol/L). Previously, a plasma concentration > 3 μmol/L was considered pathological. Using this criteria, we detected pathological lipid hydroperoxide concentrations in 9.5% of controls, 37.5% of AMI and 55.2% of stable angina patients.

Conclusion Plasma levels of lipid hydroperoxides (ox-LDL) are significantly elevated in CAD presenting with AMI and angina. This increase is not attributable to a previous cardiopulmonary bypass procedure but to the presence of atherosclerotic disease. Raised levels of plasma ox-LDL may contribute to both atherogenesis and thrombogenesis in coronary artery disease.

GENETICS OF ATHEROSCLEROSIS – EXPERIMENTAL AND CLINICAL

P1060 Oligonucleotides anti-p50 and anti-p65 inhibit the nuclear factor-κB-mediated expression of ICAM-1 in human coronary vascular cells

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Activated coronary vascular cells express adhesion molecules after angioplasty. We investigated whether an inhibition of the two subunits of nuclear factor-κB (NF-κB), p50 and p65, can reduce the expression of the intercelluar adhesion molecule-1 (ICAM-1) in human coronary vascular cells.

Methods: Smooth muscle cells from human coronary plaque material (HCPSMC, plaque material of 52 patients) and human coronary endothelial cells (HCAEC) were successfully cultured. The expression of adhesion molecules was stimulated by tumor necrosis factor-α (TNF-α, 20 ng/mL, 6 hrs). 12 hrs prior to the TNF-α stimulus anti-p65 and anti-p50 oligonucleotides (1, 2, 4, 10, 20, and 30 μM) were added to the cultures for a period of 18 hrs. The surface expression of ICAM-1 was analysed with monoclonal antibodies using an immunofluorescence microscope.

Results: In HCAEC the surface expression of ICAM-1 was inhibited in a dose dependent manner after adding of anti-p65 and anti-p50 in the concentrations of 2, 4, 10, 20, and 30 μM, reaching a maximal inhibition of more than 55% after 30 μM. In HCPSMC the first inhibition of ICAM-1 expression was seen after incubation with anti-p65 and anti-p50 in a concentration of 10 μM, a maximal inhibition of 31.8% was documented after incubation with 30 μM.

In conclusion: The presented data contribute important information for the development of therapeutic antisense strategies aiming at an inhibition of the surface expression of adhesion molecules in early restenosis.

P1061 Reduction of in-stent restenosis in porcine coronary arteries after local delivery of adenovirus encoding NOS3

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In-stent restenosis caused by neointima (NI) formation remains a challenging problem for interventionnal cardiologists. To assess the ability of adenoviral gene transfer to inhibit restenosis, porcine coronary arteries were balloon-injured with three 30 sec inflations at 8 atm. Recombinant adenovirus (1.5x10e9 PFU) encoding endothelial nitric oxide synthase cDNA (AdNOS3, n = 22) or no transgene product (AdRR5, n = 22) was blindly injected at the site of PTCA using a local drug delivery catheter. After gene transfer, a 7 mm Palmaz Schatz stent was locally deployed in the center of each transduced area, using two balloon inflations at 14 atm for 30 seconds. Coronary angiograms were obtained after stent implantation (MLDd0) and at 28 days (MLDd28) to evaluate in-stent stenosis. Coronary arteries were harvested, pressure fixed and embedded in plastic. Five-μm sections were prepared every 200 μm and stained with hematoxylin and eosin for subsequent analysis. NI area (NA), vessel area (VA), and lumen area (LA) were measured at the site of maximal NI formation. MLDd0, MLDd28 and VA were similar in AdNOS3 and AdRR5. NA area was significantly reduced, and LA was significantly increased in stented arteries transduced with AdNOS3 by comparison to controls.

Table

	AdNOS	AdRR5	P value
MLDd0 (mm)	2.97 ± 0.06	2.87 ± 0.07	NS
MLDd28 (mm)	2.33 ± 0.12	2.03 ± 0.19	NS
VA (mm^2)	10.0 ± 0.34	9.85 ± 0.57	NS
LA (mm^2)	5.04 ± 0.53	3.60 ± 0.49	0.020
NIA (mm^2)	2.92 ± 0.47	4.56 ± 0.69	0.046

These results suggest a beneficial action of NOS3 gene transfer in stented porcine coronary arteries and may represent an attractive alternative for the treatment of in-stent restenosis.

P1062 Adenoviral gene therapy with a novel dCK/ara-C suicide system for vascular smooth muscle cell proliferation after arterial injury

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Percutaneous transluminal coronary angioplasty (PTCA) has become a popular treatment for ischemic heart disease. However, restenosis of the treated lesion occurs in one third of the patients. Because of that, prevention of restenosis is one of the urgent subjects for treatment of ischemic heart disease.

Methods and Results: In this study, we demonstrated the potent inhibition of vascular smooth muscle cell proliferation after arterial injury by adenoviral gene transfer with a novel suicide gene system, called deoxycytidine kinase (dCK) /arabinofuranosyl cytosine (ara-C) system. Our system has a significant potential advantage for treatment of restenosis, because vascular smooth muscle cell were extremely sensitive to the metabolite of ara-C. Feasibility of this system for vascular restenosis was greater than the previously reported systems such as HSV thymidine kinase or bacterial cytosine deaminase gene. We first demonstrated adenoviral vector efficiently transduced the dCK gene into the vascular smooth muscle cell. The dCK converts a prodrug, ara-C, to the toxic form. Thus, expressed dCK transgene conferred the sensitivity on the vascular smooth muscle cell to the ara-C in vitro. Next, we performed an in vivo gene therapy experiment. A 2F Fogarty balloon catheter was inserted from the right femoral artery of the rats and the intima of the left carotid artery was injured. With this arterial injury model, we could easily reproduce the vascular stenosis by smooth muscle cell proliferation and the Intima/Media ratio (%) reached up to 136.4 ± 29.8 after two weeks. After the carotid arterial injury, we transferred the dCK gene by adenoviral vector and then the rats were treated with ara-C or saline. Thickness of the carotid arterial wall was assessed and we observed the dCK/ara-C treated group exhibited a significant lower Intima/Media ratio (= 18.1 ± 36.2) than other control groups (= 140.6 ± 59.1) ($p < 0.01$).

Conclusion: These data suggest that adenoviral mediated dCK gene transduction and ara-C treatment prevent the smooth muscle cell proliferation after arterial injury and may present a promising approach for restenosis after PTCA.

P1063 Isolation/characterization of canine heart nitric oxide synthase III complementary deoxyribonucleic acid and promoter region

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The endothelial nitric oxide synthase (NOS-III) is the main source for endogenous production of nitric oxide (NO) in the vasculature (e.g. endothelial cells, platelets). It is critically involved in the regulation of vascular tone and platelet function and altered expression of NOS-III is implicated in a variety of cardiovascular diseases with concomitant endothelial or platelet dysfunction (e.g. atherosclerosis, dyslipidemia, hypertension).

Aim of the study: to isolate and characterize canine NOS-III cDNA and regulatory (promoter) sequences with reference to known sequences in other species.

Methods: The complete coding sequence of NOS-III cDNA in conjunction with untranslated regions (5'- or 3'-UTR) and promoter region was identified by homologous (RT-)PCR cloning strategy. Primer sequences were derived from bovine or human NOS-III cDNA or gene (5'- or 3'-UTR) sequences to obtain 7 successful and overlapping (RT-)PCR amplifications on canine heart total RNA or genomic DNA (for promoter region) that were cloned and verified by sequencing. Sequence analysis was performed using the ENTREZ and BLAST programs.

Results: A NOS-III sequence contig of 5134 nucleotides length was established using homologous PCR cloning of canine heart RNA/DNA. An open reading frame (ORF) comprising 3609 nucleotides (1203 amino acids) with 253 bp 3'-UTR (distal to TGA codon) and 1272 bp 5'-UTR (proximal to ATG codon; promoter region) was identified. ORF sequence pair comparisons to the human and bovine NOS-III sequences at the nucleotide or amino acid level yielded 90% and 88% or up to 84% and 86% homologies, respectively. Sequence analysis of the canine NOS-III promoter regions revealed a stretch of 310 nucleotides with 83% homology to the human sequence that contains a cluster of binding sites for several regulatory elements (AP-1, cAMP, GATA-box, acute phase reactant...).

Summary and Conclusions: Isolation and characterization of the canine heart NOS-III cDNA with adjacent UTRs was readily achieved by homology PCR cloning. Canine NOS-III cDNA and promoter sequences are highly homologous to known human and bovine sequences. The homology PCR cloning strategy is presented as an alternative to common library cloning approaches. The obtained canine NOS-III sequences might serve to further analyze structure, regulated function (promoter region consensus sites), and expression of NOS-III in different pathophysiological conditions and in other species, too.

P1064 Angiotensin II receptor subtype gene expression after stent implantation in a pig model

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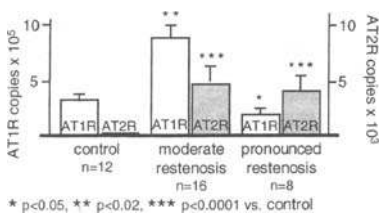
Background: Angiotensin II has been attributed as a potent growth factor on promoting proliferation of vascular smooth muscle cells. Reports on the association of ACE and AT1 receptor gene polymorphisms to restenosis after PTCA or stenting implicate an important role for this process. This study was designed to investigate the nature and magnitude of changes in the levels of the AT1R and AT2R gene expression in the proliferative response to coronary stent implantation.

Methods: Twelve pigs were implanted with slotted tube stents in the LAD and LCx. After 10 days the stented vessels were removed and snap frozen. Samples were cut in half to compare the direction and magnitude of changes in ATR subtype expression levels with histomorphometric analysis. Non-competitive RT-PCR was utilized to measure expression levels utilizing synthetic internal standard mRNAs. β-actin expression was used to correct for variation in sample size.

Results: Samples were divided in 2 groups according to the mean lumen diameter (MLD) stenosis in the histomorphometric analysis: moderate with an MLD of 19.1 ± 3.1% (n = 16) and pronounced with an MLD of 33.6 ± 5.2% (n = 8).



Conclusion: The shift in ATR gene expression levels indicates the importance of the RAS for stent restenosis. The decrease of AT1R in samples with pronounced stenosis could be due to a desensitation at the receptor level. Further studies are warranted with local ACE inhibitors/ATR antagonists applied with local delivery systems, such as biodegradable stent coatings, for reducing in-stent restenosis.

P1065 Antisense oligonucleotide *c-myb*: effects on apoptosis of porcine vascular smooth muscle cells and aortic endothelial cells

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Introduction: Local delivery of antisense oligonucleotide (AS-ODN) *c-myb* at the time of angioplasty decreases neointima formation in a number of animal models via suppression of vascular smooth muscle cell (VSMC) proliferation and migration. Recently, c-*myb* has been reported to be involved in the control of apoptosis in some cell types. We tested the effect of AS-ODN *c-myb* on apoptosis of porcine VSMC and aortic endothelial cells (PAEC) *in vitro*.

Methods: Cultures were washed and incubated with media containing 0.5% porcine serum (PS) with; vehicle sham, 5 μM AS-ODN c-*myb* or 5 μM sense (SN)-ODN c-*myb* for 24 hrs. Cultures were analysed with a commercial cell death ELISA; or filmed by time lapse video microscopy (TLVM). Apoptosis was confirmed with electrophoresis of fragmented DNA.

Results: By ELISA, apoptosis was increased 2.2 ± 0.4 fold in AS-ODN c-*myb* treated PVSMC ($p < 0.005$) compared to sham treated cultures, whilst SN-ODN *c-myb* decreased apoptosis 0.7 ± 0.1 fold (p = n.s.). By TLVM, apoptosis increased from; 1.8 ± 0.4% sham, to 6.8 ± 0.8% AS-ODN *c-myb* ($p < 0.001$) and 2.2 ± 0.4% SN-ODN c-*myb* (p = n.s.).

In PAEC, via ELISA AS-ODN c-*myb* treatment decreased apoptosis 0.8 ± 0.1 fold (p = n.s.). SN-ODN c-*myb* treatment decreased apoptosis 0.7 ± 0.2 fold (p = n.s.). Using TLVM, AS-ODN c-*myb* treatment had no effect on PAEC apoptosis; 1.4 ± 0.2% sham, 1.4 ± 0.5% AS-ODN *c-myb* (p = n.s).

Conclusions: AS-ODN *c-myb* treatment of VSMC increased apoptosis 2–3 fold whereas SN-ODN c-*myb* showed no effect. Neither AS-, or SN-ODN treatment affected apoptosis of PAEC. Local delivery of AS-ODN *c-myb* at angioplasty may modify the VSMC apoptotic profile.

P1066 The *fms*-like tyrosine kinase-1 promoter drives high-level, endothelium-restricted transgene expression in isolated cell cultures and in human saphenous vein in situ, using adenoviral-mediated gene transfer

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Background: The utility of recombinant adenoviruses (Rad) for vascular gene therapy is limited by the promiscuous tropism of the virus, and the use of non-specific viral promoters, resulting in high level transgene expression in all tissues. As an initial step in addressing this problem, we have evaluated two endothelial cell specific promoters, [*fms*-like tyrosine kinase-1 (*FLT*-1) and von Willebrand factor (*vWF*)], for their ability to drive endothelial cell-restricted transcription from recombinant adenoviruses, RAdFLT-1 and RAdvWF respectively. We have compared this to expression from the cytomegalovirus (CMV) promoter in RAdCMV in both isolated cell cultures and in the human saphenous vein model of organ culture.

Methods: Using a chemiluminescent assay, production of β-galactosidase was quantified in primary human endothelial cells (EC) from umbilical vein (HUVEC) and saphenous vein (HSVEC), and a number of non-endothelial cell types, infected with recombinant adenoviruses. Following this, either RAdCMV or RAdFLT-1 at 1.2×10^{10} plaque forming units (pfu)/ml were exposed to the lumenal surface of segments of human saphenous vein (either endothelium denuded or endothelium intact) for 1 hour. Vein segments were cultured for 7 days and infection efficiency determined by *en face* staining for β-galactosidase. Cell types producing β-galactosidase were determined using immunofluorescent cytochemistry and cell-specific markers.

Results: Levels of β-galactosidase from RAdFLT-1 and RAdvWF were 80% and 1% of RAdCMV in HUVEC and 40% and 0.05% of RAdCMV in HSVEC, respectively. In addition, β-galactosidase production from RAdFLT-1 (as a percentage of RAdCMV) was 0.5% in human primary vascular smooth muscle cells (VSMC), 0.01% in primary fibroblasts, 0.5% in HepG2 and 0.01% in HeLa. *En face* staining of infected veins revealed that RAdCMV produced transgene expression in both endothlium intact and endothelium denuded veins. However, RAdFLT-1 produced high level transgene expression in endothelium intact veins only. Immunofluorescence confirmed that transgene expression from RAdFLT-1 was restricted to endothelial cells.

Conclusion: High level, endothelium-restricted expression of therapeutic genes from the *FLT-1* promoter may be possible for use in vascular gene therapy.

P1067 Transgenic mouse model of positive vessel remodelling and smooth muscle cell proliferation

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We developed a transgenic mouse with augmented SMC proliferation in vivo by targeted expression of a simian virus 40 T antigen (TAg) under control of a 2.3 kb smooth muscle-myosin heavy chain (SM-MHC) promoter derived from rabbit. This promoter effectively restricted TAg expression to SMC in vasculature, gastrointestinal and genitourinary tract as well as to SMC of spleen capsula and stroma. TAg was not detected in skeletal and cardiac muscle. The mice displayed spontaneous neointima formation in the aorta and major branch vessels, which was accompanied by an age-dependent enlargement of vessel circumferences up to 3.1-fold in comparison with age matched non-transgenic sibling mice. Aortic neointima formation started at the age of five weeks and increased to form a neointima: media ratio of 0.62:1 at the age of eight weeks and 1.13:1 at 13 weeks. Despite this marked neointimal formation, vessels of transgenic animals conserved their luminal area by outward remodeling, with a 1.9-fold diameter increase of the aortic lumen compared with controls. This concomitant thickening and outward remodeling of the transgenic vessel wall in the context of the hyperplasia results in the maintenance of vessel wall stress as a constant parameter. These data suggest that this model of augmented SMC proliferation induces vessel remodeling via signalling mechanisms sensitive to vasuclar wall stress, thus avoiding luminal occlusion. Further manipulation of these mice will shed light on the molecular coupling between proliferation and therapeutic remodeling.

P1068 Cyclic strain stress-induced MKP-1 expression in smooth muscle cells is regulated by Ras/Rac-MAPK pathways

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Recently, we demonstrated that mechanical stress results in rapid phosphorylation or activation of platelet-derived growth factor (PDGF) receptors in vascular smooth muscle cells (VSMCs) followed by activation of mitogen-activated protein kinases (MAPKs) and AP-1 transcription factors (Hu et al., FASEB J. 1998; 12: 1135–1142). Here we provide evidence that VSMC responses to mechanical stress also include induction of MAPK phosphatase-1 (MKP-1), which may serve as a negative regulator of MAPK signaling pathways. When rat VSMCs cultivated on a flexible membrane were subjected to cyclic strain stress (60 cycles/min, 5–30% elongation), induction of MKP-1 proteins and mRNA was observed in time- and strength-dependent manners. Concomitantly, mechanical forces evoked rapid and transient activation of all three members of MAPKs, i.e. extracellular signal-regulated protein kinases (ERKs), c-Jun NH2-terminal kinases (JNKs) or stress-activated protein kinases (SAPKs) and p38 MAPKs. Suramin, a growth factor receptor antagonist, completely abolished ERK activation, significantly blocked MKP-1 expression, but not JNK/SAPK and p38 MAPK activation in response to mechanical stress. Interestingly, VSMC lines stably expressing dominant negative ras (N17) or rac (N17) exhibited a marked decrease in MKP-1 expression; the inhibition of ERK kinases (MEK1/2) by PD 98059 or p38 MAPKs by SB 203580 in VSMCs resulted in a downregulation of MKP-1 induction. Furthermore, overexpressing MKP-1 in VSMCs led to the dephosphorylation and inactivation of ERKs, JNKs/SAPKs and p38 MAPKs and inhibition of DNA synthesis. Taken together, our findings demonstrate that mechanical stress induces MKP-1 expression regulated by two signal pathways, including growth factor receptor-ras-ERK and rac-JNK/SAPK or -p38 MAPK, and that MKP-1 inhibits VSMC proliferation via MAPK inactivation. These results suggest that MKP-1 plays a crucial role in mechanical stress-stimulated signaling leading to VSMC growth and differentiation.

P1069 Overexpression of the catalytic domain of cGMP-dependent protein kinase Iβ reduces proliferation and migration of vascular smooth muscle cells

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Nitric oxide (NO) directly modulates smooth muscle cells (SMC) proliferation and migration which contribute to the neointimal response to arterial injury. These NO effects on SMC functions appear to be dependent on the second messenger cGMP and its cGMP-dependent Protein Kinase (G-Kinase). We have reported reduced soluble guanylate cyclase expression after vascular injury and we hypothesize that this contributes to neointima formation by mitigating the activation of G-Kinase. To confer constitutive cGMP-independent G-Kinase activity to vascular SMCs, an adenoviral vector carrying the Flag epitope-tagged catalytic domain of GK Iβ was constructed (AdGKcd). Expression in explanted rat aortic SMCs was confirmed using specific anti-Flag antibodies and enzyme activity in extracts from infected cells was demonstrated in a phosphorylation assay using a synthetic G-Kinase substrate. Proliferation, assessed by 5'-BrdU incorporation, was reduced in AdGKcd-infected cells but not in control AdRR5-infected cells (68 ± 10 vs 101 ± 11% of incorporation in uninfected cells, n = 3, <0.05). Transwell migration (8 μm pores) was similarly reduced in AdGKcd-infected cells but not in AdRR5 cells (67 ± 6 vs 102 ± 11% of migration of uninfected cells, n = 5, $P < 0.05$). 8-Br-cGMP (1 mM) was used as a positive control, and reduced migration by 19% ($P < 0.05$, n = 3).

Thus, overexpression of a mutant, constitutively active G-Kinase significantly reduces proliferation and migration of vascular SMCs, and may hold promise as a gene-based therapy for vasculoproliferative disease.

P1070 The cytoskeletal-associated protein moesin is re-expressed in the neointima and media of carotid-arteries after balloon angioplasty: a new approach to comprehension of the molecular biology during the process of restenosis

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Background. Migrating cells like myofibroblasts in restenosis change their cell shape and form cellular protrusions like filopodia. A prerequisite for filopodia formation is the rearrangement of actin cytoskeleton. An essential role of moesin (78 kD) is described for Rho-and Rac-dependant assembly of actin filaments. In vivo moesin is not observed in mature smooth muscle cells. The hypothesis is that during the process of restenosis moesin is reexpressed in transformed, migrating myofibroblasts in order to form cellular protrusions.

Methods. 12 hours after balloon angioplasty pig carotid arteries were embedded in paraffin after methanol/ethanol-fixation. Carotid cryosections from the rat-restenosis were obtained after 1 day, 7, 14 and 28 days. Sections were stained with specific antibodies against moesin and smooth muscle cell actin. Anti-moesin antibodies were achieved by immunisation of chickens with isolated moesin.

Results. 12 hours after angioplasty moesin expression was observed in myofibroblasts as well as in dividing cells within the media of the pig carotid artery. To determine the start of moesin expression in the rat-restenosis model immunfluorescence with antibodies against moesin and smooth muscle actin at 1 day, 7 days and 28 days after angioplasty. Even in the early period (1 day) angioplasty tissue staining was positive for moesin and smooth muscle cell actin whereas in the non-dilated control tissue no specific moesin staining could be observed.

Conclusion. These findings demonstrate for the first time a de novo expression of moesin within the arterial media after arterial injury and indicate that moesin may be important for migration and proliferation of myofibroblasts. This indicates a possible role of moesin in the pathogenesis of restenosis after angioplasty and stent implantation.

P1071 Gene transfer of the antisense RNA to 18 kDa isoform of basic fibroblast growth factor inhibits coronary smooth muscle cell proliferation

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Restenosis with coronary smooth muscle cell (cSMC) proliferation remains a major problem in PTCA. Recent data suggest that the secreted/non-nuclear targeted 18 kD isoform of basic fibroblast growth factor (bFGF) expressed by cSMC plays a prominent role in the autocrine/paracrine proliferative response to vascular injury. To investigate the possibility of (non-viral) plasmid/liposome (PL)-mediated gene transfer in the treatment of restenosis, we transfected bovine cSMC with bFGF cDNA coding for the 18 kD isoform in both the sense and antisense orientation. The plasmid pCI-neo includes the CMV promotor region and a dominant selectable marker, the neomycin phosphotransferase II (NPTII) gene. By using the pCI-neo plasmid, NPTII expression was observed in ca. 20% of cSMC 36 hr posttreatment (immunofluorescence staining). After selection with the antibiotic G418 stably transfected cSMC cultures were characterized with respects to endogenous bFGF expression, proliferation and cell cycle progression. Expression of antisense bFGF RNA (pCI-neo-AS-bFGF) markedly reduced cellular 18 kD bFGF content, whereas overexpression of the sense bFGF coding sequence (pCI-neo-S-bFGF) resulted in high 18 kD bFGF levels (Western Blot). pCI-neo-AS-bFGF cSMC showed a significant decrease in cell number (up to 30% inhibition) compared to pCI-neo transfected cells (control). Growth curves of pCI-neo-S-bFGF cSMC demonstrated an enhanced proliferation (ca. 53%) compared to control. Propidium iodid staining and FACS analysis of transfected cSMC, demonstrated that in contrast to pCL-neo-S-bFGF cSMC the most of the pCI-neo-AS-bFGF cSMC and control cells were in the G_0/G_1 phase, and there was an increase in the proportion of the cells in the S phase from 15% (pCI-neo-AS-bFGF cSMC) to 39% (pCL-neo-S-bFGF cSMC). Our data show, that i) primary cSMC could be transiently and stably transfected using a PL-mediated gene transfer and that ii) the 18 kD isoform of bFGF play an important and potent role in cSMC proliferation.

P1072 The atrial natriuretic peptide gene ScaI polymorphism and history of non-fatal myocardial infarction among males in the north region of Poland

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Atrial natriuretic peptide is one of important hormones responsible for maintenance cardiovascular system homeostasis.

The purpose of this study was to determine potential association between ANP gene polymorphism and incidence of coronary heart disease (CHD), myocardial infarction, arterial hypertension and familial history of CHD among men in the North region of Poland.

We performed a case-control study including 244 male patients with CHD confirmed by coronary angiography (mean age 55 ± 12) and 227 controls (negative history and normal ECG, mean age 46 ± 5). The genotype frequencies were not signifcantly more frequent in both study groups (CHD subjects: A2A2 63%, A1A2 34%, A1A1 3%, controls: A2A2 72%, A1A2 26%, A1A1 2%; p = 0.06). However we have found statically significant difference in genotype distribution between CHD subjects with and without history of survived myocardial infarction. A2A2 genotype was more frequent in males with positive history of myocardial infarction (69% vs. 49%; p = 0.003). There was no association between ANP gene polymorphism and arterial hypertension, familial history of CHD and coronary artery atherosclerosis. Segregation of the ScaI ANP genotypes was independent of common risk factors: body mass index, plasma lipoproteins, triglicerydes, diabetes, arterial hypertension and smoking habits.

In conclusion the A2A2 Sca1ANP genotype seems to be a risk factor for myocardial infarction among males with angiographically confirmed coronary artherosclerosis.

P1073 Functional relevance of atherosclerosis-associated Ser128Arg and Leu554Phe E-selectin mutations

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The cellular adhesion molecule E-selectin is expressed on activated endothelial cells and is involved in the process of adherence of blood cells to the vessel endothelium in inflammatory events like atherosclerosis. In a recent study we found a Ser128Arg and a Leu554Phe mutation in the E-selectin gene, as well as increased frequencies of both mutations in young patients with severe coronary atherosclerosis. In this study we investigated the influence of these mutations on the cell adhesion and release of soluble E-selectin.

Methods: Mutants were created by site directed mutagenesis and COS cells transfected with E-selectin wild-type or mutants. Using transfected COS cells and interleukin-1 beta stimulated HUVECs we performed antibody binding studies and cell adhesion assays. Soluble E-selectin in supernatants of wild-type and Leu554Phe mutant transfected COS cells was estimated by ELISA.

Results: Significant differences were found in the strength of HL-60 cell adhesion for the Ser128Arg mutant: Adhesion strength to the mutant was reduced compared to wild-type on transfected COS cells ($P < 0.01$) as well as on stimulated HUVECs ($P < 0.01$). Significantly diminished release of soluble E-selectin was detected for the Leu554Phe membrane domain mutant compared to the wild-type.

In conclusion, the Ser128Arg and Leu554Phe mutations influence the E-selectin function in vitro. The results indicate a contribution of both analysed mutations for dysregulation in inflammation and thereby in the complex pathogenesis of atherosclerosis.

P1074 No association between M235T polymorphism of the angiotensinogen gene and risk of coronary heart disease

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Background: The point mutation M235T of the human angiontensinogen gene is known to be associated with an increase of the plasma angiotensinogen level. Several studies found a correlation between the T-allele and arterial hypertension and others have reported an association with CAD.

Methods: LURIC is a prospective case control study on environmental and genetic risk factors for CAD in patients undergoing a coronarangiography. A standardized patient history was obtained and blood samples were drawn in the morning. Bloodpressure was measured by oscillometric device (average between three measurements). Angiotensinogen M235T polymorphism was determined in isolated DNA. Plasma angiotensinogen was measured by radioimmunoassay.

Results:

	Angiotensinogene genotype		
	MM	MT	TT
Number	328	454	191
pl. Angiotensinogen (nmol/L)*	1224 ± 636	1219 ± 670	1310 ± 697
Age (years)	61 ± 10	61 ± 11	62 ± 10
Blood pressure syst. (mmHg)	142 ± 23	141 ± 23	142 ± 24
Blood pressure diast. (mmHg)	81 ± 11	81 ± 11	80 ± 12
Hypertension (%)	59	60	58
Pos. family history (%)°	36	37	32
Myocard. Infarction (%)	45	44	43
Control	19	20	21
Stenosis 11–49%	8	8	7
Stenosis ≥ 50%	72	72	72

*p = 0.25, °p = 0.37 pl. = plasma

Conclusion: In this patient group there was no correlation between the M235T polymorphism of the angiotensinogen gene and the risk for cardiovascular disease, neither manifest CAD nor myocardial infarction, and for other risc factors like hypertension and positive family history.

P1075 Association of G-33A mutation in the promoter region of thrombomodulin gene with coronary artery disease

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Background: Thrombomodulin (TM) is an important endothelial anticoagulant protein. The aim of the study was to investigate the frequency of G-33A mutation in the promoter region of TM gene in patients (pts) with coronary artery disease (CAD) and to determine whether the mutation contributes a risk for CAD or myocardial infarction (MI).

Methods: We analyzed 320 pts (mean age 63 years) with CAD proven by angiography and 186 controls (mean age 54 years) without clinical or angiographic evidence of CAD. Screening for TM G-33A promoter mutation was conducted using polymerase chain reaction, single-strand conformation polymorphism, and direct DNA sequencing.

Results: The frequency of the G-33A mutation (GA+AA) was significantly higher in the CAD group (23.8% vs 15.6%, odds ratio [OR] = 1.69, p = 0.039). Multiple logistic regression analysis showed that the mutation was an independent risk factor (OR = 1.96, p = 0.019) for CAD, as was age (OR = 1.06, p < 0.001), male (OR = 2.38, p = 0.003), hypertension (OR = 3.15, p < 0.001) and diabetes mellitus (OR = 2.19, p = 0.005). There was no significant association between the G-33A mutation and the number of diseased vessels in pts with CAD (24.5% of 86 pts with 1-vessel disease, 22.9% of 92 pts with 2-vessel disease and 23.9% of 142 pts with 3-vessel disease, p = NS). There was also no significant difference of the mutation frequency in CAD pts with (n = 154) or without (n = 166) a history of MI (19.4% vs 27.7%, p = NS). However, in all MI pts, younger subjects (age ≤ 55 years, n = 43) tended to have higher incidence (30.2% vs 15.3%, p = 0.061) of TM G-33A mutation than those with age > 55 years (n = 111).

Conclusions: Our observations suggest that there is a significant association of the G-33A mutation in TM gene with CAD in a Chinese population and this mutation may be related to the occurrence of MI in younger pts with CAD.

P1076 Plasma soluble thrombomodulin level is genetically influenced by G-33A promoter mutation of thrombomodulin gene in patients with coronary artery disease

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Thrombomodulin (TM) is an important endothelial anticoagulant protein. Increased plasma soluble TM level was found in patients (pts) with coronary artery disease (CAD), and was a clinical marker for the progression of CAD. The aim of the study was to investigate the influence of G-33A promoter mutation of TM gene on the plasma soluble TM level.

Methods and Results: The plasma soluble TM levels were determined with ELISA in 280 consecutive pts undergoing coronary angiography. Screening for TM G-33A promoter mutation (GA + AA) in these pts was conducted using polymerase chain reaction, single-strand conformation polymorphism, and direct DNA sequencing. In all, the soluble TM level was significantly higher in pts with CAD (n = 206) than that with normal coronary artery (45.6 ± 25.3 vs 39.0 ± 18.7 ng/mL, p < 0.05). In pts without CAD, there was no significant difference (38.8 ± 17.1 vs 40.0 ± 25.1 ng/mL, p = NS) in the soluble TM level between pts with (n = 14; age 59.0 ± 11.9 years; male 64.3%) or without (n = 60; age 58.4 ± 13.8 years; male 63.3%) G-33A mutation. However, in CAD group, the soluble TM level was higher (47.0 ± 27.4 vs 39.0 ± 17.2 ng/mL, p < 0.05) in pts with normal genotype (n = 53; age 63.8 ± 10.7 years; male 73.2%) than that with G-33A mutation (n = 53; age 63.2 ± 11.3 years; male 66.0%). Furthermore, the soluble TM level increased with the extent of CAD (36.1 ± 14.9 vs 46.6 ± 18.4 vs 54.8 ± 35.9 ng/mL in 1-, 2-, and 3-vessel disease, p < 0.001) in pts with normal genotype. But in pts with G-33A mutation, there was no difference of soluble TM in 1-, 2- or 3-vessel disease (38.6 ± 17.2 vs 37.0 ± 15.3 vs 42.0 ± 18.4 ng/mL, p = NS).

Conclusions: The results suggest that G-33A promoter mutation in TM gene contributes to plasma levels of soluble TM in pts with CAD. For those CAD pts with normal TM genotype, the plasma soluble TM level is indeed a clinical marker for the extent of CAD.

P1077 Juvenile myocardial infarction: prognostic role of genetic polymorphisms at medium-term follow-up

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Aim of this study was to investigate the influence of different genetic factors, compared to that of conventional risk factors, on follow-up events in a sample of Italian patients with juvenile myocardial infarction.

The studied population consisted of 106 young patients (mean age 40 ± 4, range 23–45 years) with diagnosis of acute myocardial infarction (AMI). Clinical, epidemiological, biochemical and genetic data from the group of patients with events during follow-up were compared with those from patients without events. The genetic polymorphisms tested were: ACE I/D, Angiotensin II receptor A/C, ApoE e2/e3/e4, Nitric Oxide Synthase VNTR, and platelet GP IIIa A1/A2.

Coronary angiography (performed in 94 patients) showed coronary artery disease in 93% of the patients. During follow-up (46 ± 12 months, range 25–72) the overall combined end-points (cardiac death, myocardial infarction and revascularizations procedure) accounted for 21 events. Family history of coronary artery disease, smoking, and the presence of the e4 allele of the apoE polymorphism were significantly more prevalent at univariate analysis in the group of patients with events. At logistic procedure analysis Apo E polymorphism (p = 0.004, OR 6.8, 95% confidence interval 2 to 22), family history (p = 0.005, OR 8.3, 95% confidence interval 2 to 35), smoking post-AMI (p = 0.008, OR 10.9, 95% confidence interval 2 to 62) and significant stenosis of the left anterior descending at coronary angiography (p = 0.02. OR 6.6, 95% confidence interval 1.3 to 33) were independent predictors of adverse events.

Conclusions: AMI at young age is commonly characterised by multiple cardiovascular risk factors and by a favourable prognosis in short and medium-term follow-up. Evidence of significant disease at coronary angiography suggests the presence of a premature atherosclerotic process. ApoE polymorphism (e4 allele) seems to be a strong independent predictor of adverse events, suggesting a remarkable influence in the accelerated coronary disease.

P1078 3-Deazaadenosin inhibits diet-induced atherosclerotis in C57/Bl/6J mice

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Background Adhesion of leukocytes to the activated endothelium and their migration into the subendothelial space play an important role in the pathogenesis of atherosclerosis. The adenosine analog 3-Deazaadenosine (c^3Ado) has been shown to inhibit the expression of adhesion molecules in cultured endothelial cells. Therefore we hypothised that c^3Ado is able to prevent diet-induced atherosclerosis in C57/BL/6J mice.

Methods and results The animals were placed on a regular or high cholesterol (chol) diet with or without c3Ado (10 mg/kg/die) for 9 weeks (n = 10, respectively). Total chol level rose from 66 ± 13 in the control group to 474 + 34 mg/dl in mice fed the atherogenic diet. c3Ado treatment did not influence chol concentrations. Anti-von-Willebrand, anti-CD-11b, anti-VCAM-1 and anti-ICAM-1 monoclonal antibodies were used for immunohistochemical staining of endothelial cells, macrophages and endothelial ICAM-1 and VCAM-1 expression respectively. Untreated mice on atherogenic diet showed typical aortic lesions and an increase of intimal thickness up to 35% (83 ± 3 vs. 61 ± 2.0 μm in comparison to animals on control diet, (p < 0.001). c3Ado totally inhibited the expression of endothelial VCAM-1 and ICAM-1 and completely prevented lesion formation in the animals given the atherogenic diet (60 ± 2.2 μm). Mice on atherogenic diet alone showed marked endothelial expression of ICAM-1 and VCAM-1 and mild infiltration and adhesion of monocytic cells. In contrast, no expression of ICAM-1 and VCAM-1 and no infiltration or adhesion of monocytic cells was observed in c3Ado-treated mice despite atherogenic diet.

Conclusions These data demonstrate that c3Ado efficiently inhibits diet-induced atherosclerosis and the endothelial expression of VCAM-1 and ICAM-1 in C57/BL/6J mice.

P1079 Promoter dependence of persistence of the effect of the human apo E enhancer on human apolipoprotein A-I expression after adenoviral gene transfer is explained by promoter attenuation

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Stable elevation of HDL cholesterol, induced by apo A-I gene transfer, may have a dramatic impact on ischemic cardiovascular disease. We previously demonstrated that the effect of apo E enhancer(s) inserted 3′ of adenoviral constructs containing both the CMV promoter and the apo A-I promoter (CMV/A-I.gA-I adenoviruses) on human apo A-I expression in C57BL/6 mice was copy dependent and transient (≤14 days) whereas the effect of 4 apo E enhancers 3′ of constructs containing only the apo A-I promoter (A-I.gA- I.4xapoE) persisted for at least 1 month. We investigated whether this effect persisted after 1 month and whether CMV promoter shut-off may explain differences in persistence of the apo E enhancer(s) effect.

Results: Compaired with gene transfer with 5 × 108 p.f.u. of a virus containing the apo A-I promoter without enhancers (A-I.gA-I), human apo A-I levels after gene transfer with the same dose of A-I.gA-I.4xapoE were 6.0-fold ($p < 0.0001$) higher at 1 month (104 ± 8.4 mg/dl), 4.3-fold ($p = 0.009$) higher at 2 months (86 ± 31 mg/dl), 3.1 fold ($p = 0.01$) higher at 3 months (58 ± 16 mg/dl), 3.9-fold ($p = 0.006$) higher at 6 months (40 ± 7.7 mg/dl), 4.1-fold ($p = 0.006$) higher at 7 months (21 ± 5.1 mg/dl) and were below 10 mg/dl at 8 months. Compared with CMV/A-I.gA-I adenoviruses, human apo A-I levels induced by A-I.gA-I.4xapoE were on average 3.9-fold higher between 1 and 7 months. Human apo A-I copy number at 1 month was not significantly different between CMV/A-I.gA-I adenoviruses (1.2 ± 0.14), A-I.gA-I (1.1 ± 0.24) and A-I.gA-I.4xapoE (1.4 ± 0.20). In contrast, the human apo A-I mRNA signal at 1 month was 21-fold higher ($p = 0.0004$) for A-I.gA-I.4xapoE compared with CMV/A-I.gA-1 adenoviruses.

Conclusion: The enhancer effect of 4 apo E enhancers on human apo A-I expression after gene transfer with A-I.gA-I.4xapoE persists for 7 months. The human apo A-I mRNA/human apo A-I DNA copy number ratio at 1 month is significantly lower for CMV/A-I.gA-I adenoviruses compared with A-I.gA-I.4xapoE, indicating that CMV promoter attenuation is the predominant mechanism of the rapid decline of human apo A-I levels.

P1080 Rare promoter variants in the human bradykinin B2-receptor gene alter gene expression in vitro

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There is increasing evidence that the human bradykinin B2-receptor (B2-R) is a promising candidate gene for hypertension.

In recent studies we detected polymorphic sites in the promoter of the B2-R gene. Electrophoretic Mobility Shift Assays (EMSA) revealed destruction or reduction of transcription factor binding ability of three of these mutations. In this study we tried to ascertain if these variants (−704 C/T, −412 C/G, −78 C/T) could alter the B2-R gene expression in vitro.

The WT and mutant alleles of the patients' B2-R promoter (−1057 to +10) were cloned into a reporter vector (pGL3Basic). Using electroporation these constructs were transiently transfected into COS-7 cells. After 48 h the luciferase-expression could be measured and normalized with the simultaniously transfected β-galactosidase.

We report here that the −412 C/G variant, which according to EMSA destroys a SP1 consensus sequence, reduces the luciferase expression to 58% ± 18% (n = 6). The nucleotide substitution at position −704 (CT) is capable of increasing the gene expression by 17% ± 18% (n = 7), while the mutation at position −78 C/T does not influence the promoter activity (93% ± 11%, n = 5). The mutation −412 C/G was only detected in a patient with dilated cardiomyopathy, his brother and an anonymous blood donor. One patient with HCM and one further with DCM beared the −704 T allele and the −78 T allele, respectively. Thus the frequencies of these polymorphisms are below 0.5%.

In this study we were able to show that the rare mutation −412 C/G reduces the transciptional activity of the promoter of the B2-R gene because it destroys the binding site for the ubiquitous transcription factor SP1. This leads to the conclusion that SP1 is involved in the regulation of transcription of the B2-R gene. The slightly enhanced gene expression caused by the −704 T allele might be because of the loss of a repressor binding site in the distant regulatory region.

P1081 Fine mapping of a quantitative trait – measured haplotype analysis of the angiotensin-1 converting enzyme gene

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Background: Linkage and segregation analysis have shown that circulating ACE levels are influenced by a major quantitative trait locus mapping within or close to the ACE gene. The D allele of the I/D polymorphism is associated with higher ACE levels and possibly with cardiovascular risk, but this polymorphism is unlikely to be the causative variant. Multiple variants in linkage disequilibrium with the I/D polymorphism have been described, but it is unknown if any of these are directly implicated in the determination of plasma ACE. We have used a novel technique utilising evolutionary information to more precisely localise the causative variant at this locus.

Methods: Analysis of 10 polymorphisms spanning 26 kb of the ACE gene using PCR methods in 83 extended British Caucasian families comprising 555 individuals. Measurement of plasma ACE using an HPLC method. Haplotype assignment using the SIMWALK program followed by measured haplotype analysis using the PAP package.

Results: A limited number of haplotypes existed in these families owing to strong linkage disequilibrium over the region. A haplotype tree (cladogram) was constructed with three main branches, accounting for >90% of the observed haplotypes; one branch is most likely to be derived from an ancestral recombination event between the other branches. This evolutionary information was then used to direct measured haplotype analyses which excluded upstream sequences, including the ACE promoter, from harbouring the major ACE-linked variant which explains 36% of the total trait variability. Residual familial correlations were highly significant, suggesting the influence of additional unlinked genes.

Interpretation: These results demonstrate that this analytic approach has power to localise genetic variants that directly influence a quantitative trait of likely cardiovascular significance in a human population.

P1082 Association of angiotensin I gene polymorphism with coronary atherosclerosis

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Angiotensin I (AGT) plays the key role within the renin-angiotensin system and is an attractive candidate as the risk factor for cardiovascular disease. Several polymorphisms of the AGT gene have been described including a methionine for a threonine substitution at residue 174 (T174M). The aim of this study was to investigate the relation between T174M polymorphism and coronary atherosclerosis in Russian population. 94 unrelated patients with coronary artery disease (CAD) proven by angiography and 131 healthy individuals were involved in the case-control study. The frequency of M174 allele was significantly higher among CAD patients than in control group (22.4% vs. 7.6%, $p < 0.001$). Genotype frequencies were 59% (T174), 38% (T174M), and 3% (M174) in the patients group; and 85%, 15%, and 0% in control population, respectively. T174M polymorphism was not associated with the serum triglycerides, total cholesterol, HDL-, LDL, and VLDL-cholesterol levels. No statistical difference in the systolic and diastolic blood pressure in the individuals with different AGT genotypes was found. Our results suggest that AGT gene could be a important risk factor for cardiovascular disease in Russians.

LIPIDS AND LIPID LOWERING: EFFECTS ON ENDOTHELIUM

P1083 Short-term atorvastatin therapy improves endothelial adhesiveness and carotid artery geometry

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Hypercholesterolemia is associated with endothelial dysfunction, and cholesterol (CH) lowering seems able to restore, at least partly, coronary and peripheral arterial function. We studied the effects of short term atorvastatin (A) therapy on critical atherogenic events, such as the adhesion and transendothelial migration of circulating leukocytes, and on large artery geometry. Twenty pts, 7 F and 13 M (age 48.69 ± 8.years) with primary hypercholesterolemia (PH), with or without clinical cardiovascular disease (8 and 12 pts, respectively), and without other risk factors were enrolled to A monotherapy (10–20 mg once daily) after a 3-month dietary phase and at least 4-week lipid lowering therapy washout. Soluble endothelial leukocytes adhesion molecule (sELAM1), intercellular adhesion molecule (sICAM1) and vascular adhesion molecule (sVCAM1) were determined at baseline, and after 1- and 3-months of A therapy. Phlogosis indexes, acute phase reactant proteins, tumor necrosis factor alpha and interleukin 6 were also measured at the same times. Common carotid artery (CCA) was examined by high resolution B-mode ultrasound: diameter and far wall intima-media thickness (IMT) of CCA were measured on digitized zoomed 2D images, one cm proximal to flow divider.

After 12-weeks of A therapy, total CH decreased from 332 ± 76 to 215 ± 23 mg/dl ($p < 0.0001$), apoprotein-B (apoB) from 214 ± 55 to 144 ± 27 mg/dl ($p < 0.0001$) and LDL-CH from 254 ± 81 to 145 ± 25.5 mg/dl ($p < 0.0001$). Triglycerides, lipoprotein(a) and HDL-CH were unchanged. Baseline sELAM1, sICAM1 and sVCAM1 were 23.5 ± 3.6 ng/ml, 275.5 ± 35 ng/ml and 770 ± 216 ng/ml respectively. After 3-month therapy sELAM1, which is found only on activated endothelium, was significantly reduced ($p < 0.03$). Before and after treatment, mean CCA IMT was 0.71 ± 0.11 mm, and 0.59 ± 0.14 mm ($p < 0.0002$), mean CCA diameter was 6.35 ± 0.86 and 6.71 ± 0.89 mm ($p < 0.0004$). By multiple regression analysis, CCA diameter correlated inversely ($p < 0.005$), and IMT directly ($p < 0.2$) to CH and LDL-CH.

Conclusions: in pts with PH, 3-month Atorvastatin therapy significantly reduces CH, LDL-CH, and apoB, and is capable to induce significant reduction of endothelial adhesiveness and large artery remodeling in absence of changes in other clinical chemical parameters.

P1084 A triglyceride-rich fat emulsion and free fatty acids but not triglyceride-rich lipoproteins impair endothelium-dependent vasorelaxation

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Objective: It has been shown that Intralipid®, a triglyceride-rich fat emulsion, impair endothelium-dependent vasorelaxation. The present study was performed in order to further investigate the effects of triglycerides and their metabolites free fatty acids on endothelium-dependent and endothelium-independent vasorelaxation.

Methods: Femoral arterial rings from rats were studied in organ baths. The vascular segments were constricted with prostaglandin F2 alpha or phenylephrine after 20 minutes of preincubation with the triglyceride-rich fat emulsion Intralipid®, free fatty acids (palmitic acid (16:0), oleic acid (18:1) and linolenic acid (18:3)), bound to bovine serum albumin, or very low density lipoproteins. Endothelium-dependent and endothelium-independent relaxation was determined by administration of acetylcholine and nitric oxide donors (sodium nitroprusside or S-nitroso-N-acetyl-D,L-penicillamine (SNAP)), respectively.

Results: Preincubation with Intralipid® caused a concentration-dependent impairment of endothelium-dependent but not endothelium-independent relaxation. Very low density lipoproteins did not affect vascular function. Incubation with all free fatty acids impaired endothelium-dependent relaxation, while endothelium-independent relaxation was unaffected. Administration of the antioxidant vitamin C reversed the impairment of endothelium-dependent relaxation induced by Intralipid®.

Conclusion: Free fatty acids and Intralipid®, but not very low density lipoproteins, impair endothelium-dependent relaxation. This effect is reversed by vitamin C, which indicates involvement of oxidative mechanisms.

P1085 Long-term effect of lipid lowering therapy on soluble markers of endothelial cell dysfunction

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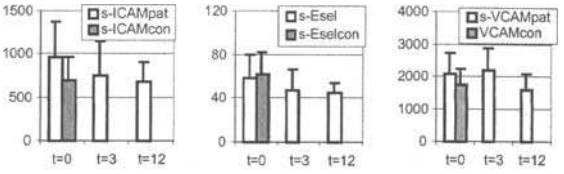
An early pathophysiological role in atherosclerosis is attributed to endothelial cell dysfunction (ECD). Levels of soluble forms of various cell adhesion molecules (CAMs) reflect ECD. Previously, it has been shown that CAMs are elevated in patients with atherosclerosis and in short-term studies it has been demonstrated that HMGCoA-inhibitors decrease CAM. We questioned whether this short term effect is sustained during long-term follow-up.

Materials and methods: In a group of 10 non-diabetic, normotensive patients (9 males) with established atherosclerosis and hypercholesterolemia, we determined the levels of s-VCAM, s-ICAM and s-Eselectine before, and after 3 and 12 months of treatment with fluvastatin 80 mg. For baseline comparisons, 28 age- and sex-matched healthy volunteers were studied.

Results: At baseline, s-ICAM ($p < 0.05$), but not s-VCAM and s-Eselectin were significantly higher in patients compared to controls. s-VCAM remained unchanged at three months and decreased after one year (2079 versus 2181 versus 1568 ng/ml; $p < 0.05$), whereas s-ICAM and s-Eselectin diminished continuously during follow-up (s-ICAM: 956 versus 745 versus 675 ng/ml [$p < 0.01$] and s-Eselectin: 59 versus 47 versus 45 ng/ml [$p = 0.05$]). Total cholesterol levels and LDL cholesterol levels also decreased during treatment (chol: 6.4 versus 4.5 versus 4.5 mmol/L; LDL 5.1 versus 3.5 versus 3.5 mmol/L) and were not related to CAMs. Triglycerides and HDL did not change



Conclusions: Soluble markers of endothelial cell dysfunction in patients with atherosclerosis improve during long-term follow-up. The decrease in CAM was differential, suggesting stages in restoring ECD. Further studies are needed to determine whether CAMs are better predictors of clinical events than total or LDL cholesterol.

P1086 LDL-apheresis and atorvastatin significantly reduce (plasma and urinary) isoprostanes

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Isoprostanes (IP) among them the vasoconstrictory and mitogenic 8-epi-$PGF_{2\alpha}$ are formed by the free radical catalyzed actions on membrane fatty acids may serve as an in-vivo measure of oxidation injury. We examined the influence of severe lipid lowering (atorvastatin [AT; 40 mg/d] therapy [n = 12; 8 m, 4 f; 27–46 a] and [dextran sulphate] LDL-apheresis [n = 9; 7 m, 2 f; 43–68 a]) in patients with familial heterozygous hypercholesterolemia (FH) on plasma and urinary 8-epi-prostaglandin ($PG)F_{2\alpha}$ (after extraction and purification) as compared to healthy controls using a specific immunoassay. In-vitro Cu^{++}-induced LDL-oxidation and thiobarbituric acid reactive substances (TBARS) were determined in parallel. AT (−16%/−19%) and LDL-apheresis (−28%/−34%) are significantly ($p < 0.01$) reducing 8-epi-$PGF_{2\alpha}$ (TBARS −44%, lag-time of oxidation +83%). Smokers show higher values of 8-epi-$PGF_{2\alpha}$ (plasma: 54.3 ± 9.6 pg/ml vs. 34.6 ± 6.2; controls: <20; urine: 481 ± 86 pg/mg creatinine vs. 336 ± 65; controls: <300). Similar kinetics are observed in all the subgroups. There is no significant age- and sex-difference. Repeated LDL-apheresis therapy shows an identical response.

These data suggest, that severe (LDL-)cholesterol lowering significantly diminishes oxidation injury. This may essentially contribute to the clinical benefit seen.

P1087 Cerivastatin prevented tumour necrosis factor-α-dependent downregulation of endothelial nitric oxide synthase: role of endothelial cytosolic proteins

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Cardiovascular disease is accompained by an impaired endothelium-dependent vasodilatory response and an increased production of tumor necrosis factor alpha (TNF-α). Loss of endothelial nitric oxide synthase (eNOS) expression may contribute to endothelial dysfunction. The aim of the present study was to analyze the effect of Cerivastatin, a novel HMG CoA reductase inhibitor, on TNF-α-related downregulation of eNOS protein expression in bovine cultured endothelial cells (EC). TNF-α (10 ng/ml)- incubated EC showed a reduced expression of eNOS protein and reduction in eNOS mRNA stabilization. This effect was associated with the binding of EC cytosolic proteins to the 3′-unstranslated region (3′UTR) of eNOS mRNA. The EC cytosolic proteins bound specifically a C-rich region (126 bases) within 3′-UTR eNOS mRNA. Cerivastatin prevented TNF-α-induced downregulation of eNOS protein expression. The effect of Cerivastatin on eNOS protein expression followed a dose-dependent manner (10^{-8} mol/l to 10^{-5} mol/l). Furthermore, Cerivastatin prevented the binding of the cytosolic protein to the C-rich region of 3′-UTR eNOS mRNA.

In conclusion: TNF-α reduced eNOS protein expression and stimulated the binding of cytosolic proteins to 3′-UTR eNOS mRNA. Cerivastatin upregulated eNOS protein expression and reduced the binding of cytosolic proteins to 3′-UTR eNOS mRNA reversing the effects of TNF-α. These findings suggest that Cerivastatin may have beneficial effects in endothelial dysfunction associated to cardiovascular diseases beyond its effect on the cholesterol.

P1088 Effects of atorvastatin treatment on endothelial dysfunction and vascular structural associated with dyslipidaemia in rabbits

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We evaluated aortic endothelial function and structural changes induced by a diet containing 0.5% cholesterol + 14% coconut oil for 14 weeks in NZ rabbits untreated or treated with atorvastatin (2.5 mg/kg/day). Plasma cholesterol and triglyceride concentrations were higher in rabbits fed the experimetal diet than control group ($p < 0.05$). Relaxing responses to Ach (10^{-9}–10^{-5} mol/L) were blunted in dyslipidemic rabbits. Incubation of aortic rings with either the thromoxane A_2 receptor antagonist, Ifetroban or with the endothelin-1 (ET_A) receptor antagonist BQ123, increased Ach-response in dyslipidemic and control rabbits. Constrictor responses to Ach in presence of the NO synthase inhibitor LNAME (10^{-4} mol/l) were higher in dyslipidemic rabbits than in control ones ($P < 0.05$), and were reduced by either ifetroban or BQ123. Atorvastatin treatment reduced lipid levels only in dyslipidemic rabbits. Atorvastain enhanced the relaxing response to Ach and reduced the contracting response to Ach + LNAME in rabbits fed with experimental diet. Incubation with either Ifetroban or BQ123 did not further increase relaxing responses to Ach or reduce constrictor responses to Ach + LNAME in atorvastatin-treated rabbits. Increased ($P < 0.05$) lesion area, degree of stenosis and media thickness were observed in dyslipidemic rabbits as compared to controls. Atorvastatin treatment markedly reduced ($P < 0.05$) these changes. In conclusion: 1) TXA_2 and ET seem to participate in the endothelial dysfunction observed in dyslipidemic rabbits. 2) the amelioration on endothelial dysfunction produced by Atorvastatin treatment in dyslipidemic rabbits could be partially due to a reduction in thromboxane A_2 and endothelin-1 availabilities. 3) the beneficial effects of Atorvastatin treatment on aortic structural alterations could contribute to the observed improvement of endothelial function.

P1089 Regulation of endothelial nitric oxide synthase by Rho-dependent actin stress fiber formation

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Inhibition of isoprenoid synthesis by HMG-CoA reductase inhibitors (statins) upregulates endothelial nitric oxide synthase (eNOS) in human endothelial cells via inhibition of geranylgeranylation and membrane-translocation of the small GTPase Rho. The anchoring of specific mRNAs to the cytoskeleton and their co-localization with ribosomes and RNA-binding protein complexes are necessary for their translational expression and stability. Since Rho plays an important role in cytoskeletal reorganization, we hypothesized that Rho-induced myosin light chain (MLC) phosphorylation and focal adhesion complexes may affect eNOS mRNA translation and stability. Inhibition of Rho activity by *Clostridium botulinum* C3 transferase (50 μg/ml) or by overexpression of a dominant-negative Rho mutant, N19RhoA, decreased focal adhesion complexes and actin stress fiber formation. These inhibitory effects on Rho correlated with increases in eNOS mRNA stability and expression. To determine whether the increase in eNOS expression was mediated by inhibition of Rho-induced MLC phosphorylation, endothelial cells were treated with specific inhibitors of MLC kinase, H-7 (100 μM) and ML-7 (0.5–5 μM). Both H-7 and ML-7 caused a 4- and 3-fold increase in eNOS mRNA and protein levels, respectively. Since MLC phosphorylation is required for the formation of focal adhesion complexes and actin stress fibers, we disrupted these cytoskeletal processes directly with cytochalasin D (0.1–10 μM) which resulted in a concentration-dependent increase in eNOS expression. Cytochalasin D, however, did not inhibit the geranylgeranylation, membrane translocation, or activity of Rho, but produced a compensatory 3-fold increase in membrane-associated Rho. The cytoskeletal effects of cytochalasin D on eNOS expression were specific since disruption of microtubule formation by nocodazole (5–500 nM) had no effect on eNOS expression. Our findings indicate that Rho-mediated actin stress fiber formation negatively-regulates eNOS mRNA stability and expression. We propose that the dynamic status of the cytoskeleton plays an important role in regulating eNOS expression via the transportation, localization, and compartmentalization of eNOS mRNA. It remains to be determined how eNOS mRNA stability is affected by its localization.

P1090 HMG-CoA reductase inhibitor, pravastatin, reduces the levels of tissue factor and plasminogen activator inhibitor-1 in human cultured monocytes

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Macrophage accumulation and activation in plaques play an important role in pathogenesis of acute coronary syndromes. Recent clinical trials of HMG-CoA reductase inhibitor, pravastatin, have shown the benefits in the treatment of coronary artery disease. In the present study, we investigated the beneficial effects of pravastatin on macrophage functions in addition to the cholesterol-lowering.

Methods: Human monocytes were obtained from peripheral blood of healthy volunteers by gradient centrifugation and adherent method. Monocytes (1×10^5/ml) were cultured in the presence of oxidized LDL and lipoprotein deficient serum in RPMI 1640 medium. Pravastatin (1–10 μg/ml) was added to this culture system. The levels of tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) in culture medium were measured by ELISA. The levels of mRNA for TF and PAI-1 were assessed by reverse-transcriptase polymerase chain reaction (RT-PCR) in the cultured monocytes.

Results: There were no changes in the levels of TF or PAI-1 in the medium between pravastatin-treated group and control after 1 day of culture. However, after 3 days of culture, pravastatin decreased the protein levels of TF and PAI-1 by 23.8 ± 14.3% ($n = 5$, $P < 0.05$) and 20.5 ± 11.5% ($n = 9$, $P < 0.001$) in the medium, respectively. Similar reductions by pravastatin (TF; 20.7 ± 14.1%, $n = 5$, $P < 0.05$, PAI-1; 18.7 ± 4.3%, $n = 6$, $P < 0.001$) were observed after 7 days of culture. RT-PCR revealed a decrease in the mRNA levels of TF in the monocytes after 3 days of culture, but not the PAI-1 levels.

In conclusion, we demonstrate that pravastatin reduced the production of TF and PAI-1 in cultured monocytes, suggesting that pravastatin may affect the procoagulant state induced by the accumulation and activation of macrophages in plaques and that this may contribute to the prevention of coronary events in patients taking pravastatin.

P1091 Influence of atorvastatin and cerivastatin on proliferation, apoptosis rate, and expression of fibronectin, MMP-1, 3, TIMP-1, -2 in human VSMC

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Inhibitors of the HMG-CoA reductase lead to a reduction of cardiovascular and total mortality in patients with CAD. To investigate the influence of statins on biochemical events related to plaque-stability, we isolated VSMC from human saphenous vein (s.v.) and coronary arteries and analysed the effect of atorvastatin and cerivastatin on proliferation, apoptosis rate, expression of fibronectin, tenascin, MMP1, MMP3, TIMP-1 and 2.

Methods: VSMC were isolated by outgrowth of samples from the media and used in passage 3–5. Proliferation was determined by use of an MTT-test, apoptosis by use of the tunel-method. Expression of fibronectin and tenascin was determined by western-blot of culture supernatants, expression of MMP1, 3, TIMP-1, and 2 by ELISA.

Atorvastatin and cerivastatin led to a dose-dependent inhibition of the proliferation of VSMC from coronaries (n = 5) and s.v. (n = 7) in response to PDGF and induced apoptosis in a dose-dependent manner (n = 4).

	Control	10 μM ator	1 μM ator	1 μM ceri	100 nM ceri
Rate of apoptosis	2.2 ± 1.3%	8.5 ± 2.6%*	4.2 ± 2.1%*	12.3 ± 1.8%*	6.3 ± 2.2%*

The expression of fibronectin, tenascin, MMP1, and TIMP-1 remained unchanged in VSMC from coronaries or s.v. after incubation with cerivastatin (10 nM) or atorvastatin (500 nM), while both substances led to a significant down-regulation of MMP-3- and TIMP-2.

	Control	PDGF 10 ng/ml	PDGF + Ator	PDGF + Ceri
MMP3 (μg/ml)	6.75 ± 3.29	25.5 ± 15.07	4.8 ± 3.54*	3.5 ± 1.83%*
TIMP-2 (μg/ml)	6.6 ± 5.5	5.5 ± 3.28	3.0 ± 2.25*	4.5 ± 3.17*

*p < 0.05 vs. control.

In conclusion atorvastatin and cerivastatin influence important events related to plaque stability.

ENDOTHELIAL AND PLATELET FUNCTION

P1092 Bradykinin is a potent dose-dependent stimulus for release of tissue plasminogen activator (tPA) in the human forearm circulation

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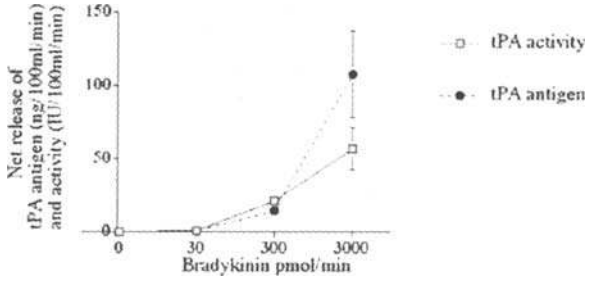
Background: A reduction in coronary thrombotic events is seen with the use of angiotensin-converting enzyme (ACE) inhibitors in ischaemic heart disease. The mechanism for this may involve an increase in tPA release which, in turn, may be mediated by mediated by bradykinin. We examined the effects of intra-arterial infusion of bradykinin on blood flow, fibrinolysis and coagulation in the human forearm circulation.

Methods: Bradykinin at 10–3000 pmol/min was infused into the brachial artery of the non-dominant forearm in 8 healthy non-smoking men. Blood flow measurements were made using venous occlusion plethysmography, the non-infused arm acting as a contemporaneous control. Venous blood samples for tPA, plasminogen activator inhibitor (PAI) and von Willebrand factor (vWF) were obtained from both forearms during saline and bradykinin infusions.

Results: Bradykinin caused a dose-dependent local increase in forearm blood flow, tPA antigen and tPA activity ($p < 0.01$ for all) in the infused arm without changes in PAI-1 or vWF ($p > 0.05$ for both).



Relationship between bradykinin and tPA.

Conclusions: Intra-arterial bradykinin causes a substantial dose-dependent release of tPA in the forearm vascular bed. This has potentially important implications for the understanding of the mechanism of action of ACE inhibitors and their role in ischaemic heart disease.

P1093 The Intervention Cardiology Risk Stratification (ICARIS) study: ACE-polymorphism genotype and coronary endothelial function

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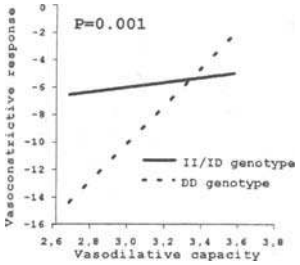
An important determinant for cardiovascular disease is the endothelial function, determined by intracoronary infusion of acetylcholine (i.e. paradoxical vasoconstriction if endothelial dysfunction is present). ACE-DD receptor genotype negatively interferes with atherosclerotic progression. In the present ICARIS study we correlated ACE-polymorphism genotype DD or II/ID with coronary acetylcholine response and maximal vasodilative capacity after nitroglycerin.

Methods: Using off-line quantitative coronary angiography, the response on intracoronary acetylcholine infusion (left main stem concentration 10^{-8}–10^{-6} molar) was determined in 91 patients with angina pectoris. After univariate analysis, multiple regression was performed for the maximal vasoconstrictive response on acetylcholine (% from baseline) with the predictors vasodilative capacity after nitroglycerine (mm), ACE- genotype and their interaction.

Results: Univariate analysis for all potential risk factors demonstrated a vasoconstrictive circumflex response in patients with DD-genotype compared to II/ID-genotype ($p = 0.001$). ST-T abnormalities at rest or on exercise, total cholesterol and previous myocardial infarction were detected via multiple regression as confounding factors. After correction for these factors in these patients (n = 76, 63% males, mean age 58), the difference between the ACE-genotypes remained borderline ($p = 0.050$).



Conclusion: These data demonstrate that ACE-DD genotype is associated with abnormal endothelial function in smaller coronary arteries.

P1094 Are ACE-inhibitors antioxidants? Effect of chronic ACE-inhibition on endothelium-mediated vasodilation and ICAM-1 plasma levels in patients with coronary artery disease

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Impaired flow-dependent, endothelium-mediated vasodilation (FDD) and increased expression of adhesion molecules, both induced by oxidative stress, are early findings in patients with coronary artery disease (CAD). Since angiotensin II (AII) can induce radical formation within the vessel wall, we hypothesized that chronic ACE-inhibition may reduce oxidative stress by reduction of AII thereby leading to improvement of FDD and reduction of adhesion molecules. Accordingly we determined the acute effect of the antioxidant vitamin C (25 mg/min; i.a.) on FDD of the radial artery in 30 patients with angiographically documented CAD at baseline and after 4 weeks of ACE-inhibition with ramipril (5 mg bid). Diameter was measured by high-resolution ultrasound (10 Mhz; precision 2 μm), blood flow (BF; ml/min) calculated from BF-velocity (8 Mhz Doppler) and cross-sectional area. Diameter changes (D%, representing FDD) and BF were determined at rest and after wrist occlusion (8 min). To determine the portion of FDD inhibited by radicals (i.e. normalized by vitamin C) the Delta-value (FDD after vitamin C minus FDD control) was calculated. In addition, plasma concentration of soluble intercellular adhesion molecule 1 (sICAM-1) and urine concentration of isoprostanes (systemic parameter of oxidative stress) were measured at baseline and after 4 weeks of ACE-inhibition.

	FDD	FDD vit.C	Delta-FDD	Isoprostane	sICAM-1
Control	7.6 ± 0.5	12.5 ± 0.6	4.5 ± 0.5	803 ± 21	317 ± 14
4 weeks	11.9 ± 0.6*	12.3 ± 0.6	0.4 ± 0.5*	632 ± 22*	274 ± 13*

(all data ± SEM; *p < 0.01 vs control).

Conclusion: Chronic ACE-inhibition concomitantly leads to improvement of endothelium-mediated vasodilation and reduction of the adhesion molecule ICAM-1 and urinary isoprostanes. The antioxidans vitamin C improved FDD at baseline but not after 4 weeks of ramipril, suggesting an antioxidant effect of the ACE-inhibitor.

P1095 High-resolution magnetic resonance imaging of the brachial artery – a novel method for assessing vascular function

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Background: Measurement of changes in brachial artery (BA) diameter by external ultrasound (EXUS) in response to reactive hyperaemia (RH) or GTN is widely used to assess vascular function. Magnetic Resonance Imaging (MRI) is extensively used for non-invasive assessment of cardiovascular function. Compared to EXUS, MRI is less observer-dependent and measures cross-sectional area (CSA) rather than solely diameter.

Methods: The CSA of the BA was measured by MRI in 16 subjects and compared to CSA from intravascular ultrasound (IVUS) in 8 patients with coronary artery disease (CAD) and BA dimensions from EXUS in 8 healthy male volunteers. The MRI was performed at 1.5 Tesla with high resolution (field of view: 100 mm) segmented FLASH. Reactive hyperaemia was induced by 5 minutes circulatory forearm cuff-occlusion. Imaging of the BA was performed over 12 cardiac cycles at baseline, following cuff release and 3 minutes after GTN challenge in the CAD patients. MRI was also used to measure BA diameter perpendicular to the skin surface at baseline and following RH, similar to EXUS.

Results: Data from the invasive IVUS measurement of brachial artery dimensions correlated strongly with the MRI measurement both at baseline ($r = 0.89$, $p = 0.003$) and after vasodilation ($r = 0.78$, $p = 0.007$). CSA by IVUS was consistently greater (24.1 ± 6.6 vs 19.0 ± 4.3 mm^2, $p = 0.004$). MRI measurement of BA diameter correlated significantly to EXUS diameter ($r = 0.69$, $p = 0.003$). BA diameter was significantly smaller by MRI compared to EXUS (4.1 ± 0.3 vs 4.9 ± 0.5, $p < 0.001$).

Conclusion: MRI diameters and areas correlate well, though are smaller than ultrasound measurements. These differences most likely relate to MRI detecting blood signal rather than the vessel wall. Measurement of CSA by MRI provides increased information compared to that from EXUS as the vessel lumen is frequently non-circular. MRI is a promising technique for non-invasive determination of vascular function.

P1096 Inverse relationship between carotid intima-media thickness and brachial artery ischaemic-mediated dilatation in healthy young subjects with history of parental myocardial infarction

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Background: Increased intima-media thickness (IMT) of the distal common carotid artery and brachial artery endothelial dysfunction may be early manifestations of the atherosclerotic process. However, little is known about the possible association between carotid IMT and brachial artery flow-mediated dilatation (FMD). The aim of this study was to evaluate the relationship between carotid IMT and brachial artery FMD.

Methods: Fifty-eight healthy young subjects with history of parental myocardial infarction [41% males; age 21 ± 5 years; 27% current smokers; body mass index (BMI) 22.7 ± 2.9; total cholesterol 171 ± 33 mg/dl; HDL cholesterol 51 ± 13 mg/dl; Lp(a) 26 ± 34 mg/dl; apo A1 144 ± 23 mg/dl; apo B 92 ± 26 mg/dl; systolic blood pressure 121 ± 10 mmHg; diastolic blood pressure 64 ± 8 mmHg] underwent: 1. carotid ultrasonography to measure the sum of IMT (SIMT) at four sites of the left and the right common carotid artery and carotid bifurcation; 2. brachial artery ultrasonography to measure the percent brachial artery diameter change (BADC) to reactive hyperemia induced by 4-min blood flow occlusion to the distal limb.

Results: SIMT correlated directly with BMI ($r = 0.36$, $p = 0.005$) and inversely with percent BADC ($r = -0.31$, $p = 0.02$). Multivariate analysis demonstrated that SIMT was an independent predictor of percent BADC.

Conclusions: In healthy young subjects with history of parental myocardial infarction increased carotid IMT is therefore associated with reduced brachial artery FMD, independent of the effects of age, BMI, blood pressure, smoking status, lipids. These combined changes in vascular structure and function may play an important role in the development of atherosclerosis and may become an useful surrogate in assessing the predisposition to atherosclerosis in healthy subjects with well known risk factors.

P1097 Brachial artery intima-media thickness measured with high-resolution (13 MHz) ultrasound: relation to coronary artery disease and endothelial function

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Background: High-resolution ultrasound allows accurate measurement of brachial artery (BA) diameter, which is used for the assessment of endothelial function (flow-mediated vasodilation, FMD). Whether BA wall thickness (WT) measured in vivo is related to coronary artery disease (CAD) and/or FMD is unknown.

Methods: In 40 patients (pts) undergoing coronary angiography, BA-FMD and WT were measured with ultrasound (13 MHz) by an observer blinded to the diagnosis. 19 pts (age 51 ± 10 years) had CAD (* 30% diameter stenosis in 1 major branch), 21 pts (age 50 ± 8 years) had smooth coronaries. The number of risk factors per patient was similar in both groups (1.8 ± 0.9 vs. 1.4 ± 0.9). Within 2 days after angio, FMD and BA wall thickness were measured: Media-to-media (MDM) minus Intima-to-intima diameter (IDM)/2 (calculated WT) and direct intima-media measurement of the BA wall (direct WT). Measurement error is <0.05 mm.

Results: CAD pts showed significantly greater WT than controls, both using calculated WT (0.35 ± 0.06 vs. 0.31 ± 0.05 mm, $p < 0.02$) and direct WT (0.4 ± 0.05 vs. 0.35 ± 0.05 mm, $p < 0.01$). Calculated and direct WT showed close correlation ($r = 0.8$, $p < 0.01$). A wall index [(MDM-IDM)/MDM)x100] was also larger in CAD pts. than in controls (13.8 ± 2.1 vs. 12.5 ± 1.7, $p < 0.05$). FMD and WT showed no correlation.

Conclusion: BA-WT is measurable in vivo with high-resolution ultrasound and is greater in CAD pts than in controls with similar risk factor profile. These findings are in accordance with recent postmortem histologic data, suggesting atherosclerotic involvement of the BA. High-resolution ultrasound measurement of WT, in addition to FMD, may help to assess atherosclerotic risk non-invasivly.

P1098 Coronary endothelial function and renin-angiotensin system-related receptor polymorphism genotype: the Intervention Cardiology Risk Stratification (ICARIS) study

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An important function of the endothelium is the presence of the angiotensin converting enzyme (ACE). ACE activates the potent vasoconstrictor angiotensin-II (ATII) and inactivates the vasodilator bradykinin (BK). ACE-dd and ATII-cc receptor genotypes interfere negatively with atherosclerotic progression and endothelial function. In the present ICARIS study we correlate the coronary response on intracoronary infusion of acetylcholine with the ACE, ATII and BK-2 receptor genotypes.

Methods: Acetylcholine was infused intracoronary (left main stem concentration 10^{-8}–10^{-6} molar) in 91 patients with angina pectoris accepted for diagnostic coronary angiography. The proximal LAD and LCX coronary response was determined using off-line quantitative coronary angiography. Multiple regression analysis was performed for all potential risk factors and first-order interactions towards the maximal vasoconstrictive response on acetylcholine (MAX%).

Results: Multiple regression analysis of these patients (n = 76, 63% males, mean age 58) showed that ATII genotype is an independent determinant of the acetylcholine response. The MAX% was −5.9% for ATII-aa genotype and −9.9% for ATII-ac genotype; $p = 0.049$. Receptor genotype of these patients was: ATII-aa 50% and ac 50%; ACE-dd 28% and id 44% and ii 28%; BK-cc 71% and ct 29%. No significant relation could be demonstrated for BK genotype, whereas ACE genotype was only a borderline predictor in combination with the maximal vasodilative diameter ($p = 0.050$).

Conclusion: ATII-ac receptor genotype is related with coronary endothelial dysfunction. This relationship was independent from the presence of clinical risk factors. No interactions with ACE or BK receptor polymorphism genotype could be demonstrated.

P1099 Tamoxifen improves endothelium-dependent vasodilatation in men with angiographically proven three-vessel coronary artery disease

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Tamoxifen, a triphenylethylene with oestrogenic and anti-oestrogenic properties, has been shown to have a major effect on cardiovascular protection in women but has not been extensively studied in men. Endothelial function declines with age and is impaired in patients with risk factors for and proven atherosclerosis. We studied the effects of tamoxifen on endothelial function in men with three vessel coronary artery disease (TVD).

Methods: 31 men with angiographic TVD, stabilised on a statin for at least 6 weeks pre-study, were randomised to tamoxifen 40 mg/day for 28 days or no additional therapy. Using high resolution ultrasonography of the brachial artery, flow-mediated endothelium-dependent vasodilatation (EDVD) was measured following reactive hyperemia. Endothelium-independent (EIVD) vasodilatation was measured after administration of sublingual glyceryl trinitrate. Results were expressed as percentage change in brachial artery diameter compared to baseline diameter. Endothelial function was studied at days 0, 7, 14 and 28.

Results: Tamoxifen significantly improved EDVD by day 7. There was no significant change in EDVD in the control group.

	EDVD (% ± SEM)			
	Day 0	Day 7	Day 14	Day 28
Control	1.6 ± 0.4%	1.9 ± 0.5%	1.8 ± 0.4%	2.0 ± 0.4%
Tamoxifen	2.0 ± 0.3%	*2.8 ± 0.4%*	*4.9 ± 5.8%*	*7.5 ± 0.7%*

$p < 0.05$ compared with day 0.

Tamoxifen had no effect on EIDV in either group.

Conclusion: Tamoxifen improves EDVD in men receiving statins with angiographic TVD. Tamoxifen may have cardioprotective effects in men mediated in part by improvement of endothelial function.

P1100 Exercise perfusion scintigraphy positivity is associated with peripheral vascular endothelial dysfunction in patients with normal coronary arteries

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Background: Patients with chest pain and angiographically normal coronary arteries often have a positive thallium-201 myocardial perfusion scintigraphy, hypothetically linked to coronary microvascular disease and endothelial dysfunction. High resolution brachial ultrasound provides a noninvasive assessment of systemic endothelial function.

Aim: To determine the endothelium dependent vasodilator function in the brachial artery of patients with chest pain, angiographically normal coronary arteries and different response during thallium-201 perfusion scintigraphy.

Methods: Forty-two patients (33 males, mean age: 59 ± 8 years) with chest pain syndrome and angiographically normal coronary arteries underwent exercise stress thallium-201 scintigraphy. The scintigraphy was considered positive in case of a transient perfusion defect. Endothelium dependent vasodilation was assessed by measuring the change in brachial artery diameter in response to hyperemic flow by vascular ultrasound.

Results: On the basis of the associated scintigraphic response, 2 groups were identified: I. (n = 14) with negative and II. (n = 28) with positive perfusion scintigraphy. Brachial artery flow mediated vasodilation was decreased in patients with positive thallium-201 scintigraphy (I. = 11.4 ± 5.9% vs II. = 5.9 ± 5.4%, $p < 0.01$).

Conclusion: In patients with angiographically normal coronary arteries, a stress induced perfusion defect is an "anatomic lie" ("false-positive" versus the angiographic standard) but a "physiologic truth" (true positive versus the physiologic assessment of systemic endothelial function).

P1101 Effect of circuit weight training on functional capacity and vascular function in non-insulin-dependent diabetes

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Background: Exercise training programs are often recommended for patients with NIDDM to improve physical conditioning and glycaemic control. We investigated the effect of a program of combined aerobic and resistance exercise on measures of functional capacity, strength, body composition and vascular function.

Methods: After familiarisation sessions, 16 patients (53 ± 2 yrs, 89 ± 4 kg; mean ± SE) undertook a randomised, cross-over design study of the effect of 8 weeks of supervised CWT. VO_2peak, sum of 7 maximal voluntary contractions and the sum of 8 skinfolds were determined at entry, cross-over and 16 weeks. Endothelium-dependent and -independent vascular function were determined by forearm strain-gauge plethysmography and intrabrachial infusions of acetylcholine (ACh) and nitroprusside (SNP). Conduit vessel endothelial function was assessed using high-resolution ultrasound and the brachial artery flow mediated response to reactive hyperaemia (FMD); nitroglycerine (GTN) being used as a non-endothelium-dependent dilator.

Results: VO_2peak significantly increased as a result of CWT (23.1 ± 1.2 v 24.8 ± 1.4 ml/kg/min; $P < 0.05$, paired t-test) as did exercise test duration (12.6 ± 1.2 v 14.8 ± 1.3 min; $P < 0.01$). Muscular strength (396 ± 29 v 456 ± 30 kg; $P < 0.01$) also increased with training. Skinfolds significantly decreased (149 ± 11 v 141 ± 10 mm; $P < 0.05$), whilst body weight was unchanged. Glycated haemoglobin decreased from 8.5 ± 0.4 to 7.9 ± 0.3 ($P < 0.05$). The forearm blood flow ratio responses to three incremental doses of ACh significantly increased after exercise training ($P < 0.05$, two-way ANOVA), as did the FMD response to hyperaemia ($P < 0.001$). In contrast, CWT did not influence the response to SNP or GTN.

Conclusions: An individually prescribed, structured and supervised CWT program improved objective measures of functional capacity and muscular strength in patients with NIDDM. In addition, anthropometric and strength data suggest that lean body mass increased, with a corresponding decrease in adiposity. CWT exercise also enhanced endothelium-dependent vasodilation in forearm vessels of patients with NIDDM, indicating that clinically relevant exercise training programmes may reverse the endothelial dysfunction which is associated with this disease.

P1102 Oleic acid, a prominent component of the Mediterranean diet, exerts direct vascular antiatherogenic properties by modulating endothelial activation through effects on intracellular reactive oxygen metabolites

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Endothelial cell activation plays an important role in the pathogenesis of atherosclerosis by allowing monocyte recruitment through the expression of adhesion molecules and chemoattractants. Intracellular production of reactive oxygen species is crucial for the trascriptional activation of these genes through the induction of Nuclear Factor-κB (NF-κB), consensus sequences for which are present in the promoters of all these genes. We stimulated human vascular endothelial cells with interleukin-1 (IL-1) and lipopolysaccaride (LPS) with or without preincubation with 50–100 μM oleic acid for 48–72 hours. This concomitantly reduced VCAM-1 and E-selectin surface expression, mRNA levels at Northern analysis and NF-κB activation at electrophoretic mobility shift assay. We subsequently investigated the possible influence of oleic acid on the oxidative status of endothelial cells, by measuring the activity of glutathione (GSH)-related antioxidant enzymes glutathione peroxidase (GSH-Px) and glutathione transferase (GSH-T), and the concentration of intracellular glutathione (GSH) and ascorbic acid. Exposure to 1μg/mL LPS caused a significant decrease of intracellular GSH (−38 ± 23%) and ascorbic acid (−60 ± 30%). When cells were grown for 48 h in the presence of 100 μM oleic acid before the exposure to LPS, the depletion of GSH and ascorbic acid were prevented. Neither LPS nor oleic acid caused changes in the activity of GSH-related antioxidant enzymes. Measurement of oleic acid incorporation in total cell lipids indicated a preferential incorporation of oleate at the expenses of saturated fatty acids. These results indicate that a prominent component of olive oil and the Mediterranean diet exerts direct vascular atheroprotective effects by inhibiting endothelial activation through a quenching of stimulus-related increase in intracellular reactive oxygen species.

P1103 Differential gene expression in canine platelets following chronic administration of non-intermittent glyceryl trinitrate

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Nonintermittent therapy with nitrovasodilators may induce tolerance (upregulation of platelet activity/reduced vasodilation). During 5 day infusion of glyceryl trinitrate (GTN; 1.5 μg/kg/min) into dogs we analyzed differential gene expression in the megakaryopoietic lineage. Platelet RNA (ribonucleic acid) from day 0 (control) or days 1, 3, and 5 of GTN treatment was subjected to differential display reverse transcription polymerase chain reaction. For each day 40 different PCR reactions (160 total reactions) were resolved by denaturing polyacrylamide gel electrophoresis. For cloning and sequencing, differentially expressed bands were reamplified. Out of the 40 PCR reactions, 16 showed differential banding patterns between different days of analysis (24 differentially expressed bands). Development of tolerance was related to quantitative (enhanced or diminished gene expression) and qualitative changes in gene expression: either the expression of a specific RNA was restricted to control platelets, or it was only detectable during GTN administration. For some RNAs, expression could be observed only on day 1 of GTN administration or was completely absent. Reamplified PCR products of interest are now being cloned for further characterization. Thus chronic administration of the nitrovasodilator glyceryl trinitrate induces profound alterations of gene expression in the megakaryopoietic lineage during development of nitrate tolerance.

Conclusion: Differentially expressed genes could be intimately implicated in nitrate dependent signal transduction or in tolerance development. Differential display of platelet RNAs during long-term administration of NO donors is an adequate approach to identify mechanisms involved in the pharmacodynamics of nitrates and in the development of tolerance.

P1104 Inhaled nitric oxide does not influence bleeding time or platelet function in healthy volunteers

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Bleeding time has been reported to increase during NO inhalation and it has been speculated that inhaled NO inhibits platelet function, but we have been unable to document any effects on circulating platelets. However, an effect on platelet-vessel wall interactions, or vasodilator response in the skin circulation might also increase bleeding time.

Methods: Because all earlier studies have been open, we performed a double-blind, placebo controlled cross-over study in which healthy volunteers (n = 15) inhaled NO (30 ppm) or air. Aspirin (640 mg orally, n = 14) was used as positive control on a third occasion. Bleeding time was measured, and platelet function was determined by measuring the expression of P-selectin on circulating platelets and locally activated platelets in wound blood using flow cytometry in whole blood. Local skin perfusion was assessed by laser Doppler flowmetry.

Results: Bleeding time was unaffected by NO, as there were slight increases during both NO and control inhalation (+20% and +14% respectively, $p = 0.9$). Similarly, NO inhalation had no effect on the time-dependent increase in P-selectin expression of platelets in wound blood or on the skin perfusion. Aspirin pre-treatment, on the other hand significantly prolonged bleeding time ($p < 0.001$) and the platelet activation in wound blood (P-selectin expression) was attenuated after aspirin compared to baseline ($p < 0.01$).

In conclusion: This first placebo-controlled study demonstrates that NO inhalation has no significant effect on bleeding time, platelet function or skin perfusion. It has previously been feared, that treatment with NO inhalation to critically ill patients will aggravate the disturbances in haemostasis that these patients often display by a direct effect on platelets. This is unlikely on the basis of present findings.

P1105 A simple point of care method for assessment of platelet function at the bedside using the ICHOR device

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There is a current clinical need for a point of care device to assess platelet function in patients receiving platelet Gp IIb/IIIa receptor blocker therapy for better safety and efficacy. Unfortunately, the traditional methods are suboptimal. The purpose of this study is to assess the feasibility of assessing platelet function as measured by platelet aggregation inhibition, using the ICHOR hematology analyzer in patients undergoing coronary angioplasty and were treated with tirofiban.

Methods: The study was conducted at Ben Taub General Hospital, an affiliated hospital of Baylor College of Medicine. Twelve patients undergoing coronary angioplasty for acute coronary syndromes and treated with tirofiban (0.4 μg/kg/min loading dose for 30 minutes and 0.1 μg/kg/min for 12–24 hours maintenance infusion) were recruited. Blood samples were collected from the arterial sheath while in place and from a peripheral intravenous catheter after sheath removal. Platelet aggregation was tested before tirofiban infusion, after completion of the bolus infusion, at 4 hours, before discontinuation and 2 hours after the infusion was discontinued. Four different platelet agonists were used: ADP, ristocetin, epinephrine, and collagen.

Results: The mean age of the patients enrolled was 52 ± 3 years. Coronary angioplasty of the LAD was performed in 6 patients, RCA in 4 patients and of the circumflex in 2 patients. Baseline studies showed a mean platelet aggregation of 65%, 86%, 88%, and 70% in response to ristocetin, ADP, epinephrine and collagen, respectively. The percentage of aggregable platelets decreased to 10%, 24%, 15% and 24% when stimulated with ristocetin, ADP, epinephrine and collagen following the tirofiban bolus infusions. This effect was maintained at 4 hours and before the discontinuation of the infusion at a mean of 17 hours. Platelet function recovered partially 2 hours after discontinuation of tirofiban with mean percent platelet aggregation of 46%, 55%, 49% and 57% as measured with the same agonists. A heterogenous response was noted when testing platelets from different patients with the same agonists in the presence or absence of tirofiban.

Conclusion: The ICHOR hematology analyzer is a simple, rapid bedside method that may have clinical utility in assessing platelet aggregability in patients undergoing coronary angioplasty who are treated with Gp IIb/IIIa receptor blockers.

P1106 Flow cytometer model markedly affects the measurements of platelet P-selectin in patients with chest pain

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Surface expression of P-selectin is known to be a marker of platelet activation in patients with acute coronary syndromes. However, direct comparisons of flow cytometry data may be obscured by differences in methodology, artifactual platelet activation during washing procedures, and choice of antibodies. We sought to test the hypothesis that the model of flow cytometer represents another variable affecting P-selectin measurements.

Methods: Platelet P-selectin in whole blood was measured by FACScan™ (Beckton Dickinson, Inc., San Diego, USA) or EPICS XL® (Coulter Corporation, Miami, USA) flow cytometry in 338 patients presenting with chest pain to the emergency departments of three community hospitals as part of a multicenter diagnostic trial.

Results: Platelet expression of P-selectin (% of cell positivity) was consistently higher for each discharge diagnosis when measured with FACScan™ flow cytometer (13.2 ± 4.1 for myocardial infarction, 10.0 ± 3.6 for unstable angina, 9.9 ± 3.5 for heart failure, 4.7 ± 0.1 for gastrointestinal illness, and 6.3 ± 0.7 for patients with non-cardiac chest pain) when compared with results obtained from the EPICS XL® instrument (2.4 ± 0.2, 2.5 ± 0.2, 2.5 ± 0.1, 1.8 ± 0.1, and 2.3 ± 0.1 respectively, $p = 0.0001$ for all groups).

In conclusion, this study reveals that the level of platelet P-selectin detected depends upon the model of flow cytometer used. If P-selectin is to become a diagnostic tool for assessing platelet hyperactivity in vascular disease, it is mandatory that standard measurements be defined for each model of flow cytometer.

P1107 The central role of the platelet ADP (P_{2T}) receptor in amplification of platelet secretion in human whole blood

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Background: ADP released from platelet dense granules amplifies responses to other agonists. AR-C69931MX is an intravenous direct platelet ADP receptor (P_{2T}) antagonist currently being investigated in patients with acute coronary syndromes. We compared the effects of this agent and aspirin (ASA) on platelet secretion.

Methods: Whole blood was venesected from healthy human volunteers before and 2.5 hours after ingestion of ASA (600 mg). Hirudin was used as anticoagulant to maintain physiological divalent cation levels. Either saline (control) or AR-C69931MX 100 nM was added to aliquots of blood. P-selectin expression (a marker of alpha granule release) and ^{14}C-5HT release (a marker of dense granule release) were measured, using flow cytometry and ^{14}C-labelled platelets respectively, in response to different agonists, including ADP, TRAP, the thromboxane A2 mimetic U46619, platelet activating factor (PAF) and collagen.

Results: P-selectin median fluorescence; mean data (n = 6) ± SD:

Agonist	Control		AR-C69931MX	
	−ASA	+ASA	−ASA	+ASA
Baseline	8.2 ± 1.1	7.7 ± 1.1		
ADP 30 μM	14.1 ± 2.2	13.6 ± 2.6	9.7 ± 4.2*	9.2 ± 1.1
TRAP 30 μM	100.9 ± 22.8	100.1 ± 14.3	83.0 ± 15.1*	76.4 ± 14.4
U46619 1 μM	67.4 ± 29.3	58.2 ± 17.7	14.8 ± 2.9*	14.3 ± 2.5
PAF 1 μM	14.1 ± 1.7	13.6 ± 1.6	10.6 ± 1.7*	10.7 ± 1.6
Collagen 8 μ/ml	20.6 ± 14.4	9.0 ± 1.5*	9.2 ± 1.4*	8.3 ± 1.0

* $p < 0.05$ for AR-C69931MX or ASA effect (ANOVA for repeated measures)

Data for ^{14}C-5HT release showed an identical pattern of inhibition for both agents with all the agonists shown, with AR-C69931MX inhibiting responses to all the agonists but ASA only inhibiting collagen-induced 5HT-release. There were significant additive effects of both agents on collagen-induced 5HT-release. AR-C69931MX, but not ASA, also inhibited 5HT- and adrenaline-induced release. Concomitant aggregation studies showed the same patterns of inhibition also.

Conclusion: AR-C69931MX is a potent inhibitor of platelet secretion indicating a central role for the P_{2T} receptor in amplification of platelet secretion. In contrast, the effects of ASA are much more limited but the two agents have additive effects on collagen-induced 5HT-release.

P1108 Heparin-induced thrombocytopenia type II: incidence and outcome in 1,000 consecutive medical patients

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Heparin induced thrombocytopenia type II (HIT) is a life-threatening side-effect of heparin therapy. Patients (pts) with HIT may subsequently develop severe arterial and venous thromboembolic complications (TECs). The reported frequency of HIT varies widely and ranges from 0% to 30%. Therefore we carried out a prospective study to evaluate the incidence of HIT in pts admitted to a cardiology department.

Methods: All consecutive pts who received subcutaneous (sc) or intravenous (iv) heparin were included in the study. Platelet counts were obtained on admission and thereafter every second day. Clinical signs of thrombosis were screened daily. HIT was defined as a) a drop of platelet counts more than 50% of baseline values and b) a positive heparin induced platelet activation assay (HIPA) and/or c) clinical signs/proof of arterial and/or venous thromboembolism. Heparin therapy was discontinued in all pts with a significant thrombocytopenia and replaced by danaparoid sodium or lepirudin when necessary and in all serologically proven HIT pts or pts with thrombocytopenia and TECs.

Results: Between 12/96 and 6/97 1000 pts (63.6 ± 32.1 years, 71% male, 270 pts sc heparin, 730 pts iv heparin) were included in this study. 33 pts (3.3%) developed a thrombocytopenia with a nadir of 95 Giga/l on day 10 (3–20). HIPA was positive in 7 of these pts (0.7%). Lowest platelet counts in HIPA positive pts were 55 ± 18 Giga/l on day 12 ± 6.7. 4/7 HIPA positive pts exhibited venous TECs, two of them pulmonary embolism. There was no arterial thrombosis nor limb amputation or even death in HIT pts.

In conclusion: Incidence of HIT in 1000 consecutive medical pts was 0.7%. The low rate of disabling or life-threatening complications and no HIT related death in our patient series may be attributed to the close monitoring of platelet counts and early recognition of this adverse event of heparin therapy.

P1109 Fibrinogen deposition to the postischaemic endothelium initiates platelet adhesion in vivo

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Background: During ischemia-reperfusion (I/R), platelets are among the first cells recruited to the postischemic microvasculature. The molecular mechanisms underlying platelet adhesion during I/R in vivo have not been completely identified. In the present study, we evaluated whether fibrinogen deposition during I/R might promote platelet accumulation to the postischemic microvasculature.

Methods and Results: The deposition of fluorescent 488-fibrinogen and the accumulation of rhodamine 6G-tagged platelets were assessed in vivo in a mouse model of intestinal I/R (90 min/60 min) using video fluorescence microscopy (n = 30). Following ischemia, fibrinogen accumulated in both arterioles and venules within minutes after the onset of reperfusion. The deposition of fibrinogen co-localized with adherent platelets (647 ± 138 and 347 ± 81 platelets/mm^2 in arterioles and venules, respectively). Following pre-treatment with an anti-fibrinogen antibody, platelet adhesion was dramatically reduced (135 ± 79 and 61 ± 22 platelets/mm^2 in arterioles and venules, respectively). Furthermore, platelet adhesion was found to involve Arg-Gly-Asp-recognition sequences, and platelets isolated from a patient with Glanzmann's disease showed decreased interaction with the postischemic endothelium. The latter indicates that the platelet alpha IIb/beta 3 integrin mediates fibrinogen-dependent platelet accumulation in I/R.

Conclusion: In I/R, the deposition of fibrinogen promotes the recruitment of platelets to postischemic microvessels. By initiating platelet adhesion, the association of fibrinogen with the endothelium might represent an important event leading to postischemic reocclusion and remodeling of the microvessels.

P1110 Endogenous nitric oxide and prostaglandins act synergistically to counteract thromboembolic processes in arterioles but not in venules

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In vitro, nitric oxide (NO) and prostacyclin (PGI2) released by endothelial cells act synergistically to inhibit the aggregation of blood platelets. It is unknown whether this synergistic interaction is also effective in vivo and whether this interaction, if any, differs between vessel types.

Methods: in the present study the combined effect of NO and PGI2, on thromboembolism was investigated in an in vivo model. Vessel walls of rabbit mesenteric arterioles and venules (diameter: 18–40 micron) were punctured with a micropipet (tip size: 6 micron). The ensuing thromboembolic reaction was followed by intravital videomicroscopy and the effects of NO and PGI2, alone or in combination, were studied. Besides, the influence of wall shear rate was investigated.

Results: in arterioles, combined inhibition of NO synthase with Ng-nitro-L-arginine (L-NA; 0.1 mM local superfusion) and of cyclooxygenase with aspirin (ASA; 100 mg/kg; i.v.) resulted in a dramatic, significant prolongation of the duration of embolization (duration on the average >600 s) as compared to control (median: 153 s; no L-NA and ASA), or treatment with either L-NA (234 s) or ASA (314 s). In 7 out of the 10 arterioles (70%) of the L-NA + ASA group embolization duration continued for 1 to 3 hours after vessel wall injury. In contrast, in venules combined treatment with L-NA and ASA (209 s) had no additional effect on embolization duration as compared to the effect of L-NA alone (230 s); treatment with ASA had no significant effect at all (122 s; control: 72 s). Only, in the L-NA + ASA arterioles ($r = 0.547$; $p < 0.041$), the duration of embolization positively correlated with wall shear rate.

Conclusion: In conclusion, this study provides evidence for an inhibitory synergistic, (inter)action of endogenous NO and PGI2 in ongoing thromboembolism in arterioles, but not in venules and for a protective effect of NO combined with PGI2 protecting the vessel wall against shear rate induced thromboembolic processes.

P1111 Identification of persistent procoagulant activity in patients with unstable angina by troponin T measurements

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The present study sought to determine the incidence of persistent thrombin generation in patients (pts) with unstable angina (UAP) despite antithrombotic therapy, and to evaluate the correlation of elevated cardiac troponin T (cTnT) with procoagulant activity.

Procoagulant activity was studied in 111 pts with UAP (n = 44), acute myocardial infarction (AMI) (n = 27) and stable angina (n = 40). Pts with UAP were further categorized by plasma cTnT concentrations $\geq$ 0.1 μg/L. All pts with UAP and AMI received antithrombotic therapy consisting of therapeutic doses of unfractionated heparin and acetylsalicylic acid. Quantitative cTnT levels and plasma concentrations of fibrin monomers, prothrombin fragments, thrombin antithrombin III complexes, plasminogen and α-2 antiplasmin were sampled serially within the first 48 hours.

18 of 44 pts (40.9%) with UAP had concentrations of cTnT $\geq$ 0.1 μg/L. In these pts mean plasma concentration of fibrin monomers were significantly higher (5.09 $\pm$ 7.03 vs 2.07 $\pm$ 1.8 μg/l, p = 0.01), and a substantially higher proportion of these pts were found to have elevated levels of fibrin monomers (13 of 18 vs 7 of 26 pts, p = 0.003). The sensitivity, specificity and positive predictive value of cTnT for the identification of increased thrombin activity as reflected by elevated fibrin monomers was 65, 79 and 72%, respectively. In the cTnT positive pts with UAP, a significant correlation (r = 0.74, p < 0.004) was found between levels of cTnT and fibrin monomers and for prothrombin fragments F1 + 2 (r = 0.71, p = 0.046) and thrombin antithrombin III complexes (r = 0.42, p = 0.055). No significant correlation was found with markers of the fibrinolytic system (plasminogen, α-2 antiplasmin).

There is ample evidence that increased thrombin generation may persist despite administration of therapeutic doses of unfractionated heparin and acetylsalicylic acid in pts with UAP. Pts with increased procoagulant activity may be identified by cTnT.

P1112 Cutaneous microcirculation during HELP-LDL-apheresis in cardiac allograft recipients with severe hypercholesterolaemia

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In hypercholesterolemic patients with coronary artery disease impaired cutaneous microcirculation can be reversed by HELP-LDL-apheresis treatment (**H**eparine-induced **E**xtracorporeal **L**DL **P**recipitation; HELP). The study aim was to proof if this is also true for heart transplant patients (HTX) with cardiac allograft vasculopathy (CAV) and hypercholesterolemia.

Patients and Methods: Cutaneous microcirculation was examined before, during, and 60 minutes after a single HELP in 8 HTX (all males, 51 $\pm$ 9 years, 8–36 months post transplantation) with CAV (IVUS, modified Stanford-class IV) and hypercholesterolemia. Mean erythrocyte velocity was measured during continuous registration of perfusion in nail-joint capillaries of patients' left hand by using an intravital capillary microscope.

Results: The mean erythrocyte velocity before HELP was tremendously lower in HTX (0.13 $\pm$ 0.07 mm/s) than in healthy controls (reference range 0.48 $\pm$ 0.72 mm/s). During and after HELP the mean erythrocyte velocity increased significantly, 60 minutes after the end of HELP the mean erythrocyte velocity was still 130.7% of baseline value (0.17 $\pm$ 0.11 mm/s; p < 0.05). Before, during, and after HELP the skin temperature was constantly at 28.1°C.

Conclusions: The mean erythrocyte velocity in nail-joint capillaries of HTX with CAV and hypercholesterolemia is tremendously reduced indicating a markedly impaired cutaneous microcirculation. This impairment can be reversed in part by HELP-LDL-apheresis.

P1113 The influence of thrombin generation on severity and prognosis of congestive heart failure

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Aim: V-HeFT trial revealed that patients with congestive heart failure(CHF) experiencing thromboembolism had a lower left ventricular(LV) function. Thrombin has been shown to enhance atrial natriuretic peptide(ANP) secretion from in vitro ventricular myocytes. Therefore thrombin generation may be related with severity and prognosis of CHF.

Methods: Prothrombin Fragment 1+2 (PT F1+2), a marker of thrombin generation, and von Willebrand factor (vWF), a marker of endothelial dysfunction, were measured in the CHF patients deteriorated by non-ischemic events(n = 30), in the unstable angina patients with normal LV function(n = 28), and in the healthy individuals (n = 17). For the patient groups, blood samples were collected both at admission and at discharge. We investigated the relations of these hemostatic factors and the indices of CHF such as neuroendocrine factors (ANP and brain natriuretic peptide(BNP)), left ventricular mass index (LVMI) and percent fractional shortening (%FS) obtained by echocardiography. Theses patients were prospectively followed for recurrence during subsequent 6-month period after discharge.

Results: In CHF patients, PT F1+2 (nmol/L) increased remarkably at admission (1.5 $\pm$ 0.12) and decreased at discharge(0.95 $\pm$ 0.08). These concentrations were significantly higher than those of healthy individuals (0.77 $\pm$ 0.44). In angina patients, PT F1+2 levels disclosed the similar changes as those of CHF. PT F1+2 significantly correlated with ANP (r = 0.55, p < 0.01) and BNP (r = 0.48, p < 0.01) in CHF at admission, and with ANP (r = 0.54, p < 0.01) and LVMI (r = 0.38, p < 0.05) in CHF at discharge. In contrast, PT F1+2 did not correlate with any indices of CHF in angina patients. Multivariate logistic regression analysis of the variables at discharge indicated significant predictors of recurrence were BNP and PT F1+2 in CHF, however, vWF in angina.

Conclusion: PT F1+2, a marker of thrombin generation, positively correlated with neuroendocrine factors and was revealed to be an independent predictor of recurrence in CHF patients.

P1114 Endocardial damage is common in the left atrial appendage of patients with mitral valve disease: implications for left atrial thrombogensis

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The process of thrombogenesis and sequence of changes in the development and progression of left atrial thrombus in patients with mitral valve (MV) disease has not been precisely described. To document endocardial changes in the left atrial appendage (LAA) and right atrial appendage (RAA) of patients with MV disease and the differences between patients with atrial fibrillation (AF) and sinus rhythm (SR), LAA and RAA biopsies were obtained immediately following commencement of cardiopulmonary bypass from 35 patients (18 males; mean age 61 years) who underwent MV surgery. The specimens were fixed in 2.5% glutaraldehyde solution, stored in phosphate buffer and examined using scanning electron microscopy. The most advanced lesion in each specimen was documented by 2 independent observers. Plasma levels of von Willebrand factor (vWf, marker of endothelial dysfunction) were measured using ELISA on all patients and in age and sex-matched controls. Changes of endothelial cell damage were seen in all LAA and RAA specimens. Advanced changes were more frequently seen in the LAA as compared to the RAA (31% v 6%; p = 0.002) whilst early minimal changes were more frequently seen in the RAA compared to the LAA (23% v 6%). Similarly, LAA of patients in AF had more advanced changes as compared to patients in SR (39% v 27%; p = 0.003). Plasma vWf levels were significantly higher in patients with MV disease compared to controls (132 $\pm$ 33 v 99 $\pm$ 37 IU/dL; p = 0.0004) and in patients with advanced LAA changes compared to earlier changes (149 $\pm$ 34 v 121 $\pm$ 31 IU/dL; p = 0.04).

Conclusions: Endothelial cell damage occurs in all atrial appendages of patients with mitral valve disease, with more advanced changes occurring in the LAA compared to RAA and in patients in AF compared to SR. The raised vWf levels in patients with MV disease and with more advanced endocardial damage is in keeping with the recognised association of vWf with endothelial damage.

P1115 Oxidative stress impairs coronary microcirculatory function in asymptomatic smokers: reversal by vitamin C

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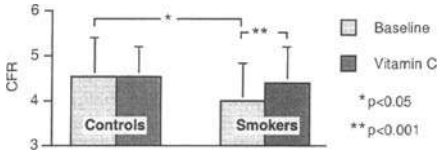
Coronary endothelial function and vasomotion are impaired in smokers without coronary disease and this is thought to be due to increased oxidative stress due to prooxidant substrates present in cigarette smoke. To test this hypothesis, we measured the coronary flow reserve (CFR) in smokers and non smoking controls before and after administration of the anti-oxidant vitamin C.

Methods: Myocardial blood flow (MBF, ml/min/g) at rest (R) and during iv adenosine (Ado; 0.14 mg/kg/min) was measured in 8 healthy non smoking males and 11 age-matched asymptomatic male smokers using positron emission tomography and oxygen-15 labeled water. Both measurements were repeated 15 minutes later following a 10 minutes iv infusion of 3 g vitamin C. CFR was calculated as Ado-/R-MBF.

Results: Heart rate and mean arterial blood pressure were similar in both groups at R and during Ado before and after vitamin C. At baseline, CFR was reduced by 21% in smokers compared to controls, but was normalised after vitamin C.



Conclusions: CFR is decreased in asymptomatic smokers and is improved by Vitamin C. This provides evidence that increased oxidative stress contributes to coronary endothelial dysfunction in smokers.

P1116 Leukocyte-platelet adhesion parallels increased platelet activation in patients with acute coronary syndromes

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To investigate whether leukocyte-platelet adhesion (LPA) is associated with platelet stimulation and consecutive release of inflammatory mediators in acute coronary syndromes, we prospectively examined 30 patients with unstable angina pectoris (UAP) vs. 16 age-matched controls. Flow-cytometry (FACS) with FITC-antibodies against the GPIIb/IIIa receptor (CD41) on monocytes (MONO) and granulocytes (GRANU) was used to identify thrombocytes adherent to these leukocytes at admission (0 d) and 2 d later. The soluble P-selectin adhesion molecule was determined as marker of platelet activation.

	UAP (0 d)	UAP (2 d)	Controls
MONO- (%)	41 ± 5**	19 ± 5	15 ± 3
LPA (MC)	9.1 ± 0.6**	7.7 ± 0.6	6.8 ± 0.4
GRANU- (%)	20 ± 2	8 ± 2	21 ± 3
LPA (MC)	7.6 ± 0.3	6.3 ± 0.4	7.9 ± 2.9
P-selectin (ng/ml)	43 ± 1.6*	36 ± 1.4	36 ± 2.7

Means ± SEM; % = positive/total cells; MC = mean channel value; * = $p < 0.05$; ** = $p < 0.01$.

Monocyte-thrombocyte conjugates are markedly enhanced during the acute phase of UAP compared with granulocyte-thrombocyte conjugates. Increased P-selectin levels prove the associated platelet activation.

Conclusion: Monocyte-platelet adhesion is transiently increased in parallel to platelet activity (as evidenced by P-selectin) during the acute phase of unstable angina and may trigger inflammation-coagulation associated pathway activity.

P1117 Patients with total coronary occlusions have a higher mean platelet volume and glycoprotein IIb/IIIa expression than patients with stenoses

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Background: Successfully dilated coronary occlusions have a higher risk of restenosis compared to non-occlusive stenoses. Patients with elevated mean platelet volume are also at increased risk of restenosis following percutaneous transluminal coronary angioplasty, possibly due to increased platelet aggregability. To investigate whether these two risk factors are related and to identify possible therapeutic targets, we studied mean platelet volume and platelet GPIIb/IIIa expression in patients with stenotic and occlusive coronary disease.

Methods: Mean platelet volume and platelet count were prospectively assessed in 30 patients undergoing successful left coronary system intervention, using an automated full-blood counter (Coulter technique). GPIIb/IIIa expression was assessed by staining platelets with a fluorochrome-conjugated monoclonal antibody directed against the integrin and quantifying the degree of binding by flow cytometry. Blood samples were collected prior to the intervention in EDTA tubes for mean platelet volume and platelet count determination. Citrated tubes were used for flow cytometric studies.

Results: Nineteen patients (15 males, mean age 63) had non-occlusive stenoses (66 ± 5% (mean ± SD) stenosis), 11 patients (4 males, mean age 62) had chronic total occlusions. There was no significant difference between the platelet counts of patients with occlusions (254 ± 19) versus those with stenoses (243 ± 17, P = 0.44). However, there was a significantly higher mean platelet volume in patients with occlusions compared to those with stenoses (mean ± SEM = 9.16 ± 0.3 fL versus 8.4 ± 0.17 fL, $P < 0.05$) and GPIIb/IIIa expression measured as mean channel fluorescence (58.32 ± 4.2 versus 45.7 ± 3, P = 0.02).

Conclusion: Our data show that patients with occlusions have higher mean platelet volume and platelet GPIIb/IIIa expression compared to those with stenoses. These findings provide direct evidence that angiographic indicators of restenosis risk may be related to thrombotic risk and support the use of GPIIb/IIIa antagonists in such patients.

P1118 Evidence for prothrombotic effects of exercise and limited protection by aspirin

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Exercise may activate platelets and leukocytes and promote thrombosis. Effects of aspirin treatment on prothrombotic effects of exercise have not been established.

Methods: 15 healthy males performed exhaustive exercise (bicycle ergometry) without and with one week's pre-treatment with aspirin (500 mg/day). Before and immediately after exercise, platelet aggregability ex vivo was measured by filtragometry and venous blood samples were obtained. Whole blood flow cytometry was used to determine platelet and leukocyte activation and platelet-leukocyte aggregates.

Results: Exercise increased platelet P-selectin expression, and enhanced the expression of CD11b in neutrophils and lymphocytes. Exercise also enhanced platelet and leukocyte activation elicited by thrombin, ADP, PAF, and fMLP in vitro. Consistent with enhanced platelet and leukocyte activation, their interaction was also enhanced, as flow cytometry detected more circulating platelet-platelet and platelet-leukocyte aggregates after exercise ($P < 0.001$ for both). Filtragometry readings were shortened, and the plasma levels of soluble P-selectin, von Willebrand factor, and F1+2 were elevated. Aspirin treatment reduced the urinary excretion of 11-dehydro-thromboxane B2 markedly, decreased P-selectin expression in single platelets at rest ($P < 0.05$), and inhibited fMLP-induced neutrophil CD11b expression. However, aspirin did not influence exercise-induced increases in platelet aggregability, platelet P-selectin expression, leukocyte CD11b expression, or platelet-leukocyte aggregate formation. Furthermore, aspirin failed to counteract exercise-induced elevations of soluble P-selectin, von Willebrand factor, and F1+2.

Conclusions: Exercise induces platelet and leukocyte activation and platelet-leukocyte aggregation in vivo, and increases their responsiveness to in vitro stimulation. Aspirin treatment attenuated certain signs of platelet activity in vivo at rest and fMLP-induced neutrophil activation in vitro, but did not attenuated the prothrombotic effects of exercise.

P1119 Enhanced antiplatelet effects of clopidogrel versus aspirin in patients following myocardial infarction

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To compare the importance of thromboxane A2 (TxA2)- versus adenosine diphosphate (ADP) pathway of platelet inhibition we determined the relative antithrombotic effects of clopidogrel (C), a selective ADP pathway inhibitor, and aspirin (A), a TxA2 pathway inhibitor, alone and in combination.

Methods: Nineteen patients who survived a myocardial infarction were consecutively given 7-days treatments with 100 mg A, 75 mg C combined with 100 mg A, and 75 mg C alone after a washout period. We measured the antithrombotic effects of clopidogrel and/or aspirin on platelet aggregation and platelet P-selectin expression following stimulation with various agonists using light transmission aggregometer and flow cytometry, respectively.

Results:

Platelet activation (P-Selectin)	ADP (10 μM) (%)	Thrombin (0.1 U/l) (%)
A 100	20.1 ± 1.9	54.8 ± 3.2
C 75	7.1 ± 0.7 *	39.9 ± 3.6 *
A 100 + C 75	6.8 ± 0.9 *	36.4 ± 4.9 *
Platelet aggregation	ADP (6 μM) (%)	Collagen (4 μg/ml) (%)
A 100	44.4 ± 3.9	35.7 ± 6.0
C 75	17.6 ± 3.4 *	53.4 ± 7.4
A 100 + C 75	21.9 ± 3.3 *	13.1 ± 2.3 *#

Wilcoxon signed rank: $p < 0.05$; *A vs C or A+C, #C vs A+C

Conclusion: Clopidogrel compared to aspirin produces a reduction of platelet activation except for collagen where the combination of clopidogrel and aspirin is more effective than the monotherapies suggesting additive antiplatelet effects. Ongoing clinical trials are further exploring the benefits of these combined antiplatelet therapies.

P1120 Plasma levels of tissue factor pathway inhibitor are decreased in the coronary sinus of patients with acute myocardial infarction

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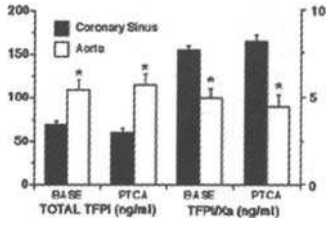
Tissue Factor Pathway Inhibitor (TFPI) is a naturally-occurring inhibitor of the extrinsic coagulation pathway. We have shown that TFPI plasma levels decrease during thrombus formation in a rabbit model of carotid artery stenosis and endothelial injury. To determine whether a similar decrease in plasma TFPI also occurs in patients with acute myocardial infarction (MI), 10 patients undergoing primary PTCA for an acute MI were included in the study. Blood samples were obtained from the coronary sinus (CS) and the ascending aorta at baseline and after balloon dilation, placed in chilled test tubes containing sodium citrate, immediately centrifuged, and stored at −70°C. Total TFPI plasma levels, as well as the complex TFPI/factor Xa, an index of factor Xa generation, were measured using ELISA kits commercially available (American Diagnostica). At baseline, all patients had a complete occlusion of either the LAD (n = 6) or the CX (n = 4) coronary artery (TIMI flow 0), and showed antegrade TIMI flow 3 after PTCA. A significant decrease in total TFPI plasma levels was observed in the CS as compared to those measured in the aorta, both at baseline and after PTCA (figure; $p < 0.05$ vs CS). In contrast, plasma TFPI/Xa levels were significantly higher in the CS than in the aorta, indicating active generation of factor Xa at the site of thrombus formation (figure).



We conclude that: 1) In patients with acute MI an increased generation of factor Xa occurs, presumably via activation of tissue factor-dependent coagulation cascade; 2) Plasma TFPI levels are decreased across the coronary circulation, indicating consumption of TFPI at the site of thrombus formation; 3) TFPI plays an important pathophysiological role as a modulator of tissue factor-dependent coagulation in patients with MI.

P1121 Regulation of ADP- or thrombin-induced platelet aggregation via AT_1 receptors

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Background: The AT_1 receptor present in heart, liver, kidney, brain, platelet and in most of vascular tissues, is a highly potent regulator of blood pressure. AT_1 receptors trigger the activation of phospholipase A_2, a key enzyme in prostanoid formation.

Methods: We investigated the AT_1 receptor inhibition (losartan) of ADP or thrombin-induced platelet aggregation and intracellular Ca^{2+} in washed platelets or in platelet rich plasma of dogs and human volunteers. Calcium was measured with FURA-1 and platelet aggregation by PACKS4 (from Helena Diagnostika Instruments).

Results: AT_1 receptor inhibition decreases ADP or thrombin induced aggregation in a dose dependent manner as shown in the table (Δ% values are mean ± SEM, n = 5, all are significantly different from control, $p < 0.05$).

Losartan (M)	10^{-6}	10^{-5}	10^{-4}
Thrombin (0.1 U/ml)	−20 ± 5	−48 ± 10	−80 ± 5
ADP (3 μM)	−37 ± 5	−54 ± 13	−70 ± 9

AT_1 receptor inhibition abolishes thrombin (0.1 U/ml) induced intracellular calcium concentration (basal: 96 ± 6 nM, thrombin: 702 ± 23 nM) at a comparable magnitude as shown for the platelet aggregation.

Conclusions: AT_1 receptor inhibition decreases intracellular free calcium, impairs thereby (e.g. inflammatory) prostanoid formation and aggregation and finally reduces the risk for enhanced thrombosis.

P1122 Renin-angiotensin system and its pathophysiological role in human monocytes and macrophages

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Increased expression of angiotensin-converting enzyme (ACE) by macrophages has been shown in human coronary atherosclerotic lesions, suggesting the presence of renin-angiotensin system (RAS) in macrophages. In the present study, we investigated the expression and regulation of angiotensin II type 1 receptor (AT1), type 2 receptor (AT2) and ACE in human monocytes and macrophages, and attempted to elucidate its pathophysiological role.

Methods: Human monocytes were obtained from peripheral blood of healthy volunteers by gradient centrifugation and adherent method. Monocyte-derived-macrophages were prepared by culture of 7 days. The levels of mRNA for AT1, AT2, ACE, tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) were assessed by transcriptase polymerase chain reaction. The levels of TF and PAI-1 in culture medium were measured by ELISA.

Results: Human monocytes expressed AT1, AT2, and ACE mRNAs. The levels of mRNA for AT1 and AT2 decreased in macrophages compared with monocytes, whereas macrophages expressed increased levels of ACE mRNA. Monocyte chemoattractant protein-1 or oxidized LDL decreased the AT1 and AT2 mRNA levels and increased the ACE mRNA levels in monocytes after 18 hours of culture. To determine the pathophysiological role of RAS in these cells, an ACE inhibitor (captopril, CPT) was added to cultured monocytes. CPT (10^{-9} ~ $^{-8}$ M) decreased significantly the protein levels in the medium of TF and PAI-1 by 51% (n = 4, $P < 0.05$) and 17% (n = 7, $P < 0.05$) after 3 days of culture. Similar reductions by CPT (TF; 34%, n = 6, $P < 0.05$, PAI-1; 17%, n = 8, $P < 0.01$) were observed after 7 days of culture. In addition, CPT reduced the levels of mRNA for TF and PAI-1 after 1 day of culture.

In conclusion, our results suggest that RAS of monocytes and macrophages may play a role in atherogenesis and procoagulant state of plaques in acute coronary syndromes.

P1123 Local delivery of a new bispecific antibody to improve retention of glycoprotein IIb/IIIa receptor antagonist at the angioplasty site

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Targeting of an anti-GPIIb/IIIa antibody to the angioplasty site might improve its local concentration and retention following local delivery, which may optimise its effects on platelets and SMCs without significant systemic side-effects. In this experiment we used an anti-tissue factor antibody as the targeting agent. Tissue factor is a membrane-bound polypeptide normally not exposed to the blood stream, but is expressed after balloon injury at the angioplasty site.

Methods: A new bispecific F(ab')2 was contructed combining the antigen binding sites of two murine anti-rabbit IgGs, which are specific to the platelet GPIIb/IIIa receptor and tissue factor, respectively. Segments of rabbit aorta were removed and balloon dilatation with an angioplasty balloon (8 atm for 60 s, three times) performed. The segments were then mounted in a perfusion circuit (0.9% Saline, 37°C, flow-rate 20 ml/min). Radio-labelled bispecific F(ab')2 or anti-GPIIb/IIIa antibody as a control was delivered through a microporous infusion catheter (Cordis Corporation, US). The radioactivity of the segments was measured in a gamma-counter after 1 ml Saline flushing and at pre-set time intervals. To compare the relative radioactivity the initial gamma-counter result of each segment was defined as 100% and subsequent counts converted.

Results: The overall delivery efficiency was low for both groups (<2%), but the retention of the bispecific F(ab')2 was significantly greater than that of the anti-GPIIb/IIIa IgG (see table).

Time interval	Bispecific Ab	Anti-GPIIb/IIIa Ab	p value (t-test)
2 hours	28.2	16.2	0.03
3 hours	23.6	14.3	0.02
12 hours	21.8	10.6	0.05

Percentage of retention at the damaged vessel wall after local delivery (N = 8)

Conclusion: These results support the concept of targeting damaged vessel wall to increase local retention of GPIIb/IIIa antagonists at the angioplasty site.

P1124 Tissue factor mRNA is up-regulated in rabbit smooth muscle cells stimulated with activated platelets

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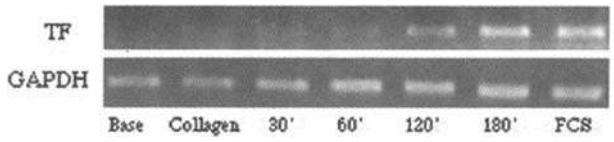
Tissue Factor (TF)-induced activation of the coagulation plays a key role in acute coronary thrombosis. We have recently demonstrated an increase in TF expression in the media of rabbit carotid arteries with recurrent thrombosis. To determine the role of platelet-derived mediators in this phenomenon, cultured rabbit smooth muscle cells (SMCs) were stimulated with activated platelets and specific TF mRNA expression was measured by RT PCR. Rabbit SMCs from thoracic aorta were grown in DMEM + 10% fetal calf serum (FCS) and made quiescent by FCS withdrawal. Human platelet rich plasma (300,000/μl) was placed into transwell cylinders, at the bottom of which a microporous membrane allowed only the passage of platelet-derived mediators. Transwells were placed into SMCs culture wells and platelets were stimulated with collagen. Activated platelets were removed after 30 min and SMCs were processed for total RNA isolation at baseline (no stimulation), and after 30, 60, 120, and 180 min following stimulation. Two μg of total RNA was retrotrascribed and specific TF mRNA was amplified by PCR. Housekeeping GAPDH mRNA was also simultaneously amplified as internal control. PCR products were run on 1% ethidium bromide-agarose gel. A progressive increase in TF mRNA, peaking at 180 min, was evident in SMCs stimulated with activated platelets with respect to baseline (figure).



Positive control included SMCs stimulated with FCS. Collagen per se had no effects on SMCs TF mRNA levels, whereas no differences were seen in GAPDH mRNA levels among various time points. In conclusion, activated platelets induce TF mRNA expression in cultured SMCs; in vivo, this platelet-induced up-regulation of TF may be responsible for sustaining thrombus formation following the initial thrombogenic stimulus.

STROKE DIAGNOSIS, THERAPY AND CONSEQUENCES

P1125 Morphological evaluation of plaques of the aortic arch in patients with acute ischaemic stroke. the diagnostic impact of transoesophageal echocardiography

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Background: The presence of large atherosclerotic plaques in the aortic arch has been shown to be an independent risk factor for ischemic stroke (IS). The importance of the plaque morphology as an independent risk factor for ischemic strokes has not been evaluated yet.

Methods: We performed transesophageal echocardiography in 62 patients (P) with acute ischemic stroke (age: >60 years) and in 62 age and sex matched subjects (C). The following plaque classification was used: small (thickness of 2–3 mm); large and uncomplicated (thickness > 4 mm; no detection of plaque ulceration and mobility) and large and complex (detection of plaque ulceration and mobility).

Results: Plaques could be proved in 69% (n = 43) of the patient group (P) and 27% of the control group ($p < 0.001$). Complex plaques were more common in the patient group than in the control group (32.4% versus 2.6%; $p < 0.001$). Furthermore there was a higher frequency of uncomplicated plaques in the patient group compared to the control group (23.7% vs 12.3%). Referring to small plaques no significant differences could be detected. Multiple logistic regression analysis showed that complex plaque morphology is the strongest independent risk factor of acute ischemic stroke (odds ratio: 16.8). Large and uncomplicated plaques represent a mild elevated risk (odds ratio: 2.4). No risk elevation could be shown for small plaques in both groups. All complex plaques were larger than 4 mm in diameter. Furthermore 65% of the large plaques showed complex morphology.

Conclusion: Transesophageal echocardiography offers the opportunity of morphological evaluation of atherosclerotic plaques within the aortic arch. Complex morphology seems to be a stronger risk factor for ischemic stroke than thickness. Diagnostic importance has been shown by multiple logistic regression analysis proving complex plaque morphology as the strongest independent risk factor of acute cerebral ischemia.

P1126 Antioxidant effect of oral dipyridamole during cerebral ischaemia associated with human carotid endarterectomy

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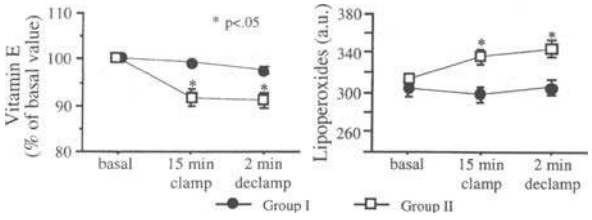
Acute cerebral hypoperfusion/reperfusion may pose an oxidative stress on human brain, detectable through a decrease in antioxidant physiologic systems (such as vitamin E) and an increase of oxyradical species (such as lipoperoxides). Dipyridamole has antioxidant properties of uncertain clinical relevance.

In order to clarify an antioxidant effect of dipyridamole in vivo in a model of controlled cerebral hypoperfusion, 21 patients (65 ± 10 years, 11 males) undergoing carotid endarterectomy were allocated in 2 groups (group I = 10 with dipyridamole 200 mg p.o. 3–4 h before surgery, group II = 11 with placebo) in a double-blind placebo controlled randomized design. Plasma vitamin E and – in a subset of 12 patients – lipoperoxides were assayed from ipsilateral jugular bulb before, at 15′ of clamp and 2′ after declamp. Dipyridamole treated (Group I) patients showed lower increases in lipoperoxides and less depletion of vitamin E plasma concentration versus untreated (Group II) patients.



In conclusion, cerebral oxidative stress associated with human carotid thromboendarterectomy can be attenuated by pre-treatment with oral dipyridamole.

P1127 Influence of acute brain infarction on sympathovagal balance

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Cardiovascular and cerebral functions are strongly related (Neurocardiology). Cerebrovascular diseases frequently cause a cardiovascular autonomic dysregulation. Aim of the study was to evaluate prospectively the sympathovagal balance during the acute phase of brain infarction in relation to infarct localization.

Methods: In the present study we evaluated the autonomic nervous system activity, using heart rate variability (HRV) indices, in time domain analysis, during 24 hour Holter recordings (Marquette 8000 V. 5.8) in 22 consecutive pts (12 M, 10 F, mean age 65 ± 8.5 year) with hemispheric brain infarction. 15 age and sex matched healthy subjects (HS), constituted the control group. 10 pts had right sided (RS) and 12 pts had left sided (LS) lesions. The HRV indices studied were: mean NN, SDNN, r-MSSD and pNN50. Pts with a history of symptoms suggesting cardiac or vascular disease or with a history of neurological disease, diabetes or other endocrinological disorders, as well as those with cardiac arrhythmias, were excluded from the study. The above referenced indices were evaluated during the first 24 hours from symptoms' onset. All pts underwent CT-scan during their hospitalization. The non-parametric anova Kruskal-Wallis and Scheffe test, were used for the statistical analysis.

Results:

n	Mean NN (ms)	SDNN (ms)	r-MSSD (ms)	pNN50 (%)
RS (n = 10)	686.2 ± 88.6	47.14 ± 3.89	16.14 ± 4.56	8.3 ± 4.2
LS (n = 12)	1009 ± 130	135 ± 18.24	42.7 ± 6.44	13.45 ± 7.95
HS (n = 15)	890 ± 100	152 ± 10.4	49.5 ± 2.25	21.7 ± 4.36

RS group is highly statistically significant at a = 0.01 compared to the LS and HS groups (all p-values were equal to 0.000 < 0.01). The difference of the means between LS and HS group is weakly statistically significant at a = 0.1.

Conclusions: These findings indicate that there is an autonomic dysregulation after ischemic infarction of either cerebral hemisphere. However, right sided lesions cause a greater parasympathetic hyponfunction compared to the left-sided lesions. A possible explanation is that brain lesion itself, damages structures regulating neurohumoral functions.

P1128 Hypo-osmolar, but not hyper-osmolar fluid intake reduces the risk of stroke: findings from the Adventist Health Study

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Objective: To investigate the effect of fluid intake on the risk of stroke.

Methods: In 1976, a total of 34,198 white, non-hispanic California Seventh-day Adventists were enrolled in a cohort study and followed for 6 years. Information on diet, water and other fluid intake was assessed at baseline. The risk of fatal stroke was analyzed according to fluid intake in persons with prevalent CHD, stroke or diabetes using Cox Proportional Hazards Model.

Results: A total of 3,809 reported having CHD, stroke or diabetes at baseline and among them, 184 persons died of stroke during follow-up. After adjusting for age, sex, hypertension, smoking, BMI and education, the risk of fatal stroke showed an inverse dose-response relationship to reported daily intake of water and hypo-osmolar fluids (see Table 1). No association was found with intake of hyper-osmolar fluids.

Table 1

Water		Hypo-osmolar		Hyper-osmolar	
Intake*	RR (95% CI)	Intake*	RR (95% CI)	Intake*	RR (95% CI)
<2	1.00	<2	1.00	<2	1.00
3–4	0.67 (0.42–1.08)	2–5.5	0.59 (0.32–1.10)	2–4	1.31 (0.82–2.09)
5+	0.47 (0.30–0.76)	5.5+	0.42 (0.22–0.76)	4+	1.24 (0.71–2.16)
	p (trend) = 0.002		p (trend) = 0.005		p (trend) = 0.41

*Glasses/day

Conclusion: Our data suggest that good hydration may be important in preventing stroke among those who already have signs of CVD or diabetes. Water and hypo-osmolar fluids, but not hyper-osmolar fluids, are associated with decreased risk. Further studies are needed to investigate the effect of intake of different fluids on risk of incident stroke.

P1129 Retrograde and rotational flow in the thoracic aorta in patients with systemic emboli: a transoesophageal echocardiographic evaluation of mobile plaque motion

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Blood flow in the thoracic aorta is complex and incompletely characterized. Mobile aortic plaques (MAP), moving freely back and forth with the pulsatile aortic flow, in fact represent natural tracers which reflect the flow pattern itself. The purpose of the present study was to use MAP motion on transesophageal echocardiography (TEE) to characterize flow patterns in the atheromatotic thoracic aorta of elderly patients with stroke and systemic emboli.

Methods. The study group was recruited from 211 patients referred for TEE to evaluate recent embolism. Among them, 17 patients (11 men, 6 women; mean age 66.8 ± 7.7 years; 12 with cerebrovascular and 5 with peripheral emboli) with MAP of ≥3 mm length formed the study group. The longest amplitudes of three spatial components of mobile lesion motions were measured: x (*antegrade/retrograde, A/R*), y (*up/down, U/D*) and z (*right/left, R/L*).

Results. A total of 27 mobile lesions were detected: 3 (one patient) in the ascending aorta, 11 (8 patients) in the arch and 13 (8 patients) in the descending aorta. The length of mobile plaque components ranged from 3 to 13 mm; amplitudes of A/R, U/D, R/L and retrograde flow (RF) motions ranged (respectively) from 3 to 26 mm, from 1 to 16 mm, from 1 to 17 mm, and from 1 to 13 mm. Rotational components in MAP motions were detected in all patients. Systolic rotation was clockwise in 5 (29.4%) of them, counterclockwise in 4 (23.5%), incomplete (semicircle) in 5 (29.4%) and alternate clockwise/counterclockwise in 3 (17.6%). Diastolic rotation was clockwise in 3 (17.6%), counterclockwise in 6 (35.3%) and incomplete (semicircle) in 8 (47.1%) patients. In addition, periodically chaotic irregular multidirectional MAP motions were registered in all patients. There were 16 multiple MAP in 6 patients: in all these cases simultaneous rotations of MAP in different directions (highly suggestive for the presence of multiple vortices) were found.

Conclusions. Retrograde and rotational blood flow in the thoracic aorta exist in all patients with systemic emboli and mobile protruding aortic atheromas. Therefore, retrograde cerebral embolism from distal aortic plaques is theoretically possible. It may have significant implications in the study of pathogenesis of embolic events.

P1130 Transcatheter closure of 100 patent foramina ovalia in patients with unexplained stroke and suspected paradoxical embolism: a comparison of five different devices

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Background: Interventional closure of patent foramen ovale (PFO) has been proposed to prevent recurrence of presumed paradoxical embolism in patients with unexplained stroke. Over the past years, several devices for transcatheter PFO-occlusion have been developed.

Patients: Between 08/94 and 01/99 transcatheter closure was attempted in 100 patients aged 17–77 years (mean ± SD: 46 ± 14). The PFOs were suspected to have caused between one and four paradoxical embolic events. In all cases, right-to-left-shunt through the PFO was proven by transoesophageal contrast echocardiography and other embolic sources were excluded. The PFO-size measured by balloon-passage ranged from 6–24 mm (12 ± 3).

Results: PFO-closure was successfully performed in 23/26 patients with SIDERIS-Buttoned-Devices, in 11/11 patients with the ASDOS-double-umbrella, in 20/20 patients with ANGEL-WINGS-device, in 20/20 patients with the Cardio-Seal-occluder and in 23/23 with the PFO-star. The primary overall success rate was 97%.

During follow-up one SIDERIS-Device was surgically explanted because of partial unbuttoning and two patients with an incomplete defect-closure suffered recurrent embolism. Asymptomatic Arm-fractures occurred in 10 cases (at least one per device), thrombus-formation was diagnosed after implantation of one ASDOS-, two ANGEL-WINGS- and one Cardio-Seal-system.

During 172 patient-years only two patients, treated with the SIDERIS-Buttoned-Device, suffered a recurrent embolic event. After use of the ANGEL-WINGS-, Cardio-Seal- and PFO-star-system no severe complications were observed.

Conclusion: All systems are suitable for transcatheter PFO-occlusion. In comparison to the older devices the ANGEL-WINGS-, the Cardio-Seal- and the PFO-star-system seem to be more stable and reliable in preventing recurrent embolism.

P1131 Takayasu's arteritis as risk factor for early development of vascular atherosclerosis

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Lipid metabolism disturbances have been described in some inflammatory diseases. In patients with acute infections hypertriglyceridemia has been found but in chronical inflammations lipid abnormalities remain poorly known.

This study is based on an analysis of data obtained during long-term observation on 38 patients (pts) with Takayasu's Arteritis (TA) (37 female, 1 male; mean age 36 + 4.5 years).

The duration of the disease from the moment of establishing diagnosis of TA is from 1 to 25 years. A diagnosis of TA was established by the Criteria of the American College of Rheumatology 1990 and confirmed by angiography.

28 (74%) pts of TA have arterial hypertension (AH). 7 pts received glucocorticoid therapy in their anamnesis but not at the period of this examination, 7 pts have received b-blokers, 1 pt has hypothyroidism, 2 pts have diabetics.

Increasing of levels of total cholesterol (Tchol) in the range of 5.2–6.4 mmol/l was discovered in 18 (47%) pts; >6.5 mmol/l in 9 (23%); only 11 (30%) of TA had normal levels of Tchol. Increasing of levels of triglycerids >2 mmol/l is observed only in 2 pts. It is important to note, that we didn't observe any lipid abnormality in patients at the initial stage of TA. However, increasing levels of Tchol were discovered in pts with long duration of disease (>10 years) of TA with high activity of inflammation processes (ESR > 25 mm per hour) in long time period.

In conclusion, the findings suggest that lipid abnormalities in TA with vascular inflammation may lead to an early development of atherosclerotic processes of main vessels.

P1132 Regulation of angiotensin II AT2 receptor gene expression after stroke in rats

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Regulation of angiotensin II AT2 receptor gene expression after stroke in rats.

Previously, we reported that both AT1 and AT2 receptor gene expression was transiently increased after myocardial infarction (MI). The increased angiotensin II (ANG II) receptor gene expression suggests that ANG II is involved in the process of cardiac remodeling after MI. It is still far being understood whether or not ANG II could contribute any beneficial effects after stroke. Therefore, it would be useful to know how ANG II receptor gene expression is regulated in stroke. We used a rat model of occlusion of the middle cerebral artery (MCA) in male Wistar rats. The MCA was occluded by electro-cauterization and the artery was then cut to complete the permanent occlusion. Rats (n = 5) were sacrificed 1 day and 3 days after surgery. Total RNA from infarct and non-infarct cortex of the brain was extracted and reverse transcribed. cDNA was amplified by the polymerase chain reaction (PCR) with specific primers of angiotensin-converting enzyme (ACE), AT1 and AT2 receptor. PCR products were analyzed and quantified by the Vilber Lourmat Imaging system. Both ACE and AT1 receptor gene expression was very weakly expressed and there was no significant difference between infarct and non-infarct cortex. Interestingly, AT2 receptor gene expression was increased in the infarct cortex 2.65-fold (1 day) and 1.72-fold (3 days) after stroke, respectively. Our results demonstrated that the up-regulation of AT2 receptor may serve as an enhancer of the tissue repairing after stroke.

MYOCARDIAL FUNCTION AND HEART FAILURE

P1133 Does high-density lipoprotein act as an endotoxin-binding protein with a potential regulatory impact for immune activation in chronic heart failure?

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Background: Tumor necrosis factor-alpha (TNF-alpha) and other cytokines are elevated in severe chronic heart failure (CHF). It has been reported in animal experiments that blood lipids, such as high-density lipoprotein (HDL), have the ability to act as endotoxin (LPS) binding proteins, thereby influencing the LPS-mediated release of TNF-alpha and other cytokines. Recently, we have shown that concentrations of LPS are elevated in decompensated CHF patients.

Methods and Results: We studied 26 patients with CHF (age 67 ± 2 y, NYHA 2.9 ± 0.2, LVEF 32 ± 4%, all mean ± SEM) and 7 healthy control subjects (age 71 ± 2 y). Venous blood samples were taken to analyse plasma concentrations of LPS (LAL test) and total TNF-alpha (high sensitivity Quantikine kit, R&D Systems). Additionally, we measured serum LDL and HDL levels as well as liver function (ASAT, total protein and albumin) and kidney function (creatinine, urea, all routine hospital techniques). In CHF patients, concentrations of LPS and TNF-alpha were higher (0.47 ± 0.03 EU/ml and 6.0 ± 0.7 pg/mL, respectively) than in healthy volunteers (0.33 ± 0.03 EU/ml, $p < 0.05$ and 3.4 ± 0.5 pg/ml, $p = 0.07$, respectively), whereas HDL and LDL levels were lower ($p = 0.008$ and $p = 0.06$). LPS correlated positively with TNF-alpha ($r = 0.71$, $p < 0.0001$) and inversely with HDL ($r = -0.54$, $p = 0.006$). The degree of immune activation (TNF-alpha) was inversely related to levels of HDL ($r = -0.37$, $p = 0.046$). CHF patients with the most abnormal LPS values (mean of controls + 2 SD) had the lowest HDL levels (1.3 ± 0.1 vs 1.6 ± 0.1 mmol/l, $p = 0.04$). These relationships were all independent of liver and kidney function parameters.

Conclusion: Our data suggest that in CHF patients, high concentrations of LPS are related to decreased HDL levels and increased concentrations of TNF-alpha. This finding supports the hypothesis of an involvement of lipoproteins, particularly HDL, in the modulation of immune activation and subsequent cytokine release in CHF. Thus, HDL may have beneficial effects other than protecting against atherosclerotic lesions.

P1134 Congestive heart failure does not affect nuclear DNA content in human cardiac myocytes

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It has repeatedly been shown that DNA synthesis occurs in adult ventricular myocytes and quantitative studies have demonstrated an increased number of nuclei and mitotic figures in hypertrophied hearts in humans. However, since DNA ploidy and multinucleation are present in cardiac myocytes, whether activation of DNA synthetic machinery leads to cell proliferation or DNA accumulation in each nucleus remains to be determined. Thus, a DNA cytophotometric study was performed on enzymatically dissociated cardiac myocytes collected at autopsy from 9 individuals who died for causes different from cardiovascular diseases and from two groups of patients with congestive heart failure (CHF). The first group consisted of 5 females and 4 males with severe cardiac hypertrophy (54%, $p < 0.001$) and the second of 11 males affected by hypertrophic ischemic cardiomyopathy (39%, $p < 0.001$) with large infarcts documented by the presence of scarred tissue in the left ventricle and severe coronarosclerosis. The average age was similar among the three groups ranging from 37 to 88 years. The mean values of the different classes of ploidy were obtained for mononucleated and binucleated myocytes of the left (LV) and right ventricles (RV) and in the interventricular septum (IS). A minimum of 350 to a maximum of 600 myocytes in each sample were evaluated and the amount of DNA present in each nucleus determined with an image analyzer after Feulgen reaction. The system was calibrated with chicken erythrocytes collected and stained on each slide together with ventricular myocytes. Different fractions of nuclei with 2C, 4C, 6C, 8C and >8C DNA content were found in isolated cells from normal and pathologic hearts. Compared to controls, DNA content per nucleus did not change in mononucleated and binucleated myocytes of LV and IS of ischemic and hypertrophied hearts. In contrast, mono- and binucleated myocytes of RV in ischemic cardiomyopathies were characterized by a 2-fold increase in diploid class and a 50% decrease in the fractions of 8C and >8C. No statistical significant correlation was seen between the different classes of ploidy in myocytes of both ventricles and corresponding myocardial weights. The percent of mononucleated (76 ± 9%) and binucleated myocytes (24 ± 9%) did not vary among the three groups of hearts. In conclusion, since DNA content per nucleus did not increase in cardiac myocytes of LV and IS of the hypertrophied and ischemic failing human hearts, DNA synthesis has to be regarded as an index of cell cycle progression and myocyte proliferation.

P1135 Early detection of anthracycline-induced cardiotoxicity in asymptomatic patients with normal left ventricular systolic function: autonomic versus echocardiographic parameters

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Backgrounds: Anthracyclines are widely used in patients with breast cancer, but bear the risk of inducing left ventricular (LV) dysfunction. Although both diastolic and systolic dysfunction have been well recognised, there are indications that autonomic abnormalities precede these changes and thus are a more sensitive marker for monitoring cardiotoxicity. Heart rate variability (HRV) analysis is a reliable tool to assess autonomic tone.

Methods: Autonomic function was compared with LV diastolic function in twenty asymptomatic females with normal systolic function (left ventricular ejection fraction (LVEF) > 0.50), treated for breast cancer with high-dose anthracycline-based chemotherapy, and twenty age-matched healthy females. LV diastolic function was echocardiographically assessed by measuring early peak flow velocity/atrial peak flow velocity ratio, isovolumetric relaxation time and deceleration time. HRV analysis was assessed for time domain and frequency domain parameters.

Results: The mean (SD) age of the patients was 45 (7) years and the mean (SD) LVEF 0.59 (0.06). The mean (SD) time interval after the end of chemotherapy was 29 (27) months. One or more diastolic parameters were abnormal in 50% of the patients. HRV frequency parameters were abnormal in 85% of patients. Mean values of both time domain and frequency domain parameters were decreased ($p < 0.05$), in particular the parasympathetic indexes.

Conclusions: Autonomic impairment occurs in a large proportion of asymptomatic patients with normal systolic LV function after high-dose anthracycline-based chemotherapy. Especially HRV analysis may potentially be a sensitive tool to identify first signs of cardiotoxicity in these patients.

P1136 Soluble and surface-bound P-selectin reveal heightened platelet activity in patients with decompensated heart failure: is aspirin therapy enough?

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Selectins may participate in the pathogenesis of congestive heart failure (CHF) by modulating platelet – leukocyte – endothelial interactions in the deteriorating myocardium. P-selectin is an important marker of platelet and endothelial activation and may be up-regulated in patients with CHF. However, no data are available on the simultaneous determination of plasma levels and platelet expression of P-selectin in patients with CHF. We sought to prospectively compare platelet and soluble P-selectin in patients with CHF and in healthy controls.

Methods: Matched soluble levels by ELISA, and platelet-bound expression by whole blood flow cytometry of P-selectin were determined in 34 patients with decompensated CHF and compared with fourteen healthy controls. Fifteen patients were aspirin-free and nineteen patients were using aspirin (81–500 mg/daily).

Results: Patients with CHF exhibited significantly elevated soluble P-selectin (189.5 ± 68.0 ng/ml, $p = 0.014$) and more than two-fold increased expression of platelet-bound P-selectin (9.31 ± 4.12% positive platelets, $p = 0.027$) compared to the P-selectin profile in controls (102.6 ± 29.0 ng/ml plasma, and 4.06 ± 1.21% positive platelets). Aspirin therapy did not affect the P-selectin profile in patients with CHF.

In conclusion, despite antecedent aspirin therapy and interindividual variability of the P-selectin profile, soluble and platelet P-selectin were elevated in the majority of patients with severe CHF, suggesting persistent platelet activation. The present data provide evidence that more potent adjunctive antiplatelet regimens deserve further study in the heart failure population.

P1137 Oxidative stress is less in non-ischaemic chronic heart failure

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Increased oxidative stress may play an important role in the pathophysiology of chronic heart failure (CHF). Coronary artery disease (CAD) is also associated with increased oxidative stress. In this study, we compared oxidative stress assessed by plasma lipid-derived free radicals in patients with CHF due to underlying CAD versus patients with CHF due to dilated cardiomyopathy (DCM).

Methods: The study group consisted of 30 patients with NYHA class II–IV symptoms of CHF, LV ejection fractions < 35% on optimal medical therapy, 15 of whom had underlying CAD, and 10 age and gender matched healthy controls. The patients were matched for age and NYHA class. Lipid-derived free radicals from plasma samples were measured by electron paramagnetic resonance (EPR) spectroscopy using the spin trap α-phenyl tert-butylnitrone with peak spectral heights recorded in arbitrary units (u).

Results: (Data expressed as mean ± SD). The mean magnitude of EPR spectra obtained from the DCM group was significantly greater than controls (0.33 ± 0.18 u vs. 0.21 ± 0.03 u, $p < 0.05$). Plasma lipid-derived free radical levels were greater in the CHF patient group with underlying CAD than both the control group and those patients with DCM (0.54 ± 0.28 u vs. 0.21 ± 0.03 u, $p < 0.05$ and vs. 0.33 ± 0.18 u, $p < 0.05$ respectively).

Conclusion: This study has demonstrated that free radical levels in venous blood are elevated in CHF patients regardless of the underlying aetiology. We have also shown that CHF patients with underlying CAD have higher levels of oxidative stress than those with DCM confirming the pro-oxidant nature of atherosclerosis. Further studies are now needed to establish the main source of free radicals in CHF, the pathophysiological mechanisms underlying this process and the potential therapeutic role of antioxidants.

P1138 Lung water content and alveolar-capillary diffusion impairment in severe heart failure

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We investigated the relationship between lung water (LW) and alveolar-capillary diffusion for carbon monoxide (DLco) in severe HF. LW, lung volumes and DLco were evaluated in 15 normal subjects and in 28 patients with severe HF (NYHA III–IV), in the latters before and after fluid removal by extracorporeal ultrafiltration (UF, 3973 ± 2205 ml; weight reduction = 5.8 ± 3.7 kg). In particular, we measured vital capacity (VC), alveolar volume (Va), LW (single breath expiratory decay of CH4, C2H2 and CO), DLco and its two components: diffusing membrane resistance (Dm) and capillary volume content (Vc).

	Controls	Before UF	After UF
VC (L)	4.7 ± 1	$2.1 \pm 0.7^{*}$	$2.5 \pm 0.7^{*\#}$
Va (L)	6.3 ± 1.3	$4.1 \pm 1.6^{*}$	$4.6 \pm 1.4^{*\#}$
LW (ml)	420 ± 13	$640 \pm 180^{*}$	$550 \pm 170^{*\#}$
DLco (ml/min/mmHg)	29 ± 5	$17 \pm 4^{*}$	$17 \pm 5^{*}$
Dm (ml/min/mmHg)	47 ± 11	$23 \pm 7^{*}$	$25 \pm 8^{*}$
Vc (ml)	102 ± 20	100 ± 38	87 ± 39
DLco/Va	4.5 ± 1	4.3 ± 0.8	$3.8 \pm 1^{\#}$
Dm/Va	7.1 ± 3	$6.0 \pm 2^{*}$	6.8 ± 2

Data are mean ± SD. * = $p < 0.01$ vs. Controls; # = $p < 0.01$ vs. Before UF.

Conclusions. In severe HF: 1) LW increase is associated with reduction in lung volumes (VC, Va) and DLco (due to its component Dm); 2) DLco, but not Dm, is normal when related to Va. After UF, LW decrease is associated with lung volumes increase but with no change in DLco. Several hypothesis may account for this finding: a) LW removal is from the perivascular, peribronchial and alveolar spaces, rather than from the alveolar-capillary membrane; b) the tendency of Vc to reduce after UF counterbalances the effect of lung volume and Dm increases on DLco.

P1139 Clinical correlates of granulocyte-macrophage colony-stimulating factor in advanced heart failure

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Background: It has been reported that cytokine activation is implicated in the pathophysiology of congestive heart failure (CHF). Granulocyte – macrophage colony – stimulating factor (GM-CSF) is an inflammatory mediator which stimulates a range of functional activities of monocytes, including regulation of monocyte adhesion and induction of cytokine production. We investigated whether serum GM-CSF is increased in advanced CHF, and we sought to determine the relationship between serum levels of GM-CSF and other clinical or neurohormonal parameters in CHF patients.

Methods: Serum GM-CSF and soluble intercellular adhesion molecule-1 (sICAM-1) were measured in 23 patients with advanced CHF (LVEF: 25 ± 4%; NYHA III: 13/23, NYHA IV: 10/23; Ischemic Heart Failure: 15/23, Dilated Cardiomyopathy: 8/23) and 15 healthy age-matched controls by Elisa assays. Furthermore, plasma norepinephrine was determined in study population by HPLC. Patients with infections, malignancies and other acute or chronic inflammatory diseases were excluded from our study.

Results: Serum levels of GM-CSF and sICAM-1 in CHF patients with ischemic heart failure did not differ significantly from those of CHF patients with dilated cardiomyopathy. CHF patients had significantly higher serum GM-CSF (25.8 ± 5.1 vs 2.1 ± 0.9 pg/ml, $p < 0.001$) and sICAM-1 (392.7 ± 34.3 vs 183.5 ± 13.1 ng/ml, $p < 0.001$) than healthy controls. Additionally, serum GM-CSF and sICAM-1 were more elevated in NYHA IV patients as compared with NYHA III patients (GM-CSF: 28.3 ± 3.9 vs 23.2 ± 3.1 pg/ml, $p < 0.05$; sICAM-1: 407.6 ± 21.7 vs 371 ± 17.1 ng/ml, $p < 0.01$). In the CHF group, GM-CSF levels were significantly correlated with sICAM-1 levels ($r = 0.72$, $p < 0.001$), plasma norepinephrine ($r = 0.52$, $p < 0.05$), right atrial pressure ($r = 0.45$, $p < 0.05$) and LVEF ($r = -0.48$, $p < 0.05$). Finally, no significant correlation was found between GM-CSF values and the age, sex or body mass index of CHF patients.

Conclusions: We have detected an increased serum activity of GM-CSF in patients with advanced CHF. This increase represents an abnormal stimulation of immune system and may be related with neurohormonal activation and haemodynamic deterioration which accompany the advanced CHF.

P1140 Regular cycle ergometer training improves endothelial function of the radial artery in patients with chronic heart failure

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In congestive heart failure (CHF) agonist-induced endothelium-dependent vasodilation is impaired. Local forearm training corrects endothelial dysfunction of the radial artery in these patients. The objective of this study was to investigate the effects of regular bicycle exercise on endothelial function of the upper extremity.

Nineteen male patients with stable CHF were prospectively randomized to a training group (T) ($n = 9$) or an inactive control group (C) ($n = 10$). At baseline (B) and after 4 weeks (4 wks) the internal diameter (ID) [mm] of the radial artery was measured using a high-resolution ultra-sound system (NIUS-02) with a 10 MHz probe. For assessment of endothelium-dependent and -independent vasodilation acetylcholine (ACH) (7.5; 15; 30 μg/min) and nitroglycerin (NITRO) (0.2 mg/min) were infused into the brachial artery. Flow-dependent vasodilation was determined after 5 minutes of upper arm occlusion (RH).

After 4 weeks of regular bicycle exercise there was a significant increase in endothelium-dependent vasodilation (ΔID 0.23 ± 0.07 at B vs. ΔID 0.43 ± 0.06 after 4 wks, $p < 0.05$ vs. B and C) (ACH 30 μg/min) as well as in flow-dependent vasodilation (ΔID 0.38 ± 0.06 at B vs. ΔID 0.57 ± 0.08 after 4 wks, $p < 0.05$ vs. B and C). Patients in the control group showed no significant change in respone to acetylcholine (ΔID 0.18 ± 0.07 at B vs. ΔID 0.16 ± 0.07 after 4 wks) (ACH 30 μg/min) or upper arm occlusion (ΔID 0.33 ± 0.03 at B vs. ΔID 0.35 ± 0.05 after 4 wks). There was no difference in the response to nitroglycerin in both groups at B and after 4 wks.

Conclusions: Regular cycle ergometer training improves endothelial function of the upper extremity in patients with stable CHF, possibly by enhanced endothelial release of nitric oxide (NO) and/or reduced degradation of NO due to intermittent increases in shear stress.

P1141 Increased soluble platelet/endothelial cellular adhesion molecule-1 and osteonectin levels in patients with severe congestive heart failure

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Platelet-endothelial interactions modulated by adhesion molecules, may play an important role in the pathogenesis of congestive heart failure (CHF). Soluble levels of these molecules and platelet-derived substances are reportedly elevated in patients with CHF. However, no data are available on the plasma levels of Platelet/Endothelial Cell Adhesion Molecule-1 (PECAM-1), and platelet-derived osteonectin in this growing population.

Methods: Soluble levels by ELISA were prospectively determined in patients with severe CHF ($n = 37$) and correlated to etiology and antecedent aspirin use, and compared with fourteen healthy controls. Left ventricular dysfunction was attributed to idiopathic dilated cardiomyopathy in 18 and coronary artery disease in 19 patients. Twenty-one patients were aspirin-free and sixteen patients were using aspirin (81–500 mg/daily).

Results: Elevated soluble PECAM-1 (51.31 ± 2.44 ng/ml, $p = 0.0001$), and osteonectin (826.27 ± 22.37 ng/ml, $p = 0.0001$) were observed in patients with CHF, as compared to healthy controls (32.56 ± 1.21 ng/ml, and 478.02 ± 31.32 ng/ml, respectively). Neither etiology of CHF, or antecedent aspirin therapy significantly affected the levels of PECAM-1 or osteonectin.

In conclusion, despite long-term aspirin therapy, soluble PECAM-1 and osteonectin were elevated in the majority of patients with severe CHF irrespective of disease etiology, thus, suggesting persistent platelet-endothelial activation. The present data provide additional evidence that more potent anti-platelet and endothelial preservation regimens deserve further study in the heart failure population.

P1142 Immune activation in chronic heart failure: the possible functional and prognostic importance of lipoproteins

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Increased concentrations of tumor necrosis factor-alpha (TNF-alpha) have been reported in severe chronic heart failure (CHF), but the regulatory mechanisms of immune activation remain unclear. The relationship between lower blood lipid levels and subsequent mortality in CHF is poorly understood. Based on the ability of lipoproteins to bind endotoxin, we hypothesised them to have beneficial immuno-regulatory effects in CHF.

Levels of cholesterol (CHOL), LDL, HDL, TNF-alpha and soluble TNF receptors 1 and 2 (sTNF-R1/2) were measured in 58 CHF patients (age 60 ± 1 y, peak VO_2 16 ± 1 ml/kg/min, NYHA class 2.7 ± 0.1, ejection fraction 26 ± 3%, all mean ± SEM) and 18 healthy controls (age 59 ± 2 y). Patients with CHF had raised concentrations of sTNF-R1 ($p = 0.005$), but TNF-alpha and sTNF-R2 were not increased. In cachectic CHF patients (cCHF, $n = 19$), the highest concentrations of TNF-alpha ($p < 0.0001$), sTNF-R1 ($p = 0.0006$) and sTNF-R2 ($p = 0.12$) were found. There was a correlation between TNF-alpha and body mass index ($r = -0.52$, $p < 0.0001$), age ($r = 0.43$, $p < 0.002$), CHOL ($r = -0.40$, $p = 0.003$) and LDL ($r = -0.30$, $p = 0.03$), independently of kidney function and CHF aetiology. In cCHF patients who had the strongest immune activation, TNF-alpha correlated with CHOL ($r = -0.55$, $p < 0.02$), HDL ($r = -0.49$, $p < 0.04$), sTNF-R1 ($r = -0.72$, $p = 0.0008$) and sTNF-R2 ($r = -0.56$, $p = 0.054$). Additionally,% weight loss was related to TNF-alpha concentrations ($r = 0.63$, $p = 0.005$) and HDL levels ($r = -0.54$, $p < 0.02$). Over a 1-year follow-up, 15 CHF patients experienced major events, defined as death ($n = 9$) and heart transplantation ($n = 6$). When the event-free survival was analysed, independent predictive values were found for peak VO_2 ($p = 0.001$), the lowest tertile of CHOL (<5.2 mmol/l, $p = 0.009$) and NYHA class ($p = 0.03$). In multivariate analysis, a lower CHOL level significantly predicted a poor 1-year clinical outcome ($p = 0.006$, RR 4.6, 95% CI 1.5–13.4) independently of peak VO_2, NYHA class, age and the presence of cardiac cachexia. When outcome was restricted to mortality, again, CHOL levels < 5.2 mmol/l significantly predicted 1-year mortality ($p < 0.05$, RR 5.6, 95% CI 1.1–29.4), independently of peak VO_2, NYHA class, body wasting and age. In patients who died, the correlation between TNF-alpha and CHOL was strongest ($r = -0.62$, $p < 0.02$).

In conclusion, serum CHOL may be involved in the regulation of immune activation in clinically stable CHF patients. These results could provide a potential explanation for the observed relationship between lower CHOL levels and impaired prognosis in CHF. This study may suggest a beneficial functional and prognostic importance of predefined lipid levels in established CHF.

P1143 Left ventricular function improvement during permanent left ventricular-based pacing in congestive heart failure

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Some studies showed acute hemodynamic and sustained clinical improvement during left ventricular (LV) or biventricular pacing in pts with severe congestive heart failure (CHF) and intraventricular conduction delay. Whether this new therapeutic option affects LV function has not already been reported.

Methods: In order to evaluate this hypothesis a radionuclide ventriculography and an echocardiographic study were performed at baseline, 1 month, 6 months and every 6 months after permanent LV-based pacing in 19 pts (68.2 ± 6 years; 17 males) with severe but stable CHF (NYHA class III: 6 pts; class IV: 13 pts) and left bundle branch block (LBBB, mean QRS duration = 182 ± 33 ms). The following data were collected: radionuclide-derived LV ejection fraction (EF), LV end-diastolic (EDD), end-systolic (ESD) diameters and fractional shortening (FS) assessed by M-mode echo, systolic pulmonary artery pressure (PAP) by continuous wave Doppler and mitral regurgitation (MR) jet area evaluated by color Doppler. After a mean follow-up (FU) of 10 ± 8 months, the following results were observed (mean ± SD):

	EF (%)	EDD (mm)	ESD (%)	FS (%)	PAS (mmHg)	MR (cm^2)
Baseline	24.8 ± 9	72.6 ± 7	63.5 ± 8	12.9 ± 4	44.2 ± 12	11.9 ± 6
FU	32.4 ± 10*	69.4 ± 8*	57.7 ± 9**	17.6 ± 6**	38.9 ± 9	7.4 ± 6**

*p < 0.05; **p < 0.01 FU vs baseline

Conclusion: LV based permanent pacing induces significant improvement in LV systolic function and significantly decreases the mitral regurgitation in pts with severe CHF and LBBB.

P1144 Haemodynamic and circulatory response to extracorporeal ultrafiltration in refractory congestive heart failure

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In rCHF, extracorporeal ultrafiltration (UF) allows clinical improvement and restores diuretic efficacy. In the course of a UF session patients are exposed to rapid variations of body fluid composition so that, as fluid is withdrawn from the intravascular compartment, hypotension or even shock could occur if compensatory mechanisms do not minimise blood volume reduction. We investigated the hemodynamic and circulatory adjustments during UF in 21 patients with rCHF, anasarcatic oedema, and oligo-anuria undergoing UF (4.1 ± 1.5 L, weight reduction of 5.3 ± 1.8 kg). Hemodynamics, plasma volume changes (ΔPV) and plasma refilling rate (PRR) were measured after every liter of plasma water removed. ΔPV and PRR were calculated by considering hematocrit and ultrafiltrate volume. Data are mean ± SD.

	Pre-UF	1 L	2 L	3 L	4 L	End-UF
CO (L/min)	3.2 ± 1	3.1 ± 1	3.4 ± 1	3.5 ± 1	3.6 ± 1*	3.8 ± 1*
PWP (mmHg)	28 ± 8	25 ± 7	24 ± 8*	22 ± 7*	21 ± 8*	19 ± 9*
RAP (mmHg)	17 ± 6	15 ± 5	14 ± 6*	11 ± 9*	11 ± 8*	9 ± 7*
MSAP (mmHg)	81 ± 15	80 ± 14	80 ± 13	82 ± 15	83 ± 12	83 ± 14
ΔPv (%)	–	−2 ± 4	−1 ± 2	1 ± 2	−2 ± 1	−3 ± 2
PRR (ml/min)	–	14 ± 4	12 ± 3	10 ± 5	8 ± 4*	7 ± 3*

* = p < 0.01 vs. Pre-UF.

The maximal PRR value observed not affecting plasma volume was 18.3 ml/min.

Conclusions. In rCHF patients, subtraction of plasma water by UF is associated with hemodynamic improvement. Refilling from the overhydrated interstitium is the major compensatory mechanism to intravascular fluid removal and hypotension does not occur when PRR is adequate to prevent hypovolemia. The upper PRR limit of 18 ml/min suggests that UF might be a safe procedure up to a fluid removal velocity of 1100 ml/hour. However, non invasive surveillance of hematocrit and body fluid balance during UF has to be done to monitor circulatory changes and to prevent hypovolemia.

P1145 Metoprolol treatment reduces sympathetic nerve activity in patients with heart failure

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Activation of the sympathetic nervous system is considered to have pathophysiological and prognostic impact in heart failure. The aim of this study was to assess the effect of 6 months metoprolol treatment on cardiac,renal,muscle and overall sympathetic function in patients with mild to moderate heart failure.

Methods: In a doubleblind design 22 patients (NYHA II-III) were randomly assigned to placebo or metoprolol (150 mg) treatment. Cardiac and renal vein catheterisation were performed at baseline and after 6 months. Regional sympathetic function was assessed by means of isotope dilution of tritiated Norepinephrine (NE) and microneurography in the peroneal nerve (MSA). Left ventricular ejection fraction (LVEF) was determined by radionuclide ventriculography.

Results: (mean ± SE) see table.

	Baseline metoprolol	Baseline placebo	6 months metoprolol	6 months placebo
LVEF(%)	32 ± 3	31 ± 3	42 ± 4*	33 ± 3
MSA (b/min)	58 ± 3	60 ± 5	43 ± 4*	58 ± 5
Cardiac NE so	357 ± 67	222 ± 83	235 ± 64	196 ± 79
Renal NE so	1033 ± 114	893 ± 115	846 ± 129	734 ± 134
Systemic NE so	4905 ± 622	4145 ± 565	3485 ± 505	4458 ± 652

*denotes a statistically significant difference p < 0.05, b/min denotes bursts/min and so denotes spillover (pmol/min)

Conclusions: Metoprolol treatment significantly reduced sympathetic nerve activity and improved LVEF in patients with mild/moderate heart failure. The decrease in nervetraffic was paralleled by trends towards lower regional and systemic NE release. Reducing the sympathoexcitation that prevails in heart failure may be one mechanism underlying the favorable effects of betablockade in this disorder.

P1146 Accurate non-invasive estimation of systolic pulmonary artery pressure by Doppler echocardiography in chronic heart failure

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Systolic pulmonary artery pressure (sPAP) can be estimated by Doppler echocardiography by summing right atrium-ventricular pressure gradient (ΔP) to right atrial pressure (RAP). ΔP is easily derived from maximal velocity (Vmax) of tricuspid regurgitation (TR) by applying the modified Bernoulli equation. Therefore, accuracy in estimating sPAP depends mostly on the accuracy of RAP measurement. To date however, no model for noninvasive estimation of RAP has been applied in clinical practice. In chronic heart failure (CHF) patients (pts) we recently demonstrated a strong correlation between acceleration rate (Ac) of early tricuspid flow and RAP. In this study we sought to verify the accuracy of summing ΔP and Doppler-derived RAP in the prediction of sPAP.

Method: 40 pts (55 ± 7 yrs) with CHF and LV systolic dysfunction (mean EF 23 ± 8%), in NYHA class II to IV, underwent simultaneous right heart catheterization and Doppler echocardiography. All but 3 pts had TR and 42% of them had a moderate to severe regurgitation. By continuous-wave Doppler of TR profile we measured Vmax and calculated ΔP. By pulsed-wave Doppler we measured Ac of early tricuspid flow to derive RAP on the basis of the equation: RAP = −1.263 + 0.01116*Ac. Doppler-derived sPAP was the sum of ΔP and RAP.

Results: Adequate Doppler recordings were obtained in all pts. Mean sPAP was 45 ± 18 mm Hg. In 3 pts without TR hemodynamic sPAP was below the 25 mm Hg normal limit. Mean ΔP and Doppler RAP were 47 ± 16 mm Hg (range 15 to 79) and 5 ± 4 mm Hg (range 0 to 17), respectively. At linear regression analysis there was a very high correlation between hemodynamic and Doppler-derived sPAP (r = 0.98). Doppler sPAP accurately predicted hemodynamic sPAP in 100% of the pts in the range of 15 to 30 mm Hg, in 92% of pts in the range of 30 to 50 mm Hg, in 92% of pts in the range of 50 to 65 mm Hg, and in 90% of pts with >65 mm Hg.

In conclusion, this study demonstrates that accurate noninvasive estimation of sPAP is possible. The sum of Doppler-derived ΔP from TR jet and RAP from diastolic tricuspid flow represents a reliable tool for predicting sPAP.

P1147 Autonomic heart rate control and JT interval during night sleep stages in coronary disease patients with congestive heart failure

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Introduction. Night sleep, due to modification of autonomic heart rate (HR) control over individual sleep stages, might be seen as a natural testing condition of cardiovascular function and reflects an ability for restoration of the latter during sleep, especially for coronary artery disease patients (CAD pts) with congestive heart failure (CHF).

The goal of the study was an investigation of autonomic HR control and JT interval during the shifts of sleep stages during the night in CAD pts with CHF.

The contingent was 184 CAD pts, aged 52.9 (SEM 1.24) yrs. CHF was evident in 125 pts.

Methods: An analysis of HR, HR variability, hemodynamics (stroke volume – SV, cardiac output – CO and total peripheral resistance – TPR), were performed during all stages of night sleep. JT interval and JT dispersion (JT_d), measured from 12 leads of electrocardiogram recording, was analyzed during sleep stages in 23 CAD pts. Hemodynamics was measured by means of impedance cardiography. Active orthostatic test (AOT) was performed before and after sleep, maximal HR response to AOT (ΔRR_B) evaluated. Analysis of HR power spectrum (σRR) with dividing into very low, low, and high frequency components was performed.

Results: CAD pts with CHF, as compared with pts without CHF, demonstrated reduced HR variability at wakefulness (σRR_W = 25 vs 42 ms, ΔRR_B = 209 vs 261 ms) and sleep ($\sigma RR_{non\ REM}$ = 19 vs 38 ms and σRR_{REM} = 37 vs 52 ms) in parallel to depressed hemodynamics ($SV_{non\ REM}$ = 67.4 vs 89.2 ml), especially during REM sleep (SV_{REM} = 65 vs 79 ml). CAD pts with CHF shown two different patterns of cardiovascular function restoration during sleep: positive (an increase of ΔRR_B and a decrease of TPR) and negative – with opposite changes. A group of CAD pts with CHF, displaying myocardial ischemia and PB's during REM sleep was characterized by the lowest level of hemodynamics and HR variability in this sleep stage. Pts with CHF, as compared with pts without CHF, demonstrated increased baseline level of JT dispersion (JT_d = 60 vs 48 ms), followed by a tendency for further increase during REM sleep. CAD pts with CHF demonstrated reduced level of autonomic HR control, especially parasympathetic one, increased JT dispersion and depressed hemodynamics. This is true particularly for REM sleep. Such combination of negative symptoms might be responsible for more frequent appearance of dangerous dysrrhythmias during REM sleep in CAD pts with CHF.

In conclusion: CAD pts with CHF demonstrated lower level of autonomic HR control and hemodynamics, increased JT dispersion at both, wakefulness and sleep. Mostly reduced parasympathetic control, hemodynamics and increased JT dispersion might be responsible for more frequent appearance of ventricular dysrrhythmias during REM sleep.

P1148 Is age a contributory factor of mitochondrial bioenergetic decline and DNA defects in congestive heart failure?

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While mitochondrial abnormalities are increasingly recognized in cardiac diseases including hypertrophic cardiomyopathy, their presence in congestive heart failure (CHF) and the role that age plays in their incidence and severity have yet not been assessed. Levels of cardiac respiratory enzyme activities and mitochondrial DNA (mtDNA) were examined in 60 patients (pts) with CHF (due to either ischemic or dilated cardiomyopathy), who were sub-divided into 3 age-groups (age range from 1 month to 60 years). Respiratory enzyme activity levels were significantly lower in 39 pts (65%) compared to age-matched controls and increased activity levels were noted in 12 (20%). Decreased activities were found in complex I (n = 11), III (n = 21), IV (n = 12) and V (n = 15) but not in II, the only respiratory complex entirely nuclear-encoded. No age-specific differences were found in the overall frequency of enzymatic abnormalities. However, older pts had significantly increased multiple enzyme activity defects as well as increases in the abundance and frequency of the 7.4 kb deletion. Interestingly, 3 pts had marked reduction in mtDNA levels. None of the pathogenic mtDNA mutations previously associated with hypertrophic cardiomyopathy were found, nor was there any relationship that could be established between levels of specific mtDNA deletions and enzyme activities. In summary, specific mitochondrial abnormalities are heterogenous and frequent in both adults and children with CHF. Older pts are more likely to have mtDNA deletions and multiple enzyme activity defects. The molecular basis for these abnormalities remains undefined.

P1149 Increased expression of CD32 on monocytes despite unchanged leukocyte apoptosis in patients with chronic heart failure

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Inflammation processes mediated by proinflammatory cytokines and varied circulating blood cells play a significant role in the pathogenesis of chronic heart failure (CHF). It is unknown if increased TNF production by myocardial macrophages and cardiac myocytes in patients with CHF is reflected by immunological changes of circulating blood cells.

Patients and Methods: We examined 10 male patients with chronic heart failure (62.8 years, ejection fraction < 40%, NYHA III) and 11 healthy controls (30.8 years). Morning blood was drawn from a peripheral vein and leukocytes were separated immediately. Fluorescein-isothiocyanate (FITC)-labeled human annexin V and phosphatidyl inositol (PI) were used to detect early stages of apoptotic cell death in lymphocytes by flow-cytometry. Expression of CD14, CD32 and CD36 on polymorphnuclear blood cells (PMN) and monocytes was measured to determine their potential scavenger role in the phagocytosis of apoptotic cells. Plasma levels of IL-6 and TNF-alpha were measured additionally.

Results: Annexin V binding of PI negative lymphocytes was not different between patients and healthy controls (1o.65% vs 6.44%). CD32 expression on monocytes was significantly higher in patients (94.75 vs 68.54 mean fluorescence intensity, $p < 0.05$). IL-6 and TNF-alpha were significantly higher in patients but did not correlate with annexin V binding. CD14 and CD36 were not different between the groups.

Conclusion: CHF patients show increased expression of CD32 as an unspecific marker of inflammation, but even in patients with extremely high TNF production there is no effect on apoptosis of circulating lymphocytes as well as on expression of scavenger receptors.

MYOCARDIAL FUNCTION AND GENE EXPRESSION

P1150 Myocardial hypertrophy elicited by blocking G protein-coupled receptor kinases in cardiomyocytes

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Background: Activation of the angiotensin II receptor (AT1) induces a hypertrophic response in cardiomyocyte cell cultures. The AT1 is a serpentine receptor, that couples to heterotrimeric G proteins (Galpha and Gbetagamma). Here we ask whether G protein-coupled Receptor Kinases (GRK's) may contribute to the hypertrophic phenotype in cardiomyocytes?

Methods: Primary cell cultures were prepared from the ventricles of neonatal 1–2 days old Wistar rats. Overexpression of the Gbetagamma sequestering protein, betaARKct, was achieved using an adenovirus construct kindly provided by Walter J. Koch. hBNP (human Brain Natriuretic Peptide)promotor linked to luciferase was used as a reporter gene assay for cardiomyocyte hypertrophy. Immunoprecipitation was performed with phophotyrosine and AT1 antibodies.

Results: betaARKct activates the hypertrophic response as evidenced by a 2–3 fold increase in the hBNP promotor activity, which is similar to the increase elicited by angiotensin II (AII). Furthermore, betaARKct results in constitutive activation of AII signaling. Accordingly, Losartan was able to partially block both the hypertrophic response and second messenger activation by betaARKct. In addition, betaARKct reduced phosphorylation of the AT1 receptor by 3–4 fold.

Conclusion: We suggest, that the activity level of GRK's in cardiomyocytes is an important element in the hypertrophic response. betaARKct downregulates GRK activity, resulting in increased AT1 signaling, inducing cardiomyocyte hypertrophy independently of agonist addition.

P1151 Unaltered mRNA levels and function of calcium/calmodulin-dependent protein kinase in endstage failing and non-failing human myocardium

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In cardiac muscle Calcium/Calmodulin-dependent kinase (CaM kinase) was shown to regulate sarcoplasmic reticulum (SR) calcium uptake and release by phosphorylating the major SR proteins including ryanodine receptor (RyR), Phospholamban (PLN), and SR Ca^{2+}-ATPase (SERCA). In failing human myocardium intracellular calcium handling is impaired.

Accordingly, we investigated mRNA levels of the cardiac CaM kinase II isoform and functional consequences of CaM kinase-dependent phosphorylation on SR calcium uptake in failing and nonfailing human myocardium. Northern blot analysis of the delta2-isoform was performed in hearts from 12 patients with endstage heart failure undergoing cardiac transplantation, and from 10 brain-dead organ donors. Relative densitometric units of CaM kinase II relative to glyceraldehyde-3-phosphate dehydrogenase were 1.17 ± 0.14 and 1.17 ± 0.15 in failing and nonfailing hearts, respectively (no significant differences). SR membranes were isolated from failing and nonfailing myocardium and phosphorylated by endogenous CaM kinase after addition of [gamma32]ATP. Membranes were subjected to SDS-PAGE, gels were dried and autoradiographed. Significant phosphorylation of RyR, PLN, and SERCA only occurred when both calcium and calmodulin were present in the reaction medium. Phosphorylation was markedly enhanced after the addition of exogenous CaM kinase II. The identity of phosphorylated proteins was verified by Western Blotting, and for SERCA by immunoprecipitation of phosphorylated SERCA with a monoclonal antibody (IID8F6). Oxalate-facilitated calcium uptake of phosphorylated and dephosphorylated membranes was investigated in 4 failing and 4 nonfailing hearts. In both types of myocardium, CaM kinase-dependent phosphorylation significantly increased calcium uptake by 108% ($p < 0.004$) and 181% ($p < 0.06$) in failing and nonfailing myocardium, respectively.

We conclude that the expression of CaM kinase II is not altered in failing myocardium. CaM kinase was shown to phosphorylate RyR, PLN, and SERCA in failing and nonfailing human myocardium. Functional implications of CaM kinase-dependent phosphorylation on cardiac performance could be preserved during heart failure.

P1152 Effect of endothelin converting enzyme inhibition on NO synthases in hypertrophied and non-hypertrophied postischaemic myocardium

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Endothelin is the most potent vasoconstrictor, blockade of its receptors or of its converting enzyme has been shown to be beneficial in ischemia/reperfusion injury. In an isolated rat heart model with 3 h of hypoperfusion (15% coronary flow) and 1 h of reperfusion we determined NO-synthase (NOS)-mRNA expression. We measured mRNA expression of eNOS, bNOS, and iNOS in hypertrophied (SHR) and non-hypertrophied (WISTAR) left ventricles. Additionally a group received the endothelin converting enzyme (ECE) inhibitor phosphoramidon (2 μmol/l; PHOS) during hypoperfusion and reperfusion. The latter regimen resulted in a 20% improvement of functional recovery. All data are mean ± SEM in CPM/μg total RNA.

		Control	Hypoperf.-NaCl	Hypoperf.-PHOS.
Wistar	eNOS	0.68 ± 0.26	1.54 ± 0.42(*)	2.56 ± 0.62#
	iNOS	0.14 ± 0.05	0.13 ± 0.02	0.16 ± 0.04
SHR	eNOS	0.70 ± 0.26	1.62 ± 0.35*	1.69 ± 0.62(*)
	iNOS	0.05 ± 0.01	0.49 ± 0.11#	0.35 ± 0.09#

(* = $p < 0.05$; # = $p < 0.01$)

Hypoperfusion/reperfusion resulted in a significant induction of eNOS mRNA expression. bNOS did not increase in either group. In SHR-rats a marked increase in iNOS mRNA was observed in contrast to WISTAR. ECE-inhib. had no effect on these changes.

Conclusion: In hypertrophied LV hypoperfusion/reperfusion results in an increased induction not only of eNOS but also of iNOS. Inhibition of ECE has a beneficial functional effect, but does not influence NO on the level of mRNA expression.

P1153 The ryanodine-channel-binding protein FKBP12.6 is increased in human heart failure

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Background: Disturbed intracellular calcium handling has been suspect to play a pathogenic role in cardiac hypertrophy and heart failure. Alterations in the function of the Ca^{2+}-release channel (ryanodine receptor; RyR2) of the sarcoplasmic reticulum may contribute to this impaired Ca^{2+}-handling. Recently, a little protein, the FKBP12 has been found to be tightly bound with the RyR. FKBP12 modulates the ryanodine receptor and may contribute to decreased Ca^{2+}-release.

Aim: The purpose of the study was to evaluate the protein expression of FKBP12.6 in hearts from patients with terminal heart failure due to idiopathic dilated cardiomyopathy undergoing cardiac transplantation (DCM, n = 8) in comparison to control hearts from organ donors without any signs of heart failure (NF, n = 8). The protein expression of FKBP12.6 and RyR2 from left ventricle myocardium was detected with monoclonal (RyR2) and polyclonal (FKBP12.6) antibodies in Westernblot-technique.

Results: The protein expression of FKBP12.6 was significantly increased in DCM (FKBP12.6: DCM 14.6 ± 2.0 vs. NF: 7.5 ± 1.03 densitometric units/μg protein, $p < 0.02$). In contrast RyR2 was identical in DCM (16.4 ± 2.2 densitometric units/μg protein) and NF (17.3 ± 4.3, $p = 0.88$).

Conclusions: This results predict to the impaired Ca^{2+}-homeostasis. The altered expression of FKBP12.6 in failing human myocardium may contribute to alterations in Ca^{2+}-release behavior of sarcoplasmic reticulum in spite of unchanged Ca^{2+}-release channel density.

P1154 Increased expression of glyceraldehyd 3-phosphate dehydrogenase in end-stage heart failure

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Glyceraldehyd-3-phosphate dehydrogenase (GAPDH) catalyzes the formation of glycerate-3-phosphate, the first ATP-forming step in the Embden-Meyerhof pathway. Based on its ubiquitous expression and the constitutive promoter, GAPDH is considered to be a housekeeping gene and is therefore used as a marker for cytosolic proteins and transcripional regulation of many genes. However, recent studies indicate, that the promoter of the GAPDH gene has positive regulatory elements. Under certain conditions, e.g. increased proliferation, the expression of GAPDH is up-regulated.

In studies of gene expression, we found a 109% increase in mRNA levels in explanted hearts from patients with end-stage heart failure, who underwent cardiac transplantation (n = 6) compared to non-failing human heart (n = 12). Signals of GAPDH were normalized against ribosomal 18 S RNA. The increased transcription resulted in an increased expression of GAPDH. Cytosolic fractions from 5 explanted failing hearts and a pool of 3 non-failing human hearts were prepared by centrifugation of supernatants from the homogenate at 100 000 g * 60 min. The cytosolic fractions were seperated in sodium dodecylsulfate polyacrylamide gelelectrophoresis and immunoblotted. Detection of GAPDH was carried out using a monoclonal antibody. Cytosolic fractions from failing human hearts showed a 92 ± 18% increase in GAPDH expression. Furthermore, GAPDH activity was increased by 102 ± 10.5% in failing human hearts, compared to non-failing hearts.

The influence of increased GAPDH expression for the energy household in end-stage heart failure remains to be resolved. However, GAPDH should not be used as a marker for comperative studies of failing and non-failing hearts.

P1155 Uniform reduction in SERCA2a content and metabolic enzyme activities in left ventricles with asymetric hypertrophy due to chronic ventricular pacing

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Recently studies from our laboratory showed that chronic ventricular pacing leads to asymmetric hypertrophy. In general, global hypertrophy is associated with diminished myocardial activities of various metabolic enzymes and sarcoplasmic reticulum calcium ATPase (SERCA2a).

Methods: We investigated activities of SERCA2a and metabolic enzymes in the left ventricular (LV) free wall (FW) and septum (S) from canine hearts after 6 months of pacing at the LV FW pacing at physiological heart rate (DDD, AV interval 25 ms, PACE, n = 8). These data were compared with those from hearts with global LV pressure overload hypertrophy (POH, aortic banding, n = 4) and from sham operated dogs (SHAM, n = 5). Wall mass of the LV FW and S was determined echocardiographically, myocyte diameter histologically, activities of fructose-6-phosphate kinase (PFK), citrate synthase (CS), 3-hydroxy-acyl-CoA dehydrogenase (HAD) and creatine kinase (CK) using biochemical techniques and SERCA2a contents via Western blotting.

Results: In PACE animals FW mass did not change but S mass increased by 39 ± 13%. Myocyte diameter in the S was 18 ± 7% larger than in the FW and was similar to that in POH hearts. SERCA2a content and activities of PFK, CS, HAD and CK were not significantly different between FW and S in any group. SERCA2a content (58%) and activities of PFK (52%), CS (32%), HAD (17%) and CK (17%) were significantly lower in PACE than in SHAM hearts. No significant differences in SERCA2a content and metabolic enzyme activities were found between PACE and POH hearts.

Conclusions: Chronic ventricular pacing induces localized hypertrophy in combination with generalized reductions in SERCA2a content and activities of metabolic enzymes. This indicates that expression of these proteins is not directly dependent on the local degree of hypertrophy, but rather to some systemic factor. The similar biochemical changes suggest involvement of the same factor in PACE and POH.

P1156 Opposite regulation of brain and C-type natriuretic peptides in the streptozotocin-diabetic cardiopathy

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C-type natriuretic peptide (CNP), a recent addition to the family of natriuretic peptides including atrial and brain natriuretic peptide (ANP, BNP), is thought to be an endothelium-derived vasodilator and to have an antimitotic effect. While ANP and BNP levels are increased in conditions such as congestive heart failure, cardiac CNP levels have not been investigated in this connection. Diabetes mellitus also involves myocardial dysfunctions without coronary artery disease or systemic hypertension. We investigated the cardiac expression of CNP versus BNP mRNA in streptozotocin (STZ)-diabetic rats. Male Wistar rats with STZ-induced diabetes (n = 4) were studied in comparison to control rats (n = 4). The animals were characterised by their mean arterial blood pressure and plasma glucose levels. After extraction of total cardiac RNA, a specific cDNA probe of BNP was used for Northern blot analysis. Myocardial CNP expression was analysed by RNase protection assay using a specific probe from the coding region of the rat CNP gene. Twelve weeks after diabetes induction, the rats were normotensive (97.3+2.1 vs. 96.1+1.7 mmHg) and hyperglycaemic (820+65 vs. 160+23 mg/dl; $p < 0.001$). STZ-diabetic rats had a 3.2-fold increase of cardiac BNP expression compared to controls. In contrast, cardiac CNP mRNA levels were decreased 2.6-fold. In agreement with others, we found an increased BNP expression in STZ-diabetic hearts. Furthermore, our data show firstly that the gene expression of CNP is downregulated in this diabetic model. Thus, CNP seems to be regulated like other peptide systems with antimitotic and vasodilatory activities (nitric oxide, prostacyclin, kinins). This may contribute to cardiac dysfunction in diabetes mellitus and suggests that stimulation of CNP expression could provide cardiac protection in such cases.

P1157 Regulation of mitochondrial biogenesis during early human cardiac development

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Previous studies in our laboratory demonstrated marked changes in bovine heart mitochondrial bioenergetics during fetal growth and development. To further understand the regulation of mitochondrial biogenesis in early human development, we examined fetal and neonatal heart tissues, for the activity and subunit content levels of specific mitochondrial enzymes. Comparing early fetal (EF, 45–65 day post conception) to later fetal (LF, 85–105 day post conception) and neonatal (birth-1 month) stages, we found:

- A 1.8 fold increase during EF to LF transition in specific activity of Krebs cycle enzyme, citrate synthase (CS), and an overall 4–5 fold increase in EF to neonatal transition.
- A 1.3 fold increase in COX/CS activity ratio during EF to LF indicating increased COX (cytochrome c oxidase) activity, and no increase in activity ratio from LF to neonatal stage.
- A 1.5–2 fold increase in peptide content of COX subunits (COX2 and COX4) as determined by immunoblot analysis during EF to LF with an overall 4–10 fold increase noted during EF to neonatal stage.
- Levels of peptide content of specific transcription factor, mt-TFA were relatively unchanged in development.
- A 1.7–2 fold increase in mitochondrial DNA (mtDNA) levels (EF to LF), and a 3.5–4 fold increase (EF to neonatal).

These data suggest that mitochondrial number doubles during early fetal cardiac development with coordinate regulation of some nuclear-encoded (COX4, CS) and mitochondrial components (COX2, mtDNA), and reveal a different pattern of regulation of mt-TFA. In the transition from LF to neonate, a further mitochondrial increase is indicated by more than 2 fold increases in CS and COX activities, COX peptides and mtDNA levels. These data are critical for identifying the regulatory events mediating mitochondrial biogenesis in early cardiac development.

P1158 The role of mitochondrial gene expression in ventricular fibrillation in isolated ischaemic and reperfused rat hearts

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In the present study we investigated the up- and down-regulation of mitochondrial genes [ATP synthase subunit 6 (ATP6) and cytochrome oxidase III (COX III)] related to ventricular fibrillation (VF) in ischemic/reperfused nondiabetic and diabetic myocardium.

Methods: We carried out subtractive screening, Northern blotting, and reverse transcription polymerase chain reaction (RT-PCR) of mitochondrial genes expressed after 30 min ischemia followed by 120 min of reperfusion in isolated rat hearts (n = 6 in each group) showed VF or did not develop VF. Cardiac function was also recorded in the nonfibrillated myocardium.

Results: ATP6 and COX III (selected out of 40 mitochondrial genes) showed an expression after 30 min of ischemia in both nondiabetic and diabetic myocardium. Upon reperfusion, using Northern blotting, the down-regulation of ATP6 (by 86% in nondiabetics and 100% in diabetics) and COX III (by 92% in nondiabetics and 100% in diabetics) mRNA was only observed in the fibrillated myocardium. A reduction in the expression of these genes was not seen in nonfibrillated hearts. Cardiac function showed no correlation between the up- and down-regulation of ATP6 and COX III genes in ischemic/reperfused myocardium. RT-PCR confirms the same expression in ATP6 mRNA and COX III mRNA after 30 min ischemia, and a decline throughout an additional two-hour period of reperfusion in both fibrillated nondiabetic and fibrillated diabetic myocardium.

Conclusion: Our data suggest that ATP6 and COX III may play a critical role in arrhythmogenesis and the stimulation of the expression of ATP6 and COX III may prevent the development of VF in both ischemic/reperfused diabetic and nondiabetic myocardium. Furthermore, the results show that the mechanism(s) of VF, in this respect, does not show any difference between the nondiabetic and diabetic myocardium.

P1159 Increased expression of atrial and brain natriuretic peptides in human myocardium is related to clinical severity of left ventricular dysfunction

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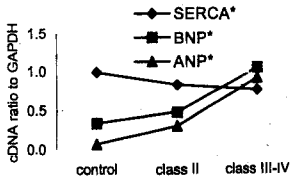
Cardiac expression of natriuretic peptides (ANP and BNP) is a well established marker in the study of left ventricular dysfunction. However, such studies are usually performed in animal models and there are few data on the relative expression of ANP and BNP in human left ventricular dysfunction. Therefore, we evaluated the ANP and BNP expression in human left ventricular dysfunction.

Methods. Total RNA was isolated from right ventricular tissue biopsies from 27 patients with idiopathic dilated cardiomyopathy (14: NYHA class II, 13: class III–IV) and 13 controls. Expression of Atrial Natriuretic Peptide (ANP), Brain Natriuretic Peptide (BNP), and Sarcoplasmic Reticulum Ca^{2+}-ATPase (SERCA) was determined by semi-quantitative PCR, expressed as a ratio to the co-amplified glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

Results. ANP, BNP, and SERCA mRNA are depicted according to NYHA class. ANP and BNP mRNA increased according to NYHA class, and according to down-regulation of SERCA (figure, *: $p < 0.05$, linear trend analysis).



Conclusion. This study demonstrates that in human left ventricular dysfunction the expression of ANP and BNP is related to the clinical severity of the disease, and is already present at the early stages of LV dysfunction. This suggests that they are useful markers in the study of molecular changes in human left ventricular dysfunction.

CARDIAC FUNCTION

P1160 Genetic polymorphisms of the ACE and AT1R genes and left ventricular function in subjects with angiographically proven coronary heart disease

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Several studies have suggested that genetic polymorphism of the renin-angiotensin system (RAS) have been associated with CHD. The aim of the present study was to estimate the potential association between ACE I/D polymorphism, and A1166C angiotensin II type 1 receptor (AT1R) genotype and left ventricular volumes and function in patients with CHD.

The study was performed in 93 patients with CHD confirmed by coronary angiography, all were younger than 50 years of age. Left ventricular volumes and function were measured during cardiac catheterisation. The polymerase chain reaction, restriction enzymes digestion and agarose gel electrophoresis were used to determine the ACE I/D and A/C AT1R genotypes.

	DD (n = 33)	ID (n = 42)	II (n = 18)
EF (ml)**	52 ± 14	57 ± 12	61 ± 12
LVEDP (mmHg)NS	17 ± 8	17 ± 7	13 ± 8
SVI (ml/m²)NS	39 ± 13	45 ± 17	60 ± 21
EDVI (ml/m²)NS	88 ± 40	78 ± 32	87 ± 29
ESVI (ml/m²)*	50 ± 37	28 ± 14	27 ± 16
	CC (n = 3)	AC (n = 23)	AA (n = 50)
EF (ml)NS	58 ± 5	58 ± 12	56 ± 16
LVEDP (mmHg)NS	17 ± 13	18 ± 14	15 ± 6
SVI (ml/m²)NS	42 ± 19	44 ± 12	44 ± 15
EDVI (ml/m²)NS	97 ± 69	79 ± 28	83 ± 35
ESVI (ml/m²)NS	27 ± 11	37 ± 18	39 ± 35

Significance was calculated as the difference between DD vs ID + II genotype and AA vs AC + CC genotype **-$p < 0.05$, *-$p < 0.03$

In conclusion, the DD genotype of the I/D ACE polymorphism is associated with significantly worse left ventricular function in younger patients with coronary heart disease. There is no association between the A/C AT1R polymorphism and left ventricular function in the study group.

P1161 Contrast echocardiography versus harmonic imaging in ejection fraction quantification

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The aim of this study was to assess whether the use of contrast and/or harmonic echocardiography improves results obtained by fundamental imaging. Twenty-four consecutive patients (age: 63 ± 8 y) with ischaemic heart disease underwent echocardiography and contrast ventriculography within a <24 hours period. Ejection fraction (EF) was determined by fundamental imaging, 2nd harmonic, 2nd harmonic with contrast (Levovist©, 8 ml ev, 400 mg/ml)) and after 5–10 min in wash-out phase. Interobserver variability was assessed.

EF by angiography was 54 ± 21%, range 24 to 82%. Mean values and correlation with angiography were

	Fundamental	Harmonic	Contrast	Wash-out
Mean	55 ± 13	54 ± 15	61 ± 17	54 ± 13
r	0.60	0.81	0.85	0.88
SEE	17.5	12.8	11.6	9.6

Absolute and percentual differences in interobserver variability were:

	Fundamental	Harmonic	Contrast	Wash-out
Absolute	1.3 ± 12.7	1.4 ± 12.6	0.5 ± 10.1	1.7 ± 3.9
Differences	5.7 ± 29%	1.1 ± 24%	0.1 ± 16%	3.1 ± 8%

Conclusions: Contrast agents, particularly in the wash-out phase, facilitates ejection fraction quantification by echocardiography, improves correlation with angiography and decreases interobserver variability.

P1162 Effect of left ventricular filling pattern on cardiopulmonary exercise response in patients with left ventricular systolic dysfunction

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We evaluated the relationship between transmitral flow filling pattern, assessed by Doppler echocardiography, and exercise tolerance during cardiopulmonary exercise testing, in pts with left ventricular (LV) systolic dysfunction.

Methods: The study included 32 pts (18 men, age 56 ± 13 years) in sinus rhythm, with angiographic LV ejection fraction < 40%. Idiopathic (17 pts) and ischaemic (15 pts) cardiomyopathy were the causes of heart failure according to coronary angiography. All pts underwent 2-D and Doppler echocardiography examinations and were classified, on the basis of early (E) to late (A) transmitral peak flow and/or peak A velocity criteria, as having a nonrestrictive (E/A < 2 or A > 35 cm/s, Group I, 15 pts) or restrictive (E/A > 2 or A < 35 cm/s, Group II, 17 pts) pattern. A modified Naughton treadmill exercise protocol was used, with gas exchange analysis, and the exercise duration and the oxygen consumption at peak exercise (peak VO_2) and at the anaerobic threshold (VO_2AT) were recorded.

Results: There were no differences between Groups I and II in the resting EF (29 ± 7 vs. 28 ± 4%, p:NS) or in exercise duration (378 ± 54 vs. 376 ± 33 s, p:NS). Group I had significantly higher values of peak VO_2 and VO_2AT than Group II (15.6 ± 1.8 vs. 12.6 ± 1.3 ml/kg/min and 12.1 ± 0.9 vs. 9.7 ± 1 ml/kg/min, respectively, $p < 0.05$ in each case). There was a good correlation between both the maximum velocity of A and the deceleration time of E and peak VO_2 (r = 0.79, r = 0.85, respectively) and VO_2AT (r = 0.8, r = 0.66, respectively), while no correlation was found for E velocity.

Conclusions: In pts with left ventricular systolic dysfunction the restrictive diastolic filling pattern, by Doppler echocardiography, is a powerful noninvasive marker for diminished exercise performance during cardiopulmonary exercise testing.

P1163 Restrictive left ventricular filling in dilated cardiomyopathy is accompanied by marked neurohumoral imbalance

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Background: Patients with idiopathic dilated cardiomyopathy (IDC) show different types of left ventricular (LV) filling on Doppler echocardiography. Restrictive filling pattern is defined as an E/A ratio ≥ 2 or by the combination of an E/A ratio between 1 and 2 with a deceleration time > 140 msec. The nonrestrictive pattern is defined as E/A ratio ≤ 1 or E/A ratio between I and 2 with deceleration time > 140 msec. Patients with the restrictive LV-filling pattern show an impaired prognosis.

Methods: We investigated 32 patients (26 male, 6 female; mean age 55 ± 2 years) with IDC. Patients were divided into a restrictive group according to the above mentioned criteria (13 male, 3 female; mean age 55 ± 3) and into a nonrestrictive group (13 male, 3 female; mean age 52 ± 4). After echocardiography was done blood samples were taken and the following parameters were measured using a RIA: N-terminal pro-ANP (NT-ANP), B-type natriuretic peptide (BNP), big endothelin 1 (big-ET), norepinephrine, epinephrine.

Results: There was no statistically significant difference between the two groups in left ventricular enddiastolic diameter and left ventricular ejection fraction. Restrictive patients had greater left atrial diameters (49 mm) than nonrestrictive patients (40 mm, $p < 0.001$). Neurohumoral parameters are given in table 1 (mean ± SEM):

	Restrictive	Nonrestrictive	p-value
NT-ANP (<0.6 nmol/l)	2.14 ± 0.31	0.50 ± 0.07	<0.001
BNP (<18.4 pg/ml)	452 ± 83	43 ± 12	<0.001
Big-ET (<0.7 fmol/ml)	1.88 ± 0.33	0.82 ± 0.33	0.002
Norepinephrine (<600 pg/ml)	325 ± 65	48 ± 6	<0.001
Epinephrine (<100 pg/ml)	83 ± 12	39 ± 5	0.007

During a follow-up period of 24 months 7 patients died and 3 underwent heart transplantation. All but one patient were from the restrictive group.

Conclusion: Patients with IDC and a restrictive LV filling pattern showed a marked neurohumoral activation. They revealed significantly higher levels of NT-ANP, BNP, big endothelin, norepinephrine and epinephrine compared to nonrestrictive patients. Furthermore, restrictive LV filling pattern and neurohumoral activation were markers of an impaired prognosis.

P1164 Correlation of end-diastolic pressure and myocardial elasticity with wave reflections

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Left atrial (LA) systolic pressure waveform was studied in 11 normal subjects (NLS), 7 patients with congestive heart failure (CHF) and 8 patients with mitral stenosis (MS) who underwent retrograde non-transseptal balloon mitral valvuloplasty (RNBMV).

Methods. LA and left ventricular (LV) pressure were simultaneously recorded from a double-tip micromanometer introduced retrogradely into the LA using a steerable cardiac catheter developed in our institution (Cordis Europa 5RE-699). We have applied real-time two-dimensional echocardiographic imaging with automatic boundary detection (HP Sonos 2500) for the estimation of LA and LV area changes. The LV chamber stiffness constant (α) was calculated by fitting the pressure (P) and the area (A) data during diastole to the exponential function $P = bxe^{\alpha A}$. In NLS and in CHF measurements were repeated at baseline, and after right atrial pacing and dobutamine infusion at equal heart rates. In MS, measurements were obtained at baseline and after RNBMV at equal pacing rates.

Results. The LA systolic pressure curve consisted of two positive waves: a first wave (A) and a second wave (A_r) influenced by wave reflection from the left ventricle.

		A (mmHg)	A_r (mmHg)	A_r/A	α (cm^{-2})	LVEDP (mmHg)
NLS	Baseline	11.8 ± 3.8	8.7 ± 2.4	0.74 ± 0.15	0.21 ± 0.11	8.7 ± 2.5
	Pacing	13.8 ± 2.7	12.1 ± 2.2	0.88 ± 0.17$^{\$}$	0.25 ± 0.14$^{\$}$	10.1 ± 3.1$^{\$}$
	Dobutamine	15.1 ± 2.8	10.3 ± 2.5	0.69 ± 0.14*	0.15 ± 0.01*	7.2 ± 1.8$^{\$}$
CHF	Baseline	15.1 ± 6.3	16.9 ± 3.1	1.12 ± 0.25	0.33 ± 0.10	16.3 ± 4.2
	Pacing	17.6 ± 2.5	21.0 ± 3.4	1.19 ± 0.21$^{\$}$	0.38 ± 0.18$^{\$}$	17.1 ± 3.1
	Dobutamine	16.2 ± 3.1	15.3 ± 2.6	0.94 ± 0.19*	0.28 ± 0.09*	15.0 ± 2.2$^{\$}$
MS	Baseline	27.0 ± 3.1	30.6 ± 4.1	1.13 ± 0.26	0.24 ± 0.38	9.0 ± 3.1
	RNBMV	16.5 ± 2.2$^{\$}$	14.8 ± 3.3	0.90 ± 0.21*	0.16 ± 0.22$^{\$}$	9.4 ± 4.1

LVEDP = left ventricular end-diastolic pressure. $^{\$}p < 0.05$, $^{*}p < 0.01$ and $^{*}p < 0.001$ for comparisons between baseline and pacing and between pacing and dobutamine in NLS and in CHF and between baseline and RNBMV in MS.

Mitral valve area was significantly increased after RNBMV in MS (from 0.9 ± 0.2 to 2.1 ± 0.5 cm^2). The A_r/A was linearly related with a and LVEDP in all circumstances.

Conclusions. The second (A_r) wave might be attributed to the increased reflection associated with increased LVEDP and intrinsic LV stiffness. The primary determinant of the A_r/A is the elasticity of the LV myocardium.

P1165 Effects of valsartan and enalapril on left ventricular diastolic function in patients with mild to moderate essential arterial hypertension

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This study investigated the effects of valsartan, a new AT1 angiotensin II receptor blocking agent, on left ventricular (LV) diastolic function assessed by a radionuclide ambulatory monitoring system (Vest) in comparison with those of the ACE-inhibitor enalapril. The study involved 24 patients (16 men, mean age 47 ± 8 yrs) with mild to moderate essential arterial hypertension and with no evidence of LV hypertrophy at echocardiography. All of the patients underwent Vest under control conditions at rest and during an upright bicycle exercise test before and at the end of each 4-week treatment period during which valsartan (80–160 mg/die p.o.) and enalapril (20–40 mg/die p.o.) were given according to a double-blind, cross-over design. At baseline, LV peak filling rate (PFR) at rest was normal (>2.5 EDV/s) in 12 patients (group A) and impaired (<2.5 EDV/s) in the remaining 12 (group B). The two groups of patients did not differ with respect to age, sex, heart rate, blood pressure and LV systolic function at baseline. In both groups, valsartan and enalapril induced a significant and comparable reduction in systolic and diastolic blood pressure. In group A, neither valsartan nor enalapril induced any significant change in PFR at rest and or peak exercise. In group B, valsartan induced a significant increase of PFR at rest (from 2.0 ± 0.3 to 2.4 ± 0.3 EDV/s, $p < 0.01$) and at peak exercise (from 4.0 ± 1.0 to 4.4 ± 20.3 EDV/s, $p < 0.05$), but PFR remained unchanged after enalapril at rest (2.0 ± 0.4 EDV/s, p = ns vs baseline and $p < 0.01$ vs valsartan) and peak exercise (3.7 ± 1.1 EDV/s, p = ns vs baseline and $p < 0.05$ vs valsartan). In conclusion, valsartan-induced renin angiotensin system blockade improves LV filling in patients with mild to moderate essential arterial hypertension and impaired diastolic function. These findings support the hypothesis that the renin-angiotensin system plays a role in the control of diastolic function in these patients.

P1166 Acute improvement in diastolic function with DDD pacing in hypertrophic obstructive cardiomyopathy

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Objective: Evaluate the hemodynamic and angiographic patterns of diastolic function in hypertrophic obstructive cardiomyopathy during DDD pacing.

Methods: 36 patients (13 male), mean age 64 ± 12 years, in NYHA functional class III-IV despite medical therapy, were treated with sequential DDD pacing. The hemodynamic study basally and after pacing evaluated left ventricle (LV) outflow tract peak and mean gradients, LV and RV end-diastolic pressures, mean capillary wedge, pulmonary and right atrial pressures, as well as cardiac output. The angiographic study analyzed the early LV filling at 30% and at 50% of diastole, the final LV filling (late 50%) and the presence of mitral regurgitation. Results are shown in the table.

Results

	Basal	DDD Pacing	P
Peak gradient	94 ± 37	37 ± 26	<0.001
Mean gradient	52 ± 22	19 ± 16	<0.001
LV end-diastolic	22 ± 6	15 ± 5	<0.001
Mean wedge	20 ± 7	15 ± 6	<0.001
Pulmonary diastolic	21 ± 7	16 ± 7	<0.001
RV end-diastolic	8 ± 4	7 ± 4	<0.01
Mean right atrium	7 ± 3	6 ± 4	<0.01
Cardiac output	3.8 ± 1.2	4.1 ± 1.1	<0.05
30% early filling	42 ± 11	52 ± 11	<0.001
50% early filling	64 ± 10	76 ± 9	<0.001
50% late filling	36 ± 10	24 ± 9	<0.001
Mitral regurgitation	1.5 ± 1.2	0.8 ± 1	<0.001

Conclusions: Sequential A-V pacing improves LV diastolic function and achieves a decrease in biventricular filling pressures. Cardiac output is not reduced during pacing. These hemodynamic and angiographic patterns and the associated decrease in LV outflow tract gradients and mitral regurgitation do suggest a beneficial effect in NYHA functional class.

P1167 Endothelin-1 increases myocardial distensibility in conditions of cardiac overload

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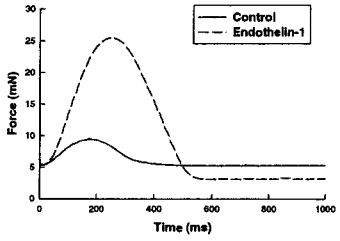
Endothelin-1 (ET-1) has vasoconstrictor, growth promoting and positive inotropic properties, with increased plasma levels in heart failure. The present study investigated the less well-known effects of ET-1 on the diastolic properties of the myocardium.

The effects of ET-1 (10 nM) were tested in isolated rabbit papillary muscles (Krebs-Ringer; 1.25 mM Ca^{2+}; 35°C) in the absence (n = 9) and in the presence (n = 5) of a non-selective endothelin receptor antagonist, PD145065. Isotonic, afterloaded and isometric twitches were recorded and analysed. Parameters for isometric contractions included: resting tension at the beginning and at the end of the twitch, active tension (AT) and peak rates of tension development (+dT/dt) and tension decline (−dT/dt). Significant results (mean ± SE, $p < 0.05$) are given, expressed as% change from baseline.



In isometric twitches (figure) ET-1 induced an increase of AT (147 ± 33%), +dT/dt (154 ± 39%) and −dT/dt (145 ± 38%). In addition, after ET-1, resting tension at the end of the isometric twitch decreased by 19 ± 3%, when compared to control and to its value at the beginning of the twitch. This effect was observed in all afterloaded twitches. It increased with afterload and was maximum in the isometric twitches. All these effects of ET-1 were abolished by PD145065.

In conclusion, this study showed that ET-1 has a novel effect on the diastolic properties of the myocardium. It decreases resting tension, or conversely increases myocardial distensibility, when afterload is elevated. Based on these results it is tempting to suggest that, in addition to hypertrophy, ET-1 might play a role in ventricular remodelling by contributing to cardiac dilatation, as for instances, in heart failure, where cardiac overload is known to be present.

P1168 Right and left ventricular diastolic function in systemic lupus erythematosus: the influence of antiphospholipid antibodies

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Background: Cardiac associations of the antiphospholipid (APL) antibodies include valvular abnormalities, coronary occlusion and cardiomyopathy. The present study examined whether right ventricular (RV) and left ventricular (LV) diastolic dysfunction precedes LV systolic dysfunction in APL(+) patients (pts) with systemic lupus erythematosus (SLE) and no clinically apparent heart disease.

Methods: Twenty four APL(+) (22 female, 2 male, age 41 ± 12 years) and 31 APL(−) (30 female, 1 male, age 43 ± 16 years) with cardiac asymptomatic SLE and preserved LV function (LV fractional shortening > 33%) were echocardiographically evaluated. Parameters measured included LV dimensions, early and late atrioventricular (AV) flow velocities (E and A wave respectively), E/A ratio, deceleration time (DT), and isovolumic relaxation time (IVRT-time from semi-lunar valve closure to AV valve opening).

Results (unpaired t-test): Heart rate (beats/min) was similar in the two groups (81 ± 9 vs 78 ± 11, p = NS). RV E/A was lower (0.9 ± 0.18 vs 1.05 ± 0.2, $p < 0.05$) while RVDT (155 ± 13 vs 141 ± 23 msec, $p < 0.01$) and RVIVRT (59 ± 11 vs 50 ± 15 msec, $p < 0.05$) were greater in APL(+) compared to APL(−) pts. Likewise, the LV E/A ratio was lower (1 ± 0.25 vs 1.2 ± 0.32, $p < 0.05$) while LVDT (163 ± 24 vs 150 ± 20 msec, $p < 0.05$) was prolonged in APL(+) compared to APL(−) pts. The LVIVRT was similar in the two groups (82 ± 11 vs 79 ± 13 msec, p = NS).

Conclusions. APL antibodies in cardiac asymptomatic SLE pts with preserved LV systolic function are associated with redistribution of AV flow from early to late diastole and prolongation of RV and LV DT as well as RV isovolumic relaxation. These findings indicate that RV and LV diastolic dysfunction may precede LV systolic dysfunction in APL(+) patients with SLE.

P1169 Decreased Ca,ATPase activity: supposed mechanism of left ventricular diastolic dysfunction and possibility of its pharmacological correction

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Left ventricular diastolic dysfunction is thought to be associated with impaired intracellular Ca homeostasis. The study was designed to determine membrane Ca,ATPase activity in patients with diastolic dysfunction and to assess the effect of lisinopril therapy on Ca pump.

Methods: A total of 28 patients (21 males, 7 females, mean age 59 ± 6 yrs) with left ventricular diastolic dysfunction were examined. Age matched control group included 16 healthy subjects. Diastolic dysfunction was detected Doppler-Echocariographically (E/A, deceleration time). All of examined patients were found to have normal systolic function. Ca,ATPase activity was measured in red blood cell membrane by the method of Raess and Vincenzi, before and after 4-week lisinopril therapy (10–20 mg/24 h).

Results: Baseline levels of Ca,ATPase activity in patients with diastolic dysfunction were significantly decreased compared to that of healthy subjects (0.81 ± 0.07 mcmol Pi/mg*h vs 1.22 ± 0.08 mcmol Pi/mg*h, $p < 0.01$) and positively correlated to the level of diastolic filling ($r = 0.64$, $p < 0.01$). After lisinopril administration Ca,ATPase activity significantly increased (0.92 ± 0.06 mcmol Pi/mg*h vs 0.78 ± 0.06 mcmol Pi/mg*h, $p < 0.05$) and was related to the improvement of diastolic filling, however did not achieve normal level.

Conclusion: Ca,ATPase activity could be considered as a marker for left ventricular dysfunction and indicates the possible role of this enzyme in the impairment of diastolic filling. Lisinopril may be a valuable medicine for correction of Ca,ATPase dysfunction.

P1170 L-NAME-induced hypertension: novel adaptation to systolic load in the absence of hypertrophy due to enhanced contractility and left ventricular concentric remodelling

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L-NAME, which inhibits nitric oxide synthesis, causes hypertension and is associated with a blunted LV growth response to pressure overload. This would be expected to cause heart failure. We utilized L-NAME-induced hypertension to test the hypothesis that successful adaptation to pressure overload occurs even when hypertrophy is suppressed.

Male rats were treated with L-NAME 50 mg/kg/day or no drug (C) for 6 weeks. The systolic wall stress (WS), relative wall thickness (RWT) and hypertrophy were also compared with aortic stenosis (AS) rats 6 weeks after the banding. LV calcium-dependent contractile reserve was measured in perfused hearts and isolated myocytes.

Systolic WS and RWT (LV diameter/2× posterior wall thickness) were increased and similar in L-NAME and AS rats. Despite of that, L-NAME rats showed a blunted increase in LV/body weight (BW) ratio ($^*p < 0.05$ vs C).

	C	L-NAME	AS
WS (kdyn/cm^2)	37 ± 4	85 ± 19*	92 ± 16*
LV/BW (g/kg)	2.1 ± 0.1	2.3 ± 0.1	4.3 ± 0.8*
RWT (mm/mm)	37.5 ± 5	51 ± 4*	51 ± 3*
LV EDD (mm)	8.9 ± 0.1	7.7 ± 0.3*	8.8 ± 0.5
LV devP/g (mmHg/g)	95 ± 6	143 ± 8*	113 ± 7

Nevertheless, L-NAME rats showed preserved LV developed pressure/g (LVdevP/g). This was maintained by a decrease of in vivo LV chamber dimension relative to wall thickness and augmented myocyte calcium-dependent contractile reserve. Thus, when the expected compensatory hypertrophic response is suppressed during L-NAME-induced hypertension, chronic pressure overload is associated with a successful adaptation to maintain systolic performance which depends on both LV remodeling and enhanced contractility.

P1171 Atrio-ventricular coupling in normals and in patients with left ventricular dysfunction: analysis based on pressure-volume relation

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Left ventricular (LV) input impedance is a definition of left atrial (LA) afterload, which is far less dependent on preload than are pressure and stress. LV input impedance can be calculated by the ratio of the LA end-systolic pressure to stroke volume (P_{es}/SV). With each ejection LA matches systolic force generation with the LV load. Thus, the atrio-ventricular coupling can be assessed by the effective LV elastance to LA end-systolic elastance ratio (E_{LV}/E_{es}). In a model heart, optimal transfer of work is predicted to occur when the E_{LV}/E_{es} ratio is equal to 1.

Methods: We performed echocardiographic assessment of LA volumes simultaneously with recordings of pulmonary wedge pressures in 30 patients. Ten patients had no structural or functional LV abnormalities, 10 had a recent myocardial infarction with LV dysfunction and 10 suffered from congestive heart failure (CHF). Pressure-volume loops were obtained at baseline and during increases in LA pressure produced by normal saline infusion. LA afterload was estimated by E_{LV} and atrioventricular coupling was calculated by E_{LV}/E_{es} ratio.

Results: The LA afterload was progressively increased in patients with myocardial infarction and in patients with CHF compared with controls ($p < 0.001$). E_{LV}/E_{es} ratio increased gradually as LV function deteriorated (controls: 1.01 ± 0.12, myocardial infarction: 1.41 ± 0.15 and CHF: 6.11 ± 0.84, $p < 0.001$).

Conclusions:. In normal subjects LA matched systolic force generation with the ventricular load. In contrast, in patients with myocardial infarction atrio-ventricular coupling was defective despite the increased stroke work. In patients with CHF there was a totally abnormal atrio-ventricular coupling associated with a considerable waste of energy. This could be another mechanism for LA lack of adaptation in this setting.

P1172 A quantitative analysis of nitrotyrosine in myocardium and serum in advanced human heart failure

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We and others have previously reported iNOS expression in the myocardium of patients with severe heart failure. The functional significance of these findings and the relationship to myocardial dysfunction remain unclear. NO reacts with superoxide radicals to produce the highly toxic peroxynitrite which can result in tissue damage. In small amounts, however, peroxynitrite may be beneficial. Peroxynitrite nitrates tyrosine residues and can be detected by measuring nitrotyrosine. In an attempt to quantify nitrotyrosine levels in heart failure we developed a nitrotyrosine ELISA to quantitate nitrotyrosine in myocardium. Twenty two patients with end stage heart failure and 9 normal donors were studied. Donor hearts were assessed prior to retrieval by transoesophageal echocardiography and ejection fraction was determined to be >55%. Nitrotyrosine levels were also measured in the serum of 26 patients with end stage heart failure and 5 normal controls. Mean myocardial nitrotyrosine levels in end stage heart failure (0.47 ± 0.07 ng/ml) were significantly greater than in donor heart (0.32 ± 0.01 ng/ml), $p < 0.05$. Mean serum nitrotyrosine was lower in end stage heart failure (10.24 ± 0.03 ng/ml) than in normal controls (0.44 ng/ml), $p < 0.05$. In conclusion this study has demonstrated for the first time markedly elevated nitrotyrosine in the myocardium of patients with heart failure suggesting a role for peroxynitrite in the pathogenesis of heart failure. These findings need to be evaluated further.

P1173 Myocardial mRNA expression of insulin-dependent transmembrane glucose transporter is increased in human insulin-dependent diabetes mellitus and decreased in non-insulin-dependent diabetes mellitus

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Transmembrane glucose transport and thus cellular high energy metabolism of the cardiovascular system depend largely on the insulin resposnsive GLUT 4 isoform of the transmembrane glucose transport molecule. Several authors have shown, that, in animals, myocardial GLUT 4 mRNA expression is decreased in experimental diabetes. There are no data on humans as yet.

Here we investigate probes (60–150 mg) of right atrial auricle from diabetic and non diabetic patients subjected to cardiac surgery which were snap frozen in liquid NO and stored at −70°C until homogenisation. Total RNA was isolated using guanidium thiocyanate, phenol-chloroform extraction and alcohol precipitation (for details see our earlier paper Mol Cell Biol 8: 2394–2400, 1988). Total RNA was hybridised with 32P labelled human GLUT 4 cDNA and re-hybridised with a human G3PDH cDNA probe to correct for equal amounts of RNA. Quantification was performed by a laser scanner and is expressed in optical densities.

Our results represent the first measurements of GLUT 4 mRNA in human myocardial tissue. Seven patients had NIDDM (determined by OGT, HbA1C, and insulin secretion), 7 had IDDM and 7 served as controls. GLUT 4 mRNA expression was 97.0 ± 10.4 ($\pm$ SEM) in the control group, 133.3 ± 15.2 in the IDDM group and 49.1 ± 6.2 ($\pm$ SEM) in the NIDDM group.

In summary, GTUT 4 isoform mRNA expression is increased in IDDM patients, but decreased in NIDDM patients. From these data, one can deduce that DM is initially associated with a decreased GLUT 4 expression, the latter then being upregulated by external application of insulin.

P1174 Inotropic effects of endothelin in isolated myocytes from human atrial and ventricular myocardium

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Endothelin (ET) and its blockade may play a major role in pathophysiology and therapy of congestive heart failure. We investigated the effect of ET on shortening of enzymatically isolated human myocytes ("chunck"-method) from right atrial myocardium (EF $57 \pm 2\%$, coronary bypass-surgery, n = 20, 16 patients) and ventricular myocardium (3 nonfailing donor hearts, n = 3; 27 explanted failing hearts, EF $22 \pm 1.5\%$, n = 48). The cells were electrically stimulated at 0.2 Hz (32°C, 1.25 mM extracellular calcium).

ET increased the fractional shortening in atrial myocytes from 3.7% to maximally $7.3 \pm 1.2\%$ at 10^{-8} M ($p < 0.05$ at 10^{-10} M). This effect was blocked by the ET_A-receptor-antagonist BQ 123 (10^{-7} M). In a small number of nonfailing left ventricular cells, ET seemed to have also a small inotropic effect (from $2.2 \pm 0.4\%$ to $3.5 \pm 0.7\%$ at ET 10^{-8} M). In contrast, ET exerts no inotropic effect in failing ventricular myocytes, neither at 2.5 mM, nor at 1.25 mM extracellular calcium. After lowering the pH-value from 7.4 to 7.0, ET was able to increase the shortening in failing left ventricular cardiomyocytes (from $4.7 \pm 0.7\%$ to $7.9 \pm 1.1\%$, $p < 0.05$). This effect was completely reversed by increasing the pH-value again and was blocked by preincubation with amilorid (10^{-6} M). Control experiments with 10^{-7} M isoproterenol (from $3.2 \pm 0.3\%$ to $7.9 \pm 0.4\%$) and increasing extracellular calcium-concentrations (from 3.7 ± 0.4 to $13.5 \pm 1.3\%$ at 15 mM) demonstrated the preserved β-receptor-function and contractile reserve. Whereas the efficiency and potency of ET in atrial myocytes is much higher than in intact muscle strip preparations, the inotropic effect in the intact ventricular preparations seems to be mediated by an acidosis of the core. Furthermore, therapeutical blockade of ET in congestive heart failure is thought to have no negative effect with respect to contractile function.

P1175 The inotropic effect of endothelin-1 in human myocardium does not depend on Ca^{2+}-release from the sarcoplasmic reticulum

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The endothelin (ET) system seems to be of pathophysiological relevance for human heart failure. In isolated human myocardium, a positive inotropic effect of ET-1 was described but whether this depends on increased intracellular Ca^{2+}-transients or myofilament sensitivity is uncertain. We investigated the influence of ET-1 on twitch force and intracellular Ca^{2+}-transients.

Methods: Isolated muscle strips from end-stage failing human hearts and nonfailing rabbit hearts for comparison. Electrical stimulation, isometric contractions (1 Hz, 37°C). Simultaneous measurement of twitch force and intracellular Ca^{2+}-transients using Fura-2/AM for: 1.) ET-1 (0.1 μM), 2.) ET-1 after blocking sarcoplasmic reticulum (SR) Ca^{2+}-storage function with cyclopiazonic acid (CPA)/ryanodine (10 μM) and 3.) ET-1 after blocking L-type Ca^{2+}-channels with diltiazem (3 and 30 μM, respectively).

Results: 1.) In failing human myocardium ET-1 (n = 14) increased twitch force by $47 \pm 7\%$ and the Fura-signal slightly by $7 \pm 2\%$ ($p < 0.05$). 2.) CPA/ryanodine (n = 9) reduced basal twitch force by $25 \pm 4\%$ and the Fura-signal by $37 \pm 4\%$ ($p < 0.05$). Addition of ET-1 in the presence of CPA/ryanodine increased twitch force by $49 \pm 13\%$ ($p < 0.05$) without changes in the Fura-signal. 3.) Diltiazem (n = 5) decreased twitch force by $27 \pm 4\%$ and the Fura-signal by $17 \pm 5\%$ ($p < 0.05$). ET-1 in the presence of diltiazem increased twitch force by $23 \pm 7\%$ ($p < 0.05$) without changes in the Fura-signal. Similar changes were found in rabbit myocardium except for a stronger increase in twitch force by ET-1 after diltiazem.

Conclusions: The positive inotropic effect of ET-1 in human and rabbit ventricular myocardium does not depend on SR Ca^{2+}, but mainly results from increased Ca^{2+}-responsiveness of the myofilaments. Moreover, increased extracellular Ca^{2+}-influx may contribute to the positive inotropic effect in failing human but not in rabbit myocardium.

P1176 Activation of c-Jun N-terminal kinases and p38-mitogen-activated protein kinases in heart failure secondary to ischaemic heart disease

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Three mitogen-activated protein kinase (MAPK) subfamilies are expressed in rodent and rabbit hearts and are activated by pathophysiological stimuli. The role(s) of these MAPKs in the pathology of the heart is unclear, but they have been implicated in cardiac myocyte hypertrophy and apoptosis in the rat. We have determined and compared the expression and activation of these MAPKs in donor and failing human hearts.

Methods: Samples were taken from the left ventricles of 4 unused donor hearts and 12 explanted hearts from patients with heart failure secondary to ischaemic heart disease. Total MAPKs or dually-phosphorylated (activated) MAPKs were detected by Western blotting. MAPK activities were measured by in gel kinase assays. Bands were quantified using laser scanning densitometry.

Results: As in the rat heart, c-Jun N-terminal kinases (JNKs) were detected in human hearts as bands of 46 kDa and 54 kDa, p38-MAPK(s) was detected as a 40 kDa band, and extracellularly-regulated kinases, ERK1 and ERK2, were detected as 44 and 42 kDa bands respectively. The total amounts of 54 kDa JNK, p38-MAPK and ERK2 were similar in all samples, although 46 kDa JNK was reduced in the failing hearts. Mean activities of JNKs and p38-MAPK(s) were significantly higher in failing heart samples than in donor heart samples ($P < 0.05$). There was no significant difference in phosphorylated (activated) ERKs between the two groups.

Conclusions: These results demonstrate that JNKs, p38-MAPK(s) and ERKs are expressed in the human heart. The activities of the "stress-regulated" MAPKs (the JNKs and p38-MAPKs), but not the ERKs, were increased in heart failure secondary to ischaemic heart disease. These data indicate that JNKs and p38-MAPKs may be important in human cardiac pathology.

P1177 Cardiac functional changes to low- and high-dose dobutamine after anthracycline therapy in patients with acute leukaemia

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To test whether cardiotoxity could be detected by dobutamine (DOB) stress test, we measured and calculated left ventricular systolic and diastolic indices by findings of 2-D echo and pulsed doppler. 26 patients who had acute leukemia after therapy off, aged 7 y 6 m–19 y 8 m were divided into three groups; without ATC therapy group (N group) (n = 7), small ATC group (S group) (n = 7, ATC < 300 mg/m^2), moderate ATC group (M group) (n = 12, ATC ≥300 – ≤860 mg/m^2) based on our previous report that cardiac function reduced more ATC therapy dosed more than 300 mg/m^2. Test were performed 2–3 years later after therapy off. Left ventricular ejection fraction (EF), heart rate corrected mean velocity of the circumferential fiber shortening (mVcfc), and the ratio of left ventricular systolic wall stress and end-systolic ventricular volume index (ESS/ESVI) were measured and calculated as a systolic functional index by 2-D echo. The ratio of maximum early filling peak velocity and atrial contraction peak velocity (E/A) was measured and calculated as a diastolic functional index by echocardiac pulsed doppler. DOB was administered starting at 5 μg/kg/min (γ) for 3 minutes up to 30 γ. We considered that the ratio of values at rest and 5 γ represented as a inotropic changes of cardiac function, and ratio of values at rest and 30 γ represented as a cardiac functional reserve. All indices were calculated and compared among three groups.

Results:

	DOB 5 γ/rest			DOB 30 γ/rest		
	N group	S group	M group	N group	S group	M group
EF	1.1 ± 0.3	1.2 ± 0.1	1.1 ± 0.3	1.2 ± 0.3	1.2 ± 0.1	1.1 ± 0.1
mVcfc	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.8 ± 0.3	1.9 ± 0.4	1.9 ± 0.5
ESS/ESVI	1.1 ± 0.1	1.2 ± 0.1	1.1 ± 0.1	1.7 ± 0.1	1.6 ± 0.2	1.2 ± 0.1*
E/A	1.0 ± 0.2	1.0 ± 0.1	1.1 ± 0.1	0.7 ± 0.1	0.6 ± 0.1	0.6 ± 0.1

*$p < 0.05$ vs. other groups

Conclusions: Changes of cardiac function to low dose DOB were no significant differences among 3 groups. On the other hand, cardiac functional reserve was significantly reduced after ATC therapy dosed more than 300 mg/kg/m^2. Thus, DOB stress test will be helpful for detection of cardiotoxity after ATC therapy.

P1178 Endogenous endothelin-1 causes a positive inotropic effect after selective endothelin$_A$ receptor blockade

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The vasoconstrictor endothelin-1 (ET-1) is involved in the development of atherosclerosis. Thus ET-receptor blockade may have an atheroprotective action. The effects of ET-1 are mediated by ET_A- and ET_B-receptors. We demonstrated in previous *in vivo* studies that activation of ET_B-receptors causes a positive inotropy while ET_A-receptors are mainly responsible for the vasoconstrictive effects of ET-1. Furthermore selective ET_A-blockade has a slight positive inotropic effect. This study examined whether this positive inotropic effect of a selective ET_A-blockade is mediated by endogenous ET-1 (via ET_B-receptors).

In open-chest rats the acute effects of the selective ET_A-antagonist BQ 610 (0.15 μmol/kg) were tested without and after inhibition of the ET-1 synthesis by 10 mg/kg phosphoramidon in comparison to NaCl-controls. Additionally to measurements in the intact circulation isovolumic measurements (isovol. LVSP, isovol. dp/dt$_{max}$) were performed for quantification of myocardial contractility.

	Without phosphoramidon		With phosphoramidon	
	BQ 610	NaCl	BQ 610	NaCl
Cardiac output	126 ± 3†	111 ± 1	116 ± 5	117 ± 5
Peripheral resistance	86 ± 2*	94 ± 1	93 ± 3	94 ± 3
Isovol. LVSP	100 ± 1*	96 ± 1	98 ± 1	98 ± 1
Isovol. dp/dt$_{max}$	106 ± 2*	100 ± 1	101 ± 2	98 ± 2

Mean ± SEM in % of preinfusion values; * = $p < 0.05$, † = $p < 0.01$ vs. NaCl.

BQ 610 causes vasodilatation with a consecutive increase of the cardiac output. Furthermore selective ET_A-blockade by BQ 610 causes a positive inotropic effect. These effects of BQ 610 are completely abolished after inhibition of the ET-1 synthesis by phosophoramidon.

Conclusions: The positive inotropic effect of selective ET_A-blockade is mediated by endogenous ET-1 via ET_B-receptors, since inhibition of endogenous ET-1 synthesis by phosphoramidon completely prevents this effect.

P1179 Influence of angiotensin II on the interaction of human cardiac fibroblasts with collagen I matrices

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The healing process after a myocardial infarction entails the migration and proliferation of cardiac fibroblasts into the infarcted region. To investigate the role of angiotensin II (ang II) in this process we isolated human cardiac fibroblasts and analysed the effect of ang II. on adhesion and migration on collagen matrices.

Human cardiac fibroblasts were isolated from explanted, end-stage failing human hearts and used in passage 1 for the experiments. By immunochemistry and FACS-analysis fibroblasts were shown to express α1-, α2-, β1- and β3-integrins. By inhibition by previous incubation with P5D2 the adhesion of human cardiac fibroblasts on a collagen matrix (20 μg/ml) was shown to be β1-integrin mediated (n = 3, $p < 0.0001$ vs. control). For the analysis of the influence of ang II on the migration of human cardiac fibroblasts, cells were serum-deprived and seeded into collagen-coated (20 μg/ml), modified Boyden-chambers. Ang II stimulated in a dose- and time-dependent manner the migration of human cardiac fibroblasts (n = 5; 16 h: 10 nM 22.3 ± 7.1%, 100 nM 38.5 ± 6.4%, 1 μM 112.5 ± 8.7%). Pre-incubation with the map-kinase inhibitor PD 98059 (10 μM) or with the AT1-blocker irbesartan significantly inhibited the migration in response to angiotensin II (n = 3). By incubation with increasing concentrations of P5D2 the influence of ang II on the β1-mediated adhesion on collagen I (20 μg/ml) was analysed. Ang II was shown to increase dose-dependently via AT1 the β1-mediated interaction of human cardiac fibroblasts with a collagen I matrix.

In conclusion angiotensin II influences via AT1-receptor the interaction of human cardiac fibroblast with collagen matrices via β1-integrins. The map-kinase is involved in the signal transduction cascade.

P1180 Abnormal segmental diastolic long-axis motion towards the apex – diastolic contraction, elastic recoil or induced by a haemodynamic event? The clinical role of strain rate imaging

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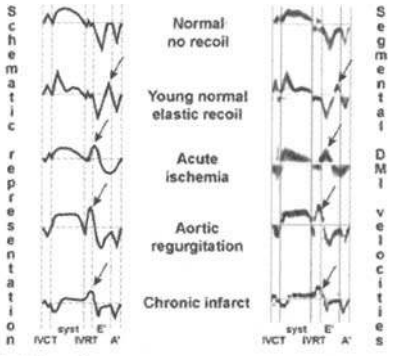
Doppler Myocardial Imaging (DMI) segmental velocity profiles can identify abnormal regional myocardial motion but cannot define the underlying pathologic mechanisms. Recent studies have shown acute ischaemia to produce early/mid diastolic contraction in the affected segment. This may be identified by DMI as a region of abnormal base apex motion during early diastole. However, abnormal diastolic base apex motion may occur passively due to a number of differing mechanisms. Potentially, Regional myocardial Strain Rate(RSR) derived from the Colour DMI data sets acquired at high frame rate (>140 f.p.s.) can be used to differentiate overall wall motion with no segmental contractile function from motion due to active contraction. To determine the potential clinical role of this new technique a series of in vivo closed chest acute segmental ischaemic animal studies and clinical studies involving both young and older normals (the latter without abnormal diastolic motion), patients (pts) undergoing routine PTCA, pts with chronic infarction and pts with aortic regurgitation were performed to study abnormal myocardial apical motion during diastole. Four different patterns and timing of abnormal diastolic segmental apical motion were identified (figure), each related to a differing pathologic mechanism. RSR values clearly differentiated passive segmental motion due to either elastic recoil, chronic infarction or motion induced by severe aortic regurgitation (low RSR) from active contraction present in diastole in acutely ischaemic segments in both the animal and PTCA patient groups.

Figure 1 Base-apex abnormal diastolic segmental motion



Abnormal segmental diastolic motion.

We conclude that RSR measurement would appear to be an important new technique to differentiate active diastolic contraction induced by acute ischaemia from passive induced segmental motion.

P1181 Evidence for an altered functional status of the Na^+/Ca^{2+}- exchanger in contracting failing human myocardium but unchanged activity in isolated vesicles

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The Na^+/Ca^{2+}-exchanger (NCX) has been suggested to compensate the altered Ca^{2+}-homeostasis in failing human myocardium through functional and expressional upregulation.

The present study aimed to investigate the function of the Na^+/Ca^{2+}-exchanger in both contracting left ventricular papillary muscle strips (PAP) and myocardial vesicles of terminally failing (DCM, dilated cardiomyopathy, NYHA IV) as compared to nonfailing (NF) human myocardium. Therefore, the effect of decreasing extracellular $[Na^+]_e$ (140 to 25 mmol/l) on force of contraction (FOC) of PAP from DCM (n = 19) and NF (n = 6) was studied. In addition, the time and Ca^{2+} dependent NCX activity was measured as Na^+-dependent $^{45}Ca^{2+}$-uptake into myocardial vesicles (NF n = 8, DCM n = 8). Decreasing $[Na^+]_e$ (which exerts its effect through alteration of the NCX driving force to extrude Ca_{2+}) enhanced contractility in DCM with higher potency than in NF (EC_{50} 73.0 vs. 45.8 mM). However, the Na^+-dependent Ca^{2+}-uptake into isolated myocardial vesicles (NCX activity) was unchanged both at different times (1–60 s, $T_{1/2}$: DCM 2.4 ± 0.3 s vs. NF 2.5 ± 0.3 s) and at different Ca^{2+}-concentrations (0.3–3000 μmol/l, t = 3 s, $K_{1/2}$: DCM 39.2 μM vs. NF 38.3 μM).

The results show a higher sensitivity of DCM to NCX dependent increases in contractility, whereas the activity of the NCX in isolated vesicles is unchanged. This observation might be explained by increased intracellular Na^+-levels due to a decreased Na^+/K^+-ATPase activity.

CARDIOVERSION OF ATRIAL FIBRILLATION

P1182 Magnitude of reversal of atrial effective refractoriness in man is related to duration of sinus rhythm post cardioversion

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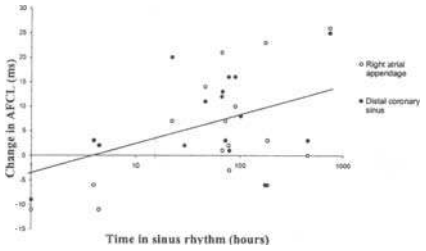
Background: The reversability of atrial electrical remodeling in man, after termination of clinical AF has not been demonstrated. We aimed to examine this important question of reversibility using AF cycle length (AFCL) as a measure of atrial refractoriness.

Methods and Results: We measured (AFCL) at the right atrial appendage (RA) and distal coronary sinus (DCS) prior to attempted internal cardioversion in 39 patients with persistent AF. Seventeen patients were restudied acutely following recurrence of AF with repeat measurement of AFCL. There was an increase in AFCL from the initial cardioversion to that measured at the time of first AF recurrence at both the RA (161 ± 22 ms versus 167 ± 26 ms, p = 0.05) and DCS (162 ± 19 ms versus 168 ± 21 ms, p = 0.01). The magnitude of increase in AFCL was positively correlated with duration of sinus rhythm prior to AF recurrence (r = +0.524, p = 0.001).



Conclusions: These findings demonstrate that changes in atrial electrophysiology associated with chronic AF in man are reversible following cardioversion and that the extent of this reversal is dependent upon the duration of sinus rhythm post-cardioversion.

P1183 Effects of calcium-channel blockers on technical efficacy and early clinical efficacy of external cardioversion of persistent atrial fibrillation

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Background. Atrial fibrillation (AF) is self-perpetutating arrhythmia causes electrophysiological changes that are mediated by rate-induced intracellular calcium overload. Calcium channel blockers (CCBs) have been demonstrated to be effective in preventing atrial electrical remodeling

Aim. Was to evaluate the effect of the concomitant use of CCBs on technical efficacy of electrical cardioversion (EC) of persistent AF and on the occurrence of early relapses of the arrhythmia after successful EC.

Methods. From june '93 to december '98, 437 consecutive patients (pts) (mean age 62 ± 12 years), NYHA class I–II, experienced EC for permanent AF (mean arrythmia duration 96 ± 129 days). One-hundred-thirty-five pts (31%) were pre-treated with CCBs before EC and 48 hours after (Group A), while 302 pts (69%) didn't receive them (Group B). Pts with AD > 72 hours were anticoagulated for 3 weeks prior to EC and for 4 weeks after. We define EC technical failure (TF) the inability of interrupting AF, and EC clinical failure (CF) early relapse of AF 48 hour after successfull EC

Results. The two group were comparable in terms of age, gender, body weight, arrythmia duration, previous AF episodes, atrial dimension, left ventricular disfunction, concomitant use of antiarryhtmic or non-antiarrhythmic drugs. The prevalence of arterial ipertension (HTx) or coronary disease (CD) was higher in Group A compared to Group B (HTx 49/135 pts, 36% *vs* 74/302 pts, 25%; p < 0.05, CD 18/135 pts, 13% *vs* 15/302 pts, 5%: p < 0.0001)

	Technical Failure	Clinical Failure	Sinus Rhythm	Chi-square test p value
Group A (n = 135)	5 (4%)*	20 (15%)	110 (81%)	* = 0.047 *v* SR
Group B (n = 302)	30 (10%)	39 (13%) 233 (77%)	* = 0.043 *v* CF + SR	

Four pts (0.9%) experienced embolic events 2, 6, 8 and 13 days after successful EC while they were correctly anticoagulated.

Conclusions. The pre-treatment with CCBs is useful in reducing technical failure of persistent AF, while no effects are detectable on preventing early relapses of the arrhythmia after successful EC. More randomized studies are mandatory to confirm the present data.

P1184 Rate control versus electrical cardioversion for persistent atrial fibrillation: the RACE study design

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Persistent atrial fibrillation (AF) does not terminate spontaneously and may cause left ventricular dysfunction and thromboembolic complications. For restoration of sinus rhythm (SR) electrical cardioversion (ECV) is most effective. However, AF frequently relapses, necessitating re-ECV and institution of potentially harmful antiarrhythmic drugs. If AF is accepted, rate control and prevention of thromboembolic complications using negative chronotropic drugs and warfarin is pursued. These strategies have never been systematically compared. It is our hypothesis that serial ECV is a futile procedure in terms of reduction of morbidity and mortality, or enhancing quality of life. RACE is a randomized comparison of serial ECV (repeat ECV as soon as possible after relapse and institute serial drug therapy: sotalol, class Ic drug, amiodarone) and rate control (resting heart rate < 100 using digitalis, calcium antagonists and/or beta-blockade).

Morbidity (heart failure, side effects of drugs, thromboembolic complications, bleeding and pacemaker implantation), mortality, quality of life and cost-effectiveness are primary and secondary endpoints. Included are patients with recurrence of persistent AF, present episode < 1 year and a maximum of 2 previous successful ECVs during the last 2 years.

This study started in 1998 and aims to include 520 patients by June 1999 in approximately 35 centers across The Netherlands. All patients will be followed during during two years.

P1185 Is cardioversion for atrial fibrillation a realistic option in the elderly?

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Background: Atrial fibrillation (AF) in the elderly is associated with significant morbidity, both from increased risks of stroke and from a higher rate of bleeding complications on warfarin. However, the elderly are often not referred for DC cardioversion. Little is known about the success rates of cardioversion in this age group or the role of adjunctive amiodarone.

Method: Case note review of 162 consecutive elective admissions for first time cardioversion of AF during a 2 year period. Data was prospectively dichotomised by age equal to or greater than 75.

Results: 48 patients were ≥75 years (mean 79, range 75–87 years) whereas the remaining 114 were <75 (mean 63.5, range 33–74 years). There was no significant difference between the groups in duration of AF (5.5 Vs. 5.7 months), LA size (46 Vs. 42 mm), LV impairment, hypertension, heart failure or valvular disease.

All patients	Initial Success	6/52 Follow-up Success
<75 years old	90/114 (79%)	52/90 (58%)
≥75 years old	44/48 (92%)	29/44 (66%
Amiodarone	Initial Success	6/52 Follow-up Success
<75 years old	44/51 (86%)	29/44 (66%)
≥75 years old	30/31 (97%)	24/30 (80%)

Both acute and follow up rates of successful cardioversion were independent of age. The use of amiodarone significantly increased success at 6 weeks in both age groups ($P < 0.001$ χ-squared test).

Conclusions: Cardioversion should not be denied to patients on the grounds of age alone. Success at six weeks is significantly increased by the use of amiodarone.

P1186 Importance of the long-axis atrial dimension in patients with chronic non-valvular atrial fibrillation

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Left atrial spontaneous echocardiographic contrast (LA SEC) indicates stasis and increased embolic risk. However, LA SEC should be searched for with transesophageal echocardiography (TEE). Therefore it would be desirable to establish a reliable indicator of LASEC which could be assessed during transthoracic echocardiografic examination (TTE).

We analyzed possible correlation between appearance or disappearance of SEC and changes of left atrial dimensions in patients after attempt of cardioversion of chronic non valvular atrial fibrillation (AF).

Sixty-one pts with chronic AF aged 60.2 ± 8.7 yrs underwent both TTE and TEE before and at least 12 month after direct current cardioversion (DCC). Initially and at follow up we evaluated dimensions of the left atrium and the presence of SEC. At follow up disappearance of SEC (+/−) occurred in pts in whom left atrium long axis diameter (LAlax) decreased while appearance of SEC (−/+) was accompanied by an increase of LA lax.

results

SEC	−/−	+/−	−/+	+/+
Pts	10	11	7	26
LAlax "0" (mm)	60.8 ± 8.3	62.0 ± 8.5	52.9 ± 8.2	63.7 ± 6.1
LAlax "12" (mm)	62.1 ± 6.5	57.5 ± 6.7	63.1 ± 4.5	67.0 ± 9.1
p	ns	<0.05	<0.05	ns

absence (−) or presence (+) of SEC (initially/at follow-up)

Conclusion: Appearance or disappearance of spontaneous echocardiografic contrast are related to the changes of left atrium long axis diameter. This may suggest that enlargement of the left atrium long axis diameter is a marker of tromboembolic risk.

P1187 Cardiac biochemical markers after cardioversion of atrial fibrillation

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Cardiac biochemical markers are known to be released from necrotic myocardial orsceletal muscle after direct current (DC) shocks. The purpose of this study was to assess Troponin T and I among conventional markers after direct current cardioversion in patients with atrial fibrillation.

Methods: Fifty consecutive patients (mean age 66 range 33–81) underwent underanaesthesia 1–4 DC-shocks (mean cumulative energy 414 J, range 100–860 J). Blood samples were drawn prior to the procedure, 1–2, 6–8, and 20–24 hours after cardioversion.

Results: Table I shows that the troponins were completely unaffected by the DC-cardioversion while CK and myoglobin were considerably elevated. CK-MB mass and ASAT were elevated in 18% and 29% patients respectively 20–24 hours after cardioversion. There was a significant association between elevated CK, myoglobin and CK-MB mass and accumulated energy given; also when age and gender were adjusted for.

Table 1: Mean values of the biochemical cardiac markers before and after DC-cardioversion Numbers in brackets are the percentages of patients with values above reference value

Marker	Before	1–2 hours after	6–8 hours after	20–24 hours after	p-value for trend
Troponin I (≤0.4 ug/l)	0.11 (0)	0.12 (0)	0.11 (0)	0.10 (0)	0.935
Troponin T (≤0.4 ug/l)	0.27 (0)	0.27 (0)	0.30 (0)	0.30 (0)	0.773
CK-MB (≤5 ug/l)	1.9 (0)	2.0 (4)	3.5 (14)	3.6 (18)	<0001
Myoglobin (<90 ug/l)	35 (0)	266 (63)	448 (64)	120 (39)	<0.001
CK (male ≤ 200 U/l) (female < 150 U/l)	110 (0)	186 (18)	856 (67)	1517 (80)	<0.005
ASAT (male: 10–50 U/l) female: 10–35 U/l)	26 (0)	27 (2)	35 (7)	50 (29)	<0.001
LD (>70 yr: <650 U/l) (<70 yr: <450 U/l)	414 (0)	394 (2)	435 (2)	475 (2)	<0.001
Ratio CK-MB/CK*100 (reference value < 3)	1.85 (0)	1.45 (0)	0.91 (0)	0.71 (0)	<0.001

In conclusion, only the Troponin I and/or T are reliable markers of myocardial necrosis in patients undergoing direct current cardioversion of arrhytmias.

P1188 Does successful cardioversion favorably affects the left heart in chronic non-valvular atrial fibrillation? Long-term echocardiographic follow-up

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Successful cardioversion was reported to decrease left atrial (LA) dimensions and improve left ventricular (LV) function.

We checked the long-term effects of cardioversion (DCC) and compared them to changes occurring in patients who continued on atrial fibrillation (AF). Left heart dimensions could be reliably evaluated by echocardiography initially (0) and both after 1 and 3 yrs in 75 pts (aged 62.0 ± 8.7, 28 F, 47 M), while LV ejection fraction (LVEF) in 48 pts. In almost half of these pts sinus rhythm (SR) was maintained throughout the follow-up period. Initially the groups were similar clinically and echocardiographically except for LA short axis diameter (LA sax) which was slightly greater in pts who had AF at 3 yrs follow-up. During follow-up LA dimensions showed divergent trends in AF and SR. This resulted in highly significant differences between these groups in both LA long axis (LA lax) and LA sax. At 1 yr and at 3 yrs pts in SR had significantly higher LVEF than in AF.

Results:

	LA lax (mm)		LA sax (mm)		LVEF (%)	
	SR	AF	SR	AF	SR	AF
Pts	35	34	36	39	23	25
0	58.6 ± 7.3	61.8 ± 7.6	43.2 ± 5.4*	46.9 ± 4.7	63.4 ± 12.6	57.9 ± 12.3
1 yr	54.6 ± 7.5*	63.8 ± 7.4	43.0 ± 6.8*	48.8 ± 4.9**	65.5 ± 5.6*	59.4 ± 10.5
3 yrs	56.5 ± 7.2*	66.6 ± 6.8**	42.2 ± 6.0*	49.3 ± 4.6**	64.6 ± 6.8*	56.2 ± 10.3

*p < 0.05 compared with pts with AF, **p < 0.05 compared with initial value

Conclusion: Patients with chronic non-valvular atial fibrillation in whom it is possible to restore and maintain sinus rhythm keep their dimensions and LVEF on initial level for at least 3 years. This favorably compares to the deterioration of respective parameters in pts who continue to fibrillate, and occurs despite lack of initial differences between the two groups.

P1189 Left ventricle function after dc shock of atrial fibrillation compared to pharmacological treatment

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Introduction: Electrical cardioversion and chemical treatment are both methods of restoration of the sinus rhythm (SR) in patients with atrial fibrillation (FA). The purpose of this study was to compare this different methods in its influence on left ventricle (LV) function after reversion of FA to SR.

Material and methods: We studied 68 patients with nonrheumatic FA before and one hour after pharmacological (20 cases) and electrical (48 cases) reversion of FA to SR. LV function was assessed using following parameters recorded from transthoracical approach: LVEDs, LVEDd, EF, SF, Etime, Edcct, Eampl, Vmax, LVET. Consequently TEE was performed with Doppler probe at the opening of the left superior pulmonary vein to measure: PVS, PVD, PVS/PVD, PVDdcct. Then differences (diff) between values of each parameter before and after restoration of SR were calculated

Results:

Parameter	Transthoracical cardioversion n = 48	Pharmacological reversion n = 20	p
diff LvEDs (cm)	0.31 (± 0.04)	0.13 (± 0.03)	0.05
diff LvEDd (cm)	0.09 (± 0.05)	0.09 (± 0.02)	NS
diff EF LV (%)	4.7 (± 1.2)	1.1 (± 0.6)	0.03
diff SF LV (%)	2.4 (± 0.8)	0.5 (± 0.31)	0.04
diff E time LV (msec)	4.83 (± 0.87)	5.9 (± 0.91)	NS
diff E dcct LV (msec)	3.11 (± 1.32)	2.68 (± 1.21)	NS
diff E ampl LV (cm/s)	5.01 (± 1.23)	4.93 (± 1.28)	NS
diff V max LV (cm/s)	0.88 (± 0.53)	1.12 (± 0.49)	NS
diff LvET (msec)	26.3 (± 8.9)	23.7 (± 8.6)	NS
diff PVS (cm/s)	−1.41 (± 0.55)	0.88 (± 0.33)	0.002
diff PvD (cm/s)	2.86 (± 0.82)	3.29 (± 0.59)	NS
diff PvS/PvD	−0.01 (± 0.006)	0.01 (± 0.004)	0.006
diff PvD dcct (msec)	27.4 (± 6.54)	25.3 (± 6.54)	NS

Conclusions: There is significant impairment of left ventricle systolic function after transthoracical cardioversion of atrial fibrillation compared to pharmacological restoration of sinus rhythm.

PACING AND ATRIAL FIBRILLATION

P1190 The intra-operative atrial refractory period in relation to the presence of chronic or paroxysmal atrial fibrillation or sinus rhythm

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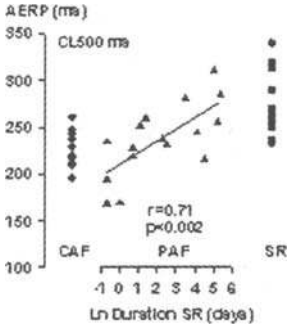
During recent years, the results from animal experiments have led to the concept of tachycardia-induced atrial electrical remodeling, in which prolonged episodes of AF induce shortening of the atrial effective refractory period (AERP) with loss of rate-related shortening at higher rates. After restoration of sinus rhythm (SR), these changes have proven to be reversible. Limited data exists on whether electrical remodeling plays an important role and is reversible in clinical chronic AF (CAF) or paroxysmal AF (PAF).

Methods: In the present study we measured the AERP at cycle lengths (CL) between 250 and 600 ms using epicardial pacing leads in 46 patients (15 SR, 16 PAF, 15 CAF) during cardiac surgery. Carefull history taking and patient file evaluation was performed to determine the duration of AF and the duration of SR after a last episode of PAF at the time of surgery.

Results: Patients with CAF and PAF had significant shorter AERPs ($p < 0.01$ at all CL>300 ms) and a reduced rate-adaptation compared to patients in SR. In patients with PAF, there was a significant logarithmic correlation between the duration of SR after the last episode of PAF and the AERP, with normal AERPs in the PAF patients with more than 4 days of SR (Ln{4} = 1.4 = median duration of SR, see figure). There was no relation between the duration of CAF or PAF and the AERP.



Conclusion: In humans, CAF and PAF are associated with short atrial refractory periods and a reduced rate adaptation of the atrial refractory period. Although the logarithmic correlation between the AERP and the duration of SR after the last episode of PAF does not provide absolute proof, it is in agreement with the concept of recovery from electrical remodeling of the atria after restoration of SR.

P1191 Different refractory period changes induced in the human atria by rapid high right atrial pacing and the effect of verapamil

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Rapid high right atrial pacing induces a shortening of the atrial effective refractory period (ERP), defined as atrial remodelling. This has been related to intracellular calcium overload. The purpose of this study was to assess a) rapid high right atrial pacing-induced ERP changes in the right and left human atrium, b) the effect of verapamil, an intracellular calcium lowering drug, on these changes. In order to exclude possible autonomic influences, pharmacological autonomic blockade preceded a) and b).

Methods: Ten patients without structural heart disease or history of atrial fibrillation were included in the study. Their mean age was 42 ± 19 years. After autonomic blockade (propranolol, 0.2 mg/kg IV, followed by atropine, 0.04 mg/kg IV), right and left atrial ERP were measured by electrode catheters placed in the high right atrium and distal coronary sinus respectively (drive cycle length 500 ms). For the first part of the study, ERPs were assessed before and after 5 mins of rapid high atrial pacing (pacing cycle length 200 ms). For the second part, similar ERP assessments were conducted following intravenous verapamil infusion (10 mg). ANOVAR followed by Scheffe's test were used for analysis.

Results: Significant results were obtained (ANOVAR F = 3.39, p < 0.03):

	Right atrial ERP		Left atrial ERP	
	before verapamil	after verapamil	before verapamil	after verapamil
Before pacing	220 ± 34	216 ± 30	211 ± 41	208 ± 30
After pacing	184 ± 26	205 ± 24	202 ± 41	201 ± 31
P value	<0.003	NS	NS	NS

Conclusions: Under autonomic blockade, 5 mins of rapid high right atrial pacing induce electrical remodelling only in the right atrium. Verapamil, possibly through its intracellular calcium lowering properties, attenuates this effect.

P1192 Long-term survival in 6326 patients with cardiac pacemakers – influence of gender on survival

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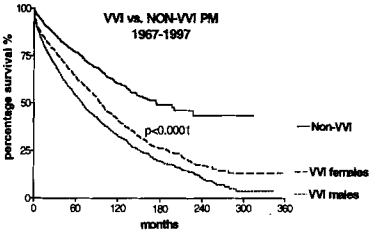
Cardiac pacemakers (PM) are the treatment of choice for severe bradycardias. However there are few data on long-term surival of these patients with particular regard to gender.

Methods: In a multivariate analysis we investigated the influence of gender in comparison to other clinical factors on long-term survival in 6326 pts who received a PM in our hospital during the last 30 years and were followd by 6/12 months control intervals.

Results: 4569 pts received a VVI-PM (2134 females), the other 1757 pts received a NON-VVI PM (AAI, DDD). Despite a higher age of women with VVI-PM (73.2 vs. 71.6 y, P < 0.05) their median survival time was significantly longer (94 vs 68 months, p < 0.001, figure 1). Similar findings were made for NON-VVI-PM. The advantage in survival began as early as 20 months after the implantation.

Atrial fibrillation, past myocardial infarction and and type of pacemaker had an additional influence on the difference survival times of men and women.



Conclusion: Gender-specific differences in survival times are evident within the first 20 months after implantation and are enhanced by other clinical factors.

P1193 Does overdriving intrinsic rate at rest by atrial pacing prevent atrial fibrillation in patients with a pacemaker due to a symptomatic sinus node disease?

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First retrospective data report a reduced incidence of atrial fibrillation in patients with sinus node disease and an overdrive stimulation of their rest rate by atrial pacemaker stimulation

The aim of our randomized prospective cross-over trial was to determine the risk for atrial fibrillation (AF) in patients with pre-existing paroxysmal AF pacing them at a rest rate of either 40 or 65 ppm. Thus comparing inter- and intra individually intrinsic rhythm to atrial pacemaker stimulation.

Ninety four patients were randomized to either 40 or 65 ppm for a one year follow-up with a consecutive cross-over. Every three months patients presented in our outpatient department. Cardiac rhythm was controlled by a holter-ECG, the data of the inherent holter function and a questionnaire. Statistical analysis was performed by SAS multivariate analysis.

Results: Episodes of paroxysmal AF were highly significant more often pacing at a basic rate of 40 than of 65 ppm (n = 164 vs. 49, p < 0.005). 66 of the 94 patients paced at 40 ppm and 23 paced at 65 ppm had a recurrence of paroxysmal AF (p < 0.005). The number of episodes and of patients with recurrence of AF was approximately three times higher with intrinsic rhythm, when compared to atrial overdrive stimulation at rest.

Conclusion: Patients with pacemaker implantation due to symptomatic sinus node disease with paroxysmal AF exhibited a significantly higher number of AF episodes being in intrinsic rhythm at rest when compared to an atrial overdrive stimulation under the same conditions. Increased basic rate in atrial pacing therefore should find a wider application in this patient population.

P1194 Ablate and pace is equally effective for treatment of paroxysmal recurrent and permanent fast response atrial fibrillation

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The study investigated the impact of A-V junction ablation and PM implantation (A-P) for treatment of both highly symptomatic permanent fast response atrial fibrillation (PFAF) and paroxysmal recurrent atrial fibrillation (PRAF) not controlled by drug therapy.

Methods: Group A (G A) included 13 pts (8 M), aged 58–80 (mean 68 ± 6) with PFAF (mean ventricular rate at rest: 110 ± 5), while Group B (G B) included 7 pts (3 M), aged 54–87 (mean 65 ± 12) with PRAF (3 or more episodes in the previous 6 months). The two groups were comparable in respect to age, sex and specific heart disease distribution (hypertensive 9, valvular heart disease 7, CAD 2, cardiomyopathy 2). Persistence of A-V block, stimulation threshold (ST) and pacing impedance (PI) were evaluated at follow-up (FU). The Minnesota Living with Heart Failure Questionnaire (LHFQ), NYHA classification, a specific score for palpitations (P score = 0 to 5) and the number of tablets/pt (T/P) daily consumed were employed in both groups to compare quality of life before and after the procedure (7 ± 3 m).

Results: A-V junction was successfully ablated in all the pts by right-sided approach. No pt resumed A-V conduction at follow-up. VVIR pacing mode was reserved for all G A pts while G B pts were paced with VVIR (2) and DDD (5) mode-switching PMs. No PM failure occurred and ST and IP negligibly increased from implantation to FU visit in both groups. No death occurred in the study population. A significant clinical improvement was equally evident in both groups despite G B pts experienced many recurrences (asymptomatic) of pathological atrial rhythm, as detected by PM recordings, and two of them developed permanent AF.

	LHFQ			NYHA			P score			T/P score		
	pre		post	pre		post	pre		post	pre		post
GA	36 ±17	vs	7.2 ±6.9*	3.1 ±0.8	vs	1.7 ±0.4*	4.4 ±0.9	vs	0.2 ±0.4*	5.3 ±2	vs	2.8 ±1.4*
GB	32 ±24	vs	4.2 ±4.7°°	2.7 ±1	vs	1.5 ±0.5°	4.5 ±1.2	vs	0.3 ±0.8*	5.2 ±1.1	vs	2.8 ±1.5°°

°p < 0.05, °°p < 0.02, *p < 0.001. A decrease of LHFQ, NYHA, P and T/P scores ≥ 80%, 40%, 90% and 45% respectively was detected in both groups.

Conclusions: We conclude that 1) A-P is equally effective for treatment of both PFAF and PRAF not controlled by drug therapy when associated with structural heart diesease 2) In these pts a sensor-driven, regular, paced ventricular rhythm improves clinical status despite permanent or recurrent loss of atrial contribution to ventricular filling.

P1195 Factors predicting quality of life outcome following atrioventricular node ablation and DDDR mode-switching pacing for paroxysmal atrial fibrillation

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Atrioventricular node ablation and DDDR mode-switching pacing (A/P) usually improves quality of life (QOL) in patients with drug resistant paroxysmal atrial fibrillation. However, some patients do not respond as well as expected. This study assesses factors which may predict improvements in QOL and hence aid patient selection.

Methods: Patients undergoing A/P were prospectively assessed with a detailed history and echocardiography. The following parameters were recorded: age; sex; other heart disease or lone AF; number of antiarrhythmic drugs failed; length of history; number of episodes per month and average duration of episodes (multiplied to produce days of AF per month); left atrial size. Antiarrhythmic drugs were withdrawn 3 days before the procedure. QOL was assessed before and 3 months after ablation using the Psychological General Well Being questionnaire, the McMaster Health Index questionnaire and a visual analogue scale cardiac symptom score. At 3 months, patients were also assessed to see if they had developed chronic AF (absence of sinus rhythm on Holter monitor and >95% AF on pacemaker diagnostics). Association of preoperative factors with the percentage change in overall QOL score was assessed using multivariate, stepwise, linear regression.

Results: Forty-eight patients entered the study. Only the number of days spent in AF per month showed a significant association with percentage change in QOL score (regression coefficient 1.92; standard error 0.72; 95% confidence limits 0.43–3.3; p = 0.014). QOL was not significantly influenced by the development of chronic AF (17 patients).

Conclusions: In this study, a greater improvement in quality of life was seen in patients with a higher arrhythmia burden preoperatively. This supports the hypothesis that A/P should be considered preferentially for patients with frequent prolonged episodes of AF. However, the data also demonstrate that the transition to chronic AF after A/P does not necessarily result in a detrimental effect on QOL.

P1196 Predictors of chronic atrial fibrillation following atrioventricular node ablation and DDDR mode-switching pacing for paroxysmal atrial fibrillation

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Atrioventricular node ablation and dual chamber mode-switching pacing (A/P) is effective therapy in patients with drug resistant paroxysmal atrial fibrillation. About a third of patients develop chronic atrial fibrillation (CAF) soon after the procedure. This effectively results in VVIR pacing and may lead to symptoms of loss of atrial transport. It is not clear which factors predispose patients to develop CAF in this setting.

Methods: Patients undergoing A/P were prospectively assessed with a detailed history and echocardiography. The following parameters were recorded: age; sex; other heart disease or lone AF; number of antiarrhythmic drugs failed; length of history; number of episodes per month and average duration of episodes (multiplied to produce days of AF per month); left atrial size. It was also noted if patients were in AF at the start of their ablation procedure. Antiarrhythmic drugs were withdrawn 3 days before the procedure. Three months after the procedure, patients were assessed to see if they had developed chronic AF (absence of sinus rhythm on Holter monitor and >95% AF on pacemaker diagnostics). Association of preoperative factors with the development of CAF was assessed using multivariate, stepwise, linear regression.

Results: Forty-eight patients entered the study. 17 had developed CAF at the three month assessment. Pre-operative factors predicting CAF are shown in table 1: no other factors showed significant association with the development of CAF.

Table 1. Factors predicting transition to chronic AF

	Regression coefficient	Standard error	5% confidence limits	P
Lone AF	−0.295	0.125	−0.547 to −0.042	0.023
Days AF per month	0.023	0.011	0.002 to 0.045	0.036
AF at time of ablation	0.305	0.134	0.034 to 0.575	0.028

Conclusions: These data suggest that following A/P with antiarrhythmic drug withdrawal, atrial fibrillation is more likely to become permanent if it is secondary to other cardiovascular disease or is present at the time of the procedure. A higher arrhythmia burden also predisposes to the development of CAF. These findings may help target those patients who either require only a VVIR pacemaker or in whom other efforts to maintain sinus rhythm should be made.

P1197 Survival of patients with atrial fibrillation and VVI-pacemaker: a comparison of 30 years and 1670 patients

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Atrial fibrillation (AF) is the most common arrhythmia in adults, but data on long-term survival in these patients are rare. We analyzed the survival time of patients with chronic AF after implantation of a cardiac pacemaker (PM) for symptomatic or asymptomatic bradycardia over a period of 35 years.

Patients and Methods: Survival analysis was based on standardized control intervals of 6/12 months over a period from 1967–1997 and included other factors such as gender, symptoms and known coronary artery disease (CAD).

Results: During the 3 decades 6327 pts received a PM, 1670 (26%) had AF. Of these 915 were males, 761 females, (mean age: 72.9 y and 73.7 y, p = n.s.), 98% received a VVI-PM, 2%DDD-PM. Pts in the first decade (D1, 1967–1977, n = 401) were significantly younger (mean age 71.3 y ±10.2) than those in the second (D2, 1978–87, n = 704) (mean age 73.7 y, ±8.6) or third decade (D3, 1988–97, n = 565) (mean age 75.2 y, ±9.0) ($p < 0.003$). 50% mortality was reached in D1-pts at 39 months, in D2-pts at 86 months and in D3-pts at 94 months ($p < 0.0001$ D1 vs D2/D3) Prognosis of pts with chronic AF was not different for pts presenting between 1978–87 and 1988–97.

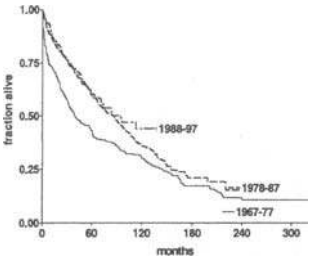

Figure 1 demonstrates Kaplan-Meier-survival plots of the three group of pts.

Conclusion: Despite advances in medical treatment, pts with chronic AF show nearly no difference in survival during the first 10 years after PM implantation.

EVALUATION OF ELECTROPHYSIOLOGY

P1198 Monitoring of initial changes of atrial fibrillation at multiple sites helps to define therapeutic options

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Knowledge of the initial changes of atrial fibrillation (AF) could contribute to understand and justifie some therapeutic options.

Methods: A computerized method for continuous evaluation of AF intervals (f-f intervals: as an index of local refractoriness) at different atrial sites was utilized to study the beginning of induced human AF. In order to analyze the shortest and the longest f-f intervals, the 5th (P5) and the 95th (P95) percentiles were also calculated. 82 AF episodes were induced (atrial burst pacing: 400/min, parasinusal zone) in 22 pts (60 ± 14 yrs). Atrial activity was recorded (bipole: 5 mm) and continuously analyzed at 3 atrial sites (parasinusal zone, os and distal part of coronary sinus). Recordings were also subdivided according to Wells classification.

Results: Type I AF was observed for all the time in 51 episodes (range, 2–103 sec.) which terminated spontaneously. Disorganized AF was observed from the beginning in 13 episodes (range, 3–664 sec.) which terminated spontaneously, and in 4 episodes > 10 min. treated by propafenone (P) or low energy endocavitary cardioversion (LEEC). A progressive disorganization of AF (from type I to III) was observed in 6 episodes (range, 59–1800 sec.) which terminated spontaneously, and in 4 > 10 min treated by P or by LEEC. During progressive disorganization the value of mean f-f intervals and of P5 tended to continuously decrease at all atrial sites indicating an increase of circulating wavelets and a reduction of refractoriness. The duration of episodes with a progressive or immediate disorganization (1129 ± 2367 sec.) was significantly longer ($p < 0.0067$) than that of organized episodes (48 ± 181 sec.). Progressive disorganization always appeared initially at the coronary sinus os (interatrial septum) and supervened after different time legs which never exceeded 7–8 min.

Conclusion: Disorganization being rapid and prolonging AF justifies an early interruption of the arrhythmia (atrial defibrillation). The beginning of disorganization at coronary sinus os probably represents another clue to support atrial septal pacing for prevention of AF.

P1199 The virtual atria, a new model to study atrial flutter and atrial fibrillation

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Atrial fibrillation is the most frequent and costly arrhythmia, provoking heart failure and embolism. There is no biologic model to test therapeutic interventions, therefore we need to develop new research tools. Computer simulations offer the advantage of showing details difficult to study in nature and of being reproducible. Furthermore, the limited surface and thickness of atria compared to the ventricles allows us to develop a realistic 3D model of atria with today computer power.

Methods: Based on a 2D heterogeneous and anisotropic model of cardiac tissue we have developed a new 3D anatomic model of human atria which uses a modeling of the membrane ion kinetics given by Beeler-Reuter or Luo-Rudy. The simulated size of both atria is 3 cm × 3 cm × 7 cm with about 250'000 cardiac cells. Holes of adapted size have been placed to simulate the veins and the valves. The propagation of a normal sinus beat at 50 cm/s is initiated from the sino-atrial node (SA node).

Results: Experiments for initiation of atrial flutter and atrial fibrillation have been performed, using a programmed stimulation protocol similar to those of electrophysiological studies. S^2 and S^3 have been initiated from several locations, intensities and timings and different action potential duration have been tested by a modulation of the ionic channels. Most of the attempts have led to nonsustained arrhythmias proving the stability of the tissue. However, we have identified that some locations are more likely to generate atrial flutter: the region between the inferior vena cava and the tricuspid valve and the region of the pulmonary veins. This observation correlates with the observations made in humans. We have been able to induce in our computer model of atria sustained atrial flutter with a periodic pattern and atrial fibrillation with a random pattern containing up to 6 independent wavelets.

Conclusion: This new virtual model of the atria can reproduce clinical observations and it allows us to observe the evolution of the action potential and the underlying ionic currents in any point on the surface of the atria, before, at the onset and during the arrhythmia. The possibility to test anti-tachy pacing techniques, ablation, defibrillation and pharmacological interventions is given.

P1200 Left atrial activation from the right atrium through two septal inputs

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Introduction: Interatrial activation routes and left atrial (LA) endocardial activation have not been delineated in humans.

Methods: In 13 patients (11 M, 2 F, mean age 26 ± 8 years; WPW syndrome, n = 8; AVNRT, n = 1; PSVT, n = 1; atrial tachycardia, n = 3) with a patent foramen ovale, complete LA endocardial activation mapping was performed during sinus rhythm and lateral right atrium (RA) pacing (680 ± 80 ms) using the Cordis Biosense system after ablation. No patient had structural heart disease, atrial fibrillation or had undergone linear ablation.

Results: A mean of 71 ± 20 points was used to reconstruct endocardial LA maps with a volume of 34 ± 10 cc. During sinus rhythm and relatively high lateral RA pacing, the LA was activated craniocaudally in 71 ± 10 ms from a single high anterior septal breakthrough including the anterior aspect of the right superior pulmonary vein (PV) (in 8) correlating with an inferior P wave vector (58 ± 28°). Terminal LA activation occurred posterolaterally in the vicinity of the mitral annulus. During low lateral RA pacing (n = 9), the LA was activated caudocranially in 71 + 11 ms (no major anisotropy): in one case from a midseptal breakthrough and in 8 from a single inferior breakthrough 24 ± 12 mm below the breakthrough site in sinus rhythm. Terminal LA activation occurred near the left superior PV and correlated with a superior P wave vector (−25 ± 64°). In all but one case the posterior mitral annulus margin was activated from septal to lateral.

Conclusions: Two main inputs ('Bachman's bundle' and coronary sinus region) provide the route for RA to LA activation. Their spatial positions correlate with craniocaudal and caudocranial activation as well as the resulting P wave vector.

P1201 Trends in the prematurity of premature beats before atrial fibrillation onset: evidence for two distinct mechanisms

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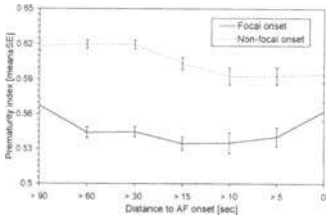
Previous studies from ourselves and others have documented that atrial premature beats (APB's) from a single focus are responsible for initiating paroxysmal atrial fibrillation (AF) episodes in some patients.

Methods: Holter recordings from 177 subjects with paroxysmal AF were analysed and AF episodes were identified by a previously validated technique. The distribution of coupling interval ratios (prematurity index, PI) of ABP's was calculated for successive time windows prior to AF onset. The distributions were classified as suggestive of focal onset or not based upon an automated analysis which detected whether a higher than expected proportion of all APB's with a uniform PI was present.

Results: 74 recordings in 39 pts (24 male, 62 ± 13 years old) were analysable. 15 (20%) were classified as having probable unifocal APB's. Subjects without unifocal APB's had a longer mean PI at 0.61 ± 0.11 vs. 0.55 ± 0.1 ($p = 1.3 \times 10^{-112}$, absolute values for mean coupling intervals of 512 ms and 483 ms respectively) but exhibited a progressive decline in PI towards AF onset (figure). There was no change in PI in subjects with presumed focal onset.



Conclusion: (1) Subjects with unifocal APB's prior to AF onset have more premature APB's than other paroxysmal AF patients. (2) Ectopics do not become more premature in subjects with the unifocal APB's, but do so in other patients. These data are consistent with there being two distinct mechanisms of AF; unifocal APB's and increasing atrial instability.

P1202 Regional differences in the recovery course of tachycardia-induced changes of atrial electrophysiological properties

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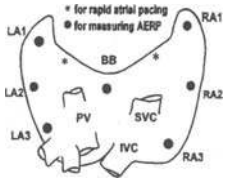
Background: Regional differences in recovery of tachycardia-induced changes of atrial electrophysiolgical properties have not been well studied.

Methods: In experimental group I (15 dogs), atrial effective refractory period (AERP) and inducibility of atrial fibrillation (AF) were assessed before and after complete atrioventricular junction (AVJ) ablation with 8-week rapid right atrial (RA) pacing (780 bpm) and VVI pacing. In experimental group II (7 dogs), AERP and inducibility of AF were assessed before and after 8-week rapid left atrial (LA) pacing and VVI pacing (fig).

Results: In the two experimental groups, recovery of atrial electrophysiological properties included a progressive recovery of AERP shortening, recovery of AERP maladaptation, and decrease of episodes of reinduced AF. However, recovery of shortening and maladaptation of AERP and inducibility of AF was slower at the LA than at the RA and Bachmann's bundle. The time with disappearance of the three events were shown in table (presented as hours after termination of pacing).



Site	Post-pacing AERP↓		Maladaptation of AERP		AF(+)	
	I	II	I	II	I	II
RA1	12	4	12	4	12	8
RA2	4	0	4	0	4	4
RA3	4	0	4	0	4	0
BB	4	0	4	0	4	0
LA1	24	20	24	20	24	20
LA2	24	20	24	16	24	20
LA3	28	20	28	20	28	20

Conclusions: The LA might play a critical role in initiation of AF.

P1203 Reduction in the susceptibility to atrial fibrillation by modification of atrial electrophysiology despite non-linear atrial ablations

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Background: I has been suggested that long linear lesions are mandatory for curative ablation in the setting of atrial fibrillation (AF). Even in non-trabecularized areas of the right atrium lesion continuity is often difficult to achieve over a long distance. We tested the hypothesis that atrial ablations may modify the electrophysiologic substrate and may decrease the susceptibility to AF.

Methods: Eight sheeps (75–86 kg) with rapid atrial pacing for 6 ± 2 months to produce chronic AF (>3 weeks of sustained AF) underwent this study. Three long lesions were created in the right and left atrium using a novel ablation catheter with coiled electrodes.

Results: Examination of the explanted hearts showed multiple, discontinuous lesions in both atria. Lesion continuity over the whole distance of preselected target sites were only found in the cavotricuspid isthmus. The mean AF cycle lengths increased from 105 ± 25 ms to 170 ± 35 ms ($p < 0.05$). The internal atrial defibrillation threshold was reduced from 7 ± 2 Joule to 2 ± 1 Joule ($p < 0.05$). Reproducible induction of AF was achieved by using one single extrastimulus before ablation in all animals. After ablation AF was induced with a single extrastimulus in only one animal ($p < 0.05$).

Conclusions: A decrease in the susceptibility to AF and a significant modification of atrial electrophysiology is possible despite predominant discontinuous lesions in both atria in a sheep model of chronic atrial fibrillation.

P1204 Repeated electrophysiological evaluation of sinus node function following internal electrical cardioversion of chronic atrial fibrillation

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In an era when the future of implantable atrial defibrillators is being evaluated, there is little information about the functional state of the sinus node in patients with chronic atrial fibrillation (AF) who have undergone electrical cardioversion. Here we present the preliminary results of an ongoing study of the functional state of the sinus node in cases of long lasting AF following internal current cardioversion.

Methods: We studied 32 consecutive patients, free of antiarrhythmic drugs, with chronic AF (>3 months), following successful internal electrical cardioversion. Each patient who remained in sinus rhythm underwent an electrophysiological study (EPS) immediately after cardioversion (t0), after 24 hours and after 30 days.

Results: The results of the 3 EPS examinations are given in the table below, where SNRTc = corrected sinus node recovery time, ERP500 = effective refractory period of right atrium at 500 ms pacing cycle length, d% SCL/A = percentage change in sinus node cycle length after atropine administration, P dur = duration of P wave.

Table

Time of study	SNRTc	ERP500	d% SCL/A	P dur.
t0	294 ± 109	203 ± 14	21.3 ± 10	155 ± 33
24 hrs	313 ± 104	249 ± 26#	23.8 ± 8	142 ± 27*
30 days	318 ± 112	255 ± 25#	20.6 ± 12	141 ± 24*
		#$p < 0.001$ vs. t0		*$p < 0.05$ vs. t0

Conclusion: These preliminary data indicate a change in atrial refractoriness and P wave duration during the first month after successful conversion of AF, with the main changes developing during the first 24 hours. In contrast, they do not confirm any changes in sinus node functional tests during the same period.

P1205 Electrophysiological characteristics of the human atria after cardioversion of persistent atrial fibrillation

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Background: In animal models induced Atrial Fibrillation (AF) shortens the atrial Effective Refractory Period (aERP) and reverses physiological adaptation to rate. This could be related to changes in Monophasic Action Potential (MAP) behaviour. The aim of our study was to analyze aERP, MAP duration and rate adaptation in patients (pts) with persistent AF after cardioversion.

Methods and Results: With determined aERP and MAP90 at 5 paced cycle length (300–700 ms) and 5 atrial sites after internal cardioversion of persistent AF in 25 pts: 14 in wash-out (WO) and 11 on Amiodaron (A). the mean aERPs were 195.5 ± 18.8 ms in WO and 206.3 ± 17.9 ms in A, $p < 0.001$. The mean MAP90 duration was 220.8 ± 31.1 in WO and 240.8 ± 36.7 in A, $p < 0.0001$. The aERP/MAP90 ratio was 0.89 ± 0.15 in WO and 0.87 ± 0.10 in A, p = ns. Slope values indicating a normal (> 0.007) or nearly normal (0.005–0.006) adaptation of ERP to rate were found in 77% of the paced sites. Accordingly, MAP90 duration constantly increased from the shorter pacing cycle (300 ms) to the longer one (700 ms): 206.1 ± 24.9–237.3 ± 27.2, r = 0.95 in WO and 219.9 ± 25.5–257.3 ± 31.1, r = 0.94 in A.

Conclusions: After cardioversion of persistent AF: 1) aERP adaptation to rate was normal o nearly normal in the majority of the pts; 2) MAP90 duration showed a similar behaviour increasing at longer pacing cycle length; 3) no differences have been observed in aERP/MAP90 ratio between WO and A pts.

PREDICTING AND PREVENTING POSTOPERATIVE ATRIAL FIBRILLATION

P1206 Predictors of persistent atrial fibrillation following open heart surgery

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Purpose. Although atrial fibrillation (AF) is the most common postoperative complication in patients (pts) undergoing open heart surgery (OHS), routine use of antiarrhythmic treatment is not recommended. In these pts AF usually converts spontaneously to sinus rhythm and farmacological interventions are often effective. However AF may persist. The aim of this study was to identify the factors that predict the persistence of AF after OHS.

Methods and results. We examined 121 consecutive pts who developed AF after OHS. Over a period of 30 ± 2 days, AF converted to sinus rhythm in 108 pts (89%), while persisted at discharge in 13 pts (11%). Variables associated with persistent AF to univariate analysis are listed below:

	Persistent AF	Converted AF	p
Age (years)	72 ± 8	63 ± 9	0.006
Female gender (%)	70	30	0.01
NYHA class (1–4 score)	2.5 ± 0.5	1.8 ± 0.6	0.004
Valvular procedure vs CABG (%)	90	10	0.0001
History of AF (%)	30	7	0.02
Left atrial diameter (mm)	51 ± 4	41 ± 6	0.0001
Left ventricular EF (%)	47 ± 4	53 ± 8	0.04

Multivariate analysis revealed that valvular procedure was the strongest indipendent risk factor of persistence of AF (OR 33.6, p 0.007) and older age and left atrial dilatation provided a small contibution in predicting events.

Conclusions: in pts undergone OHS followed by AF, valvular procedure, particularly when associated to advanced age and left atrial dilatation, identifies patients at high risk of persistence of arrhythmia who should particularly benefit of preoperative prophylactic treatment.

P1207 Single-day loading dose of oral amiodarone does not prevent atrial fibrillation after coronary artery bypass surgery

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It has been shown that one-week loading dose of oral amiodarone can reduce presence and severity of atrial fibrillation (AF) following coronary artery bypass surgery (CABS). However, there is no evidence whether single-day loading dose of oral amiodarone has beneficial effect in preventing AF after CABS.

In order to assess the effect of single-day loading dose of oral amiodarone in prevention of AF after CABS we conducted double-blind randomized study and evaluated 315 consecutive patients (pts). Pts received either amiodaron (159 pts) or placebo (156 pts) in a dose of 1200 mg one day before CABS, following with 200 mg daily during next 7 days, including the day of operation. All pts were monitored for AF during first 48 h in the ICU. After that serial electrocardiogram(twice daily routinely, and if heart rate (HR) was >100/min, or pt had angina, hypotension, dyspnea or sweating) and HR measurements (4 times daily routinely) were obtained in order to detect AF. Only episodes of AF that lasted more than 1 hour, or were shorter but associated with symptoms and/or hemodynamic disturbances, were taken into consideration. In addition, overall mortality, other rhythm disturbances, and duration of hospital stay were also evaluated.

Results: Pts with and without postoperative AF were similar regarding age, sex, preoperative EF and severity of coronary artery disease, operative data, and electrolyte status. The incidence and characteristics of AF, as well as mortality and duration of hospital stay are shown in table:

	Amiodarone (n = 159)	Placebo (n = 156)	P value
AF (pts,%)	31 (19.5)	33 (21.2)	NS
AF episodes	1.92 ± 1.2	2.27 ± 2.2	NS
AF duration (h)	28.4 ± 39.9	21.2 ± 29.0	NS
Total mortality (pts,%)	7 (4.4)	5 (3.2)	NS
Hospital stay (days)	10.3 ± 6.2	10.0 ± 3.6	NS
Other arrhythmias (pts,%)	48 (30.2)	45 (28.8)	NS

Conclusion: Single-day loading dose of amiodarone does not prevent occurrence, duration and number of episodes of AF in pts undergoing CABS and has no effect on overall mortality and duration of hospital stay.

P1208 Signal-averaged p-wave duration accurately stratifies risk for atrial fibrillation after coronary artery bypass grafting

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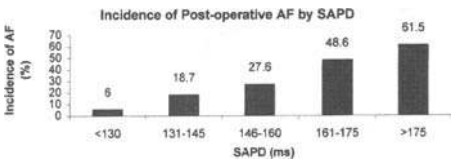
Atrial fibrillation (AF) occurs in 20–40% of patients after coronary artery bypass grafting (CABG). Signal-averaged P-wave duration (SAPD) has been proposed as a predictor for AF after CABG. We determined the influence of pre-operative SAPD on incidence of post-operative AF in 326 patients undergoing elective CABG.

Ninety two (28.2%) patients developed post-operative in-hospital AF. The mean SAPD was significantly longer in AF compared to non-AF patients (158 v 145 ms; $p < 0.0005$). The incidence of AF increased progressively with increasing SAPD such that 3/50 (6%) patients with a SAPD < 130 ms compared to 8/13 (61.5%) patients with a SAPD > 175 ms developed AF (figure). The odds ratio (95% confidence interval) for AF was 2.11 (1.62–2.74) for each increase of 15 ms in SAPD, and 4.95 (2.96–8.28) for patients with a SAPD > 155 ms. SAPD > 155 ms predicted AF with a sensitivity of 63%, a specificity of 74%, and positive and negative predictive accuracies of 49% and 82%, respectively.



There is a clear relationship between SAPD and incidence of AF after CABG which may be used to identify patients at high and low risk for the arrhythmia.

P1209 Atrial conduction changes after cardiopulmonary bypass and their relationship to the development of post-operative atrial fibrillation

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Background Atrial fibrillation (AF) is common after cardiopulmonary bypass (CPB). The mechanism is unclear but may involve slowed intra-atrial conduction due to ischaemic injury. Prolongation of pre-operative P-wave duration appears to be a weak predictor of post-op AF, but no study has explained the changes in atrial conduction following CPB or their relationship to the development of AF.

Methods Signal-averaged P-wave duration was analysed in 97 consecutive patients undergoing first-time CABG with no prior history of AF, using a previously validated P-wave selective averaging system. Measurements were performed pre-operatively and at day 1, day 5 and week 6 post-operatively and compared in patients who developed AF (>30 mins or requiring treatment).

Results AF developed in 31 patients (32%).

P-wave duration	Pre-op (SEM)	1 day post-op (SEM)	5 days post-op (SEM)	6 weeks post-op (SEM)
AF	139 ms ± 2.7	129 ms ± 3.6*	130 ms ± 2.8	131 ms ± 2.8**
Non-AF	136 ms ± 1.8	129 ms ± 1.6*	127 ms ± 1.6	139 ms ± 2.5
Total	137 ms ± 1.5	129 ms ± 1.5*	128 ms ± 1.4	136 ms ± 1.9

*$p < 0.005$ cf pre-op; **$p < 0.05$ cf non-AF

Conclusion Contrary to expectation, intra-atrial conduction accelerates after CPB, indicating that the pro-fibrillatory effects must be mediated by shortening of atrial refractoriness to enable re-entry. Moreover, the failure of P-wave duration to return to baseline values in patients who developed AF suggests that they sustained persistent structural changes of atrial myocardium, possibly due to ischaemic injury. Further studies are needed to evaluate the nature and cause of these alterations in atrial electrophysiology

P1210 Exon 7 gene polymorphism as a risk factor for atrial fibrillation following surgical coronary artery revascularisation

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Background and Methods: Atrial Fibrillation is a leading cause of morbidity post coronary artery bypass grafting and has an incidence of approximately 30% in most series. It is thought to be due to intraoperative myocardial ischaemia. Polymorphisms involving the gene encoding endothelial Nitric Oxide Synthase (eNOS) could indeed influence coronary flow. We have investigated the influence of the Glu298Asp polymorphism in the gene encoding eNOS in a group of 109 patients undergoing surgical coronary artery revascularisation with reference to postoperative atrial fibrillation.

Results: A new polymorphism (named E7II) was detected by SSCP-PCR in the exon 7 genomic amplicon that was apparently unrelated to the previously described Glu298Asp polymorphism (E7I). E7I was present in 67% of the patient population compared to 28.2% of controls and was homozygous in 8.8% of the patient population and none of the controls. ($P < 0.001$) (Gene frequency 0.379 vs 0.141). For E7II, the allele was present in 62.9% of the patient population and 50.5% of controls (Gene frequency 0.317 vs 0.258)($P = 0.06$). 13.6% of patients with the E7I gene experienced atrial fibrillation compared to none of the normal population. 9.1% of those with the E7I gene experienced other arrythmias while none of the normal population was affected (n = 67). Similarly, 18.2% of patients with the E7II gene experienced atrial fibrillation whilst 3.1% of the normals in this group were affected ($p = 0.05$). 12.7% of patients with the E7II gene experienced other arrythmias while none of the normals were affected(n = 87).

Conclusions: This study has documented for the first time an association between atrial fibrillation post CABG and eNOS gene polymorphisms at exon 7. These findings could have important prognostic and possibly therapeutic implications for patients undergoing coronary artery bypass grafting.

P1211 Preoperative low-dose intravenous amiodarone in preventing atrial fibrillation after coronary artery bypass grafting

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Background: Atrial fibrillation (AF) occurs commonly after coronary artery bypass grafting (CABG) and may result in hemodynamic compromise and severe symptoms. The purpose of this study was to assess the use of preoperative low-dose intravenous amiodarone as prophylaxis against AF after CABG in a prospective, randomized, placebo-controlled fashion.

Methods: One hundred and forty patients were given either intravenous amiodarone (66 patients) or placebo (74 patients) for three days before elective CABG. Therapy consisted of 150 mg amiodarone for loading and 0.4 mg/kg/hr for 72 hours.

Results: Postoperative AF occurred in 8 of the 66 patients in the amiodarone group (12%) and 25 of the 74 patients in the placebo group (34%) ($p = 0.02$). The maximal ventricular rate during AF was significantly lower in the amiodarone group than that in the placebo group (110 ± 23 vs 137 ± 26 bpm, $p < 0.01$). The amiodarone group had significantly shorter intensive care unit stay (104 ± 32 vs 138 ± 28 hours, $p < 0.01$). Nonfatal postoperative complications occurred in six amiodarone-treated patients (9%) and in eight patients receiving placebo (11%, p = NS). Fatal postoperative complications occurred in two patients who received amiodarone (3%) and in five who received placebo (7%, p = NS).

Conclusions: Preoperative low-dose intravenous amiodarone significantly reduced the incidence of postoperative AF. Furthermore, low-dose intravenous amiodarone did not increase the risk of intraoperative and postoperative complications in the patients receiving CABG.

P1212 How good is the pre-operative signal averaged p-wave for prediction of post-operative atrial fibrillation? – a prospective study in 465 patients

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Background: Analysis of the pre-operative signal averaged P wave (SAPW) is reported to be of variable utility as a predictor of atrial fibrillation (AF) after coronary bypass grafting (CBG). Many studies reporting high diagnostic accuracy are flawed by small numbers of patients and retrospectively derived diagnostic criteria. We report the results of a large prospective study that utilises a prospectively derived diagnostic criterion to predict AF after CBG.

Methods: SAPW recordings were made in 465 pts (363 M, mean age 62.6 yrs) before CBG in 2 UK centres. A P wave specific averaging system was used that has been previously described. Continuous electrocardiographic (ECG) monitoring was performed for 48 hrs after CBG with routine ECG recordings thereafter until hospital discharge.

Results: 130 (28%) pts developed AF > 1 hr duration (group AF). Mean P-wave duration was significantly longer in these pts than in those who remained in sinus rhythm (147 ± 13 ms vs 143 ± 15 ms $p < 0.002$). The positive predictive accuracy of a P-wave duration of ≥ 141 ms was 33% with a negative predictive accuracy of 80%. Specificity was 57% and sensitivity 71%.

Conclusion: We have found that when applied to a large number of patients with prospectively defined diagnostic criteria analysis of the pre-operative SAPW is a poor predictor of AF after CBG. However, a short P wave duration (< 141 ms) implies a low risk of postoperative AF which may be clinically useful. These findings confirm the results of previous moderately large investigations.

P1213 Bi-atrial synchronised pacing prevents atrial fibrillation after coronary artery bypass surgery

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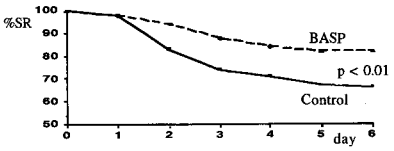
Background Atrial Fibrillation (AF) after coronary artery bypass surgery (CABG) is common and associated with increases in cost and morbidity. Pharmacological prophylaxis is of limited efficacy and often contra-indicated because of haemodynamic instability. We designed a prospective randomised trial to determine whether bi-atrial synchronised pacing (BASP) via epicardial wires can prevent AF after CABG.

Methods 230 patients undergoing first-time CABG, in sinus rhythm pre-operatively with no prior history of AF, randomised to post-operative BASP (using a standard SSI-generator programmed to AAT mode) or control. Pairs of epicardial wires placed on the right atrium and posterior aspect of the left atrium. Pacing commenced within 4 hours of surgery and continued for 96 hours with pacing parameters measured daily. Episodes of AF > 30 mins or requiring treatment noted.

Results BASP successfully maintained to 96 hours in 89% of cases, intermittent/total loss of capture or sensing at maximum settings occurring in 11%. BASP reduced the incidence of AF from 33.9% to 17.9% (RR 0.53) with no excess haemorrhage, infection or other morbidity.



Conclusion Bi-atrial pacing following cardiopulmonary bypass is technically feasible, safe, and effectively reduces the incidence of AF.

PACING FOR PREVENTION OF ATRIAL FIBRILLATION

P1214 Temporary left atrial pacing reduces atrial fibrillation incidence early after cardiac surgery

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Acute electrophysiological studies have shown that left atrial pacing (LAP) could prevent atrial fibrillation (Afib) initiation. The early postoperative period of cardiac surgery (CSurg) is associated with a high incidence of Afib. Thus we evaluated the role of temporary LAP on Afib incidence following CSurg.

Methods: Temporary pacing leads were implanted on the roof of the LA during CSurg in 24 patients (pts) (Gr I). The atrial pacing rate was set either at 100 bpm for 3 days and decreased to 90 bpm for the 2 following days or at 10 bpm above the intrinsic sinus rate in order to obtain a permanent atrial capture. Incidence of Afib in Gr I was compared to that of an age-matched control group during the same period (Gr II, n = 21). In this group, pts were paced in the RA whenever clinically necessary. Chronic Afib, LA diameter (D) > 50 mm, thyroid dysfunction, and prior use of antiarrhythmic drugs were exclusion criteria. Presence of Afib was evaluated using 24 hour Holter monitoring (Day 1), ECG telemetry and a continuous loop recording system for the 5 days following CSurg. Aortic valve replacement was performed on 4 Gr I and 4 Gr II pts. The remaining pts underwent coronary artery bypass grafting. No pt received postoperative prophylactic beta blocker therapy.

Results are expressed as mean ± SD and number of pts.

	N	Age (y)	EF (%)	LAD (mm)	BB	Ao Cl. (mn)	I	Afib*
Gr I	24	60 ± 10	60 ± 14	41 ± 9	16	76 ± 36	9	5
Gr II	20	61 ± 7	64 ± 11	40 ± 7	12	82 ± 27	5	11

*$p \leq 0.05$. Ao Cl: Aortic clamp duration; BB: preoperative beta blocker therapy; I: postoperative inotropic drugs. No difference could be found between the two study groups except for the incidence of Afib.

Conclusions: These preliminary results suggest that in the early post operative phase after cardiac surgery temporary left atrial pacing may reduce atrial fibrillation incidence.

P1215 Long-term biatrial pacing. what happens with interatrial condiction disturbances?

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IACD plays important role in pathogenesis of atrial arrhythmias and in some pts RA pacing can aggravate recurrence of arrhythmia; BiA pacing is accepted mode of non-pharmacological prevention of atrial arrhythmias in pts with IACD. In 91 pts with implanted split BP BiA pacing system we examined acute and chronic atrial timing values.

Examined Parameters	S(P)-Q	PII duration	IACT*	TAAT**
	Average (median)			
Sinus rhythm	210 (200)	157 (160)	117 (110)	183 (180)
RA pacing	245♣ (240)	178♣ (170)	154♣ (150)	214♣ (210)
BiA pacing	201♣ (190)	126♣ (125)		133♣ (135)

*IACT = S(PII)-outset A of opposite atrium; **TAAT (Total Atrial Activ. Time) = S(PII)-end A of opposite atrium; ♣ – Average difference significant in comparison to sinus rhythm

Values of TAAT were examined monthly (presented in ms):

Months	1	2	3	4	5	6
No of pts	54	36	34	23	17	32
Sinus rhythm	184	178	179	179	190	178
BiA pacing	127	123	127	124	120	119

RA pacing aggravates significantly IACD in comparison to sinus rhythm. BiA pacing normalise all atrial activation times. IACD seems to be stable during long term BiA pacing and its values (obtained with temporary reprogramming to sinus rhythm) do not change.

P1216 Intermittent or continuous overdrive atrial pacing significantly reduces paroxysmal atrial fibrillation recurrences in brady-tachy syndrome

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Overdrive Atrial Pacing (OAP) has been associated with a lower rate of recurrent paroxysmal Atrial Fibrillation (PAF).

Aim of the study was to evaluate the impact of intermittent or continuous OAP on PAF recurrences in a selected population of highly symptomatic brady-tachy patients implanted with a DDDR pacemaker. Study population included 35 patients (mean age 75 + 11, 12 M, 23 F) affected by brady-tachy syndrome with at least three symptomatic episodes of PAF during the last month before implantation. Intermittent OAP was obtained by programming the device in DDDR mode, continuous OAP through a dedicated algorithm, named *Consistent Atrial Pacing* (CAP), which updates beat by beat the Atrial Escape Interval to overdrive suppress spontaneous atrial activity (both sinus rhythm and premature atrial complexes (PAC). Patients were randomized in two groups, DDDR + CAP versus DDDR and followed for two months. After the first month the pacing modality was crossed over. 45% of patients were on antiarrhythmic treatment which did not change during the study period.

Results: 90% of patients in DDDR and 85% in DDDR + CAP were free from symptomatic PAF recurrences. 50% in DDDR and 35% in DDDR + CAP had no mode switching episodes stored in the pacemaker memory (p = n.s.)

	AP%	MS/d	Msd/d	PAC/d	PVC/d	ARP1	ARP2
CAP	97 ± 3	1.5 ± 2.8	117 ± 224	0.4 ± 0.7	375 ± 570	253 ± 48	250 ± 32
DDDR	87 ± 16	1.4 ± 2.9	98 ± 267	2.1 ± 4.3	521 ± 694	261 ± 53	247 ± 31
p	<0.01 n.s.	n.s.	<0.1	n.s.	n.s.	n.s.	

Legenda: AP = Atrial Pacing; MS = mode switching; d = day; MSd = MS duration (min); PAC = premature atrial complexes/1000; PVC = premature ventricular complexes; ARP1 = Atrial Refractory Period (600 ms); ARP2 = ARP (400 ms).

Conclusions: Both intermittent and continuous OAP strongly decrease PAF recurrences in selected highly symptomatic brady-tachy patients. Continuous OAP significantly increase AP percentage and decrease the number of PAC/day without a major impact on arrhythmia recurrences.

P1217 First occurrence of paroxysmal atrial fibrillation in patients inplanted with preformed vs non preformed atrial leads

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The **Aim** of this study was to evaluate if the primary occurrence of paroxysmal atrial fibrillation (PAF) in patients (pts) that had received a dual chamber pacemaker could be due to the shape of the atrial lead.

Methods: A population of 57 patients (pts) was divided into two groups: 26 pts (group 1) were inplanted with J-shaped screw-in bipolar atrial leads (Medtronic CapSure Fix 7.2 french, silicone, steroid eluting Model 5568, Medtronic CapSure Fix 7.5 french, polyurethan, steroid eluting Model 4568 and Medtronic 6.6 french, polyurethan, Model 4557 leads), 31 pts (group 2) were implanted with non preformed screw-in bipolar atrial leads (Medtronic 7.2 french, silicone, steroid eluting CapSure Fix Model 5068, Medtronic 7.2 french, silicone, steroid eluting CapSure Fix Model 5078 and Medtronic 7.2 french, polyurethan, steroid eluting CapSure Fix Model 4068 leads). There were no significant differences between the two groups in terms of age, sex, pathologies left atrial size and implant site. Follow up visits were performed at discharge and every 3 months for 1 year in both groups.

Results: Only 1 patient of group1 developed PAF at 12 months follow up (1/26 = 4%), while 8 pts belonging to group 2 (8/31 = 29%) developed PAF (3 of them were found in AF at 1st month follow up, 2 at 3th month follow up, 2 at 6th month follow up and 1 at 12th month). A significative difference between occurrences in two groups ($P < 0.05$, Fisher Exact Test) was found No adverse event occurred in either group during the study (dislodgement, infections, etc.).

Conclusions: Data collected seem to confirm significant AF proarrhythmicity with non preformed atrial pacing leads. This proarrhytmicity is probably due to the fact that this kind of non-preformed lead in the atrium results in a larger lead curve thus causing a mechanical stimulation of the right atrial wall that in turn could induce AF.

P1218 Is suppression of paroxysmal atrial fibrillation by synchronised bi-atrial pacing related to shortening of intra-atrial conduction delay?

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Background Multisite atrial pacing has been reported to prevent paroxysmal atrial fibrillation (PAF). Postulated mechanisms include the shortening of intra-atrial conduction times and alteration of atrial refractoriness. We investigated the effects of synchronised bi-atrial pacing on P-wave duration and energy using signal averaged electrocardiography (SAECG) and the relationship of these changes to the suppression of AF.

Methods 10 patients with refractory PAF (mean age 63, 8 male, 6 lone AF) were treated with bi-atrial permanent pacing (ELA Chorus RM, left atrial pacing via coronary sinus). P-wave SAECG was recorded using a previously validated P-wave selective averaging system. Patients were continuously monitored by the device for episodes of AF during three month periods in biatrial (DDDbi) and control (DDI) modes.**Results** P-wave duration was significantly reduced during bi-atrial pacing compared with control but this did not correlate with the degree of suppression of AF (r = 0.25, p = NS). No differences in P-wave energy were detected between pacing modes.

	DDI	DDDbi
P-wave duration (ms)	178 ± 5.6	147 ± 5.2*
% time in AF	22.5 ± 10.3	4.8 ± 4.1*
Median AF episodes (range)	151 (12–255+)	28 (0–255+)
P 30 (μV^2.s)	24.9 ± 4.1	22.1 ± 3.7
P 60 (μV^2.s)	3.8 ± 0.5	3.3 ± 0.5

*$p < 0.05$

Conclusion Bi-atrial synchronised pacing reduces P-wave duration and suppresses paroxysmal AF. However, the magnitude of the anti-arrhythmic effect did not correlate with the degree of reduction in intra-atrial conduction delay and may involve alternative electrophysiological mechanisms.

INITIATION OF ATRIAL FIBRILLATION

P1219 Characteristics of epicardial electrograms from the right atrial free wall distinguish patients in whom induced atrial fibrillation is sustained

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Background: It has been suggested that the functional properties of the crista terminalis (CT) have a central role in the atrial myocardial substrate for sustained atrial fibrillation (AF). We tested the hypothesis that the characteristics of epicardial atrial electrograms, particularly along the CT, distinguish atria in which induced AF is sustained.

Methods: Epicardial mapping was performed on 10 patients, with no history of AF, undergoing coronary artery bypass surgery before atriotomy or cardioplegia. The mapping plaque was made up of 112 unipolar electrodes at 3.5 mm spacing and was placed over the right atrial free wall such that the line of the CT traversed the middle of the array. Electrograms were recorded during steady state pacing from near the sinus node at cycle lengths of 500 ms and 660 ms. Electrogram duration and morphology (simple or complex) were determined. AF was induced by 7 Hz pacing for 5 sec up to four times and then twice for 10 sec. AF was defined as sustained if it lasted >30 sec. The electrogram data from the region of the CT (42 electrodes) and of the non-CT myocardium (70 electrodes) were then compared for each patient.

Results: Sustained AF was induced in 5 of the 10 patients. During 500 ms pacing, overall electrogram duration was greater in AF (42.15 ± 11.1 ms) than non-AF patients (25.7 ± 6.4 ms; $p < 0.001$). In the atria that sustained AF the electrogram duration was longer in the CT region compared to the non-CT myocardium when pacing at 500 ms ($p < 0.002$). By contrast, although at 660 ms pacing the overall electrogram duration was longer in patients with AF ($p < 0.03$), there was no significant difference between the CT and non-CT myocardium. Differences in electrogram complexity were not significant.

Conclusions: In atria that will sustain AF, electrogram duration, particularly in the region of the CT, is greater than in atria that will not. Only in atria that will sustain AF do epicardial electrograms in the region of the CT become distinctly different from surrounding myocardium and only at shorter cycle lengths. Interval dependent functional properties of the CT may, therefore, play a central role in the myocardial substrate maintaining AF.

P1220 Analysis of onset of paroxysmal atrial fibrillation during holter recordings

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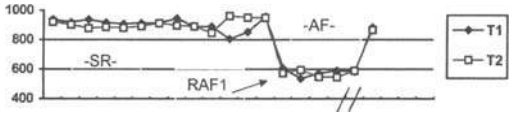
To evaluate the pattern of paroxysmal atrial fibrillation (PAF) onset and the relation between the preceding cycles and the coupling interval (RAF1), we studied 31 pts (71% males, 42–87 yrs) with 62 PAF lasting >30 sec on Holter recordings. These parameters were considered: RAF1, RR-1 (the last cycle before RAF1), RR-2, RR-3, RR-5, RR-10, RR-15, RR-30, RR-45, RR-60, RR-5 m, RR-10 m, RR-15 m and RR-30 m (the corresponding cycles before RAF1). The first three RR intervals and the mean cycle of first 100 RR intervals during AF (AFcl) as well as of 5 min after sinus rhythm recovery were also calculated. According to presence or absence of short-long sequence before arrhythmic events, PAF episodes were classified as Type 1 (T1; n = 25) and Type 2 (T2; n = 37).



The AFcl was similar in both type of PAF onset (581 ± 30 vs 589 ± 21 ms). In comparison to preceding cardiac cycles, a reduction in RR-3 was observed in T1 onset, whereas a slight increase was noticed in T2. Percentage of episodes without ectopic beats was significantly higher in T2 than T1 onset (65 versus 24%). By regression analysis, a significant correlation between RAF1 and preceding cardiac cycles was consistently evident only in T2 onset. These data suggest that an increase in heart rate is uncommon before T1 and T2 PAF onset. The major variations in cardiac cycles seem to be confined within a few beats before PAF onset.

CELLULAR, GENETIC AND BASIC MECHANISMS OF ATRIAL FIBRILLATION

P1221 Plasma atrial and brain natriuretic peptides in patients with lone atrial fibrillation

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Background: Enhanced production of natriuretic peptides have been identified as a marker of left ventricular (LV) systolic dysfunction and hypertrophy. Only a few studies have investigated the influence of atrial fibrillation on plasma atrial and brain natriuretic peptides (ANP and BNP).

Methods: Plasma ANP and BNP levels were examined in 30 patients (male/female: 20/10) with chronic lone atrial fibrillation (group AF). The data were compared with those in age and sex matched healthy subjects with normal sinus rhythm (CONTROL, n = 30). Clinical characteristics, findings of echocardiography and Holter ECG were also analysed. All patients in groupAF attended at the out patient clinic regularly and attained heart rate (HR) at rest < 90 beats/min. Patients with LV ejection fraction (LVEF) < 55% were excluded from the study.

Results: ANP and BNP levels were significantly higher in groupAF than in CONTROL (ANP: 55 ± 32 vs 29 ± 13 pg/ml p = 0.004, BNP: 123 ± 80 vs 36 ± 20 pg/ml p < 0.001). No significant difference was found in mean blood pressure (MBP: 92 ± 10 vs 93 ± 10 mmHg), LV mass index (LVMI: 92 ± 13 vs 91 ± 15 g/m2), LV enddiastolic dimension (LVDd: 45 ± 5 vs 44 ± 4 mm), LV endsystolic dimension (LVDs: 28 ± 6 vs 26 ± 7 mm) and LVEF (62 ± 5 vs 64 ± 5%). In CONTROL, both ANP and BNP levels showed significant correlation with age (ANP: r = 0.70 p < 0.001, BNP: r = 0.81 p < 0.001). But in group AF, only BNP levels had significant correlation with age (r = 0.72, p < 0.001). MBP, LVMI, LVDd, LVDs, LVEF, average HR and maximum HR on Holter ECGs had no significant correlation with ANP and BNP levels in groupAF.

Conclusion: Plasma ANP and BNP levels were elevated even in patients with atrial fibrillation without LV systolic dyfunction and hypertrophy. Aging provided further increase in plasma BNP in patients with atrial fibrillation which might be the result of accelerated diastolic dysfunction.

P1222 Paroxysmal atrial fibrillation initiated from plurifocal pulmonary vein sources

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The pulmonary veins (PV) are the dominant source of ectopic beats (APB) initiating paroxysms of atrial fibrillation (AF). The extent of arrhythmogenic substrate has not been defined.

Methods: For the last 10 months, 35 patients (7 females, 28 males, 53 ± 10 years, 10 with heart disease) were successively referred for catheter ablation of drug resistant AF. In 13 patients, spontaneous APB were frequent enough to guide mapping whereas in 22 patients APB were rare or absent, requiring provocative manoeuvers. Two or 3 multielectrode catheters were used to map the PV simultaneously (when needed) and PV angiograms to define precisely the targetted sites.

Results: 71 foci were identified: 97% from the PV and 3% from the atrial tissue. Repetitive discharges were documented in 48 and AF initiation in 37. All foci discharging only in bursts inducing AF without producing isolated APB originated from the PV. There were 1, 2 and 3–4 arrhythmogenic PV in 40%, 26% and 34% of patients. In addition, 2 or 3 distinct APB sources were recognized to originate from the same PV (but from ostia of different branches) in 15 patients. These different foci could fire sequentially or simultaneously, produce conducted or non conducted spikes and required separate RF applications. In 4 patients, the ectopic source 'wandered' from within the PV to the atrial edge after ablation. A single ablation session was performed in 15 patients while in the remaining 20, 29 sessions were necessary owing to recurrent ectopy: 1) from the same source (7); 2) from a different part of the same PV (8); 3) from a different PV (14).

Conclusions: The PV are the dominant source of AF initiation even in patients with few or no APB. Multiple PV are involved in 60% of patients and the sources of AF are frequently plurifocal in a given PV, sometimes being displaced to the atrial edge after ablation. Multiple RF applications were necessary to abolish such plurifocal sources.

P1223 Variability of provocative manoeuvers for inducing pulmonary vein ectopy

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A significant problem in successfully ablating pulmonary vein (PV) ectopy initiating atrial fibrillation is the requirement for sufficient ectopy to allow precise mapping and localisation.

Methods: 80 consecutive patients with paroxysmal atrial fibrillation (63 M, 17 F, mean age 54 ± 10 years, 24 structural heart disease) underwent mapping and ablation of PV ectopy initiating atrial fibrillation. In the absence of sufficiently frequent spontaneous ectopics, various provocative manoeuvers were used to elicit enough ectopy to permit mapping and successful ablation. Usually in the following order they included carotid sinus massage, deep breathing and Valsalva, slow rate (100–200 bpm) pacing, Isuprel infusion, high rate pacing and combinations. IV Digoxine and Adenosine were also tried.

Results: Several manoeuvers were successful in eliciting ectopy from the same focus while different foci in the same patient exhibited varying sensitivity. If atrial fibrillation was induced, reinitiation was noted after cardioversion. All manoeuvers were unsuccessful in 2 patients.

Provocative manoeuvers	Positive responses (pts)
Slow rate pacing (100–200 bpm)	15
Isoproterenol infusion (2–4 μg/min)	37
Valsalva	14
Carotid massage	3
High rate pacing (200–300 bpm)	12
Adenosine triphosphate (20–80 mg in bolus)	5
Digoxin 0.5 mg intravenous	0
Propanolol 5 mg intravenous	0
Verapamil 10 mg intravenous	0
Post cardioversion	5

Conclusions: Isoprenaline infusion, respiratory manoeuvers and the pause following pacing (short-long sequence) were most effective. The response of PV ectopy suggests a (Ca++ mediated) mechanism sensitive to mechanical stimuli. Stretch mediated triggered activity is a likely possibility.

P1224 How does duration and dispersion of atrial refractoriness influence persistence of atrial fibrillation?

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The electrophysiologic mechanisms of the persistence of atrial fibrillation (AF) after its initiation are not well understood. Therefore, the electrophysiological characteristics of the right atrium were evaluated in order to identify parameters associated with persistence of AF.

Methods: AF was induced by rapid atrial pacing in 30 anesthetized, open-chest, juvenile pigs. Activation mapping and programmed stimulation (S1S1 = 200 ms) were performed at 56 electrodes on the right atrial free wall. ERP (mean and minimum), dispersion of refractoriness, conduction velocity, wavelength, AF cycle length (mean of 10 beats) and AF cycle length/time (electrical remodeling) were determined.

Results: Sustained AF (AF lasting >30 min) was induced in 10 pigs, non sustained AF (NSAF) in 9 and no AF (AF duration < 30 s) in 11 pigs. AF cycle length was shorter in SAF and/vs NSAF vs no AF. Mean ERP (107 ± 9 and/vs 122 ± 5 vs 142 ± 9). and wavelength (7 ± 1 and/vs 9 ± 1 vs 11 ± 1) were shorter in SAF and/vs NSAF and no AF. Minimum ERP was shorter in SAF and NSAF vs no AF. Conduction velocity at cycle lengths of 200 and 150 ms was not different between groups. Dispersion of ERP was greater in SAF and/vs NSAF vs no AF. (8 ± 1 and/vs 11 ± 1 and 19 ± 4).

Conclusions: There was no correlation between duration of AF and conduction velocity. However, persistence of AF correlated with shorter ERP and wavelength, and greater dispersion of ERP and electrical remodeling. These findings may have important pharmacological and other therapeutical implications.

P1225 The degree and area of effective refractory period shortening required for occurrence of focal localized fibrillation in the canine right atrum

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It has been well known that atrial fibrillation (AF) occurs under the condition of conduction delay, shortening of atrial effective refractory period (ERP) and the dispersion of these factors. Recently important reports have been made, suggesting the presence of focal AF localized at the small area in the right/left human atrium, which made it possible to be ablated at a point. However, the substrate and electrophysiological properties of the local AF have not been clear. The purpose of this paper is to clarify the condition allowing the presence of regional AF, the degree and area of ERP shortening in the dog right atrium (RA).

Methods: We prepared thick filter paper disks with a variable diameter (D) of 6–10^{mm}, which could contain a liquid for a long time, having 6–8 bipolar electrodes to stimulate and record electrical activities of atrial tissues within and surrounding it. We sutured the disk of variable size to RA free wall of 15 anesthetized dogs. Before and after an administration of 10^{-4}–10^{-3} M acetylcholine (Ach), S_1S_2 programmed stimulation was applied to measure ERP and induce focal AF (continuous irregular electrical activity of variable amplitude with cycle length (CL) of 40–60^{ms}).

Results: 1) ERP shortening: Ach of 10^{-4} or 10^{-3} M shortened ERP from 131 ± 14 to 87 ± 10, 32 ± 10^{ms}, respectively, only beneath the disk. 2) Induction of focal AF: No focal AF was provoked in any size of disk at 10^{-4} M Ach. At 10^{-3} M Ach, focal AF occurred at a rate of 0, 25, 75% in the local area of RA beneath the disk of D = 6, 8, 10^{mm}, respectively. During focal AF, regular activity with CL of 100–150^{ms} was recorded on RA around the disk (2^{mm} apart), RA appendage and LA.

Conclusion: Thus, it was known that ERP shortening of a critical degree and area might allow the presence of focal localized AF.

P1226 Up-regulation of inositol 1,4,5-trisphosphate receptor (ip3r) in the atrial tissue of patients with chronic atrial fibrillation

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Background We have previously reported the alterations in cardiac sarcoplasmic reticulum Ca^{2+} regulatory proteins (ryanodine receptor and Ca^{2+}-ATPase) in atrial tissue of patients with chronic atrial fibrillation (AF). The IP3Rs have been found to be intracellular Ca^{2+} release channels. Recently, the IP3R was detected in both intracellular and plasma membrane fractions and may be to play a possible role to modulate intercellular communication via the intercalated discs. The purpose of this study was to determine whether AF patients have alterations in IP3Rs in the atrial myocardium.

Methods We analyzed expression level of IP3R by Western blotting analysis in right atrial myocardium from 10 mitral valvular disease (MVD) patients with AF (MF), 3 MVD patients with normal sinus rhythm (NSR) (MN). As a control group (C), right atrial myocardium from 7 patients with NSR, obtained during cardiac surgery for coronary artery bypass or thoracic aortic aneurysm. Hemodynamic and echocardiogram data were obtained from preoperative cardiac catheterizations and echocardiograms.

Results The relative expression level of IP3R in MA was significantly increased as compared to MN (MA vs MN; 0.81 ± 0.26 vs 0.47 ± 0.06: $p < 0.05$). In both MA and MN, these levels were also significantly increased as compared to C (0.13 ± 0.07). There were positive correlations between the IP3R expression level and left atrial dimension, right atrial pressure, *or* pulmonary capillary wedge pressure. However, there were no significant differences in these parameters between MA and MN.

Conclusions This study shows that chronic mechanical overload to atrial myocardium increases the expression level of IP3R, and this level was more increased in patients with chronic AF. These results suggest that in patients with AF, up-regulated IP3R may play an important role to modulate intercellular communication.

P1227 Effects of chronic atrial fibrillation on calcium and sodium currents in humans

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Atrial fibrillation (AF) leads to a change in atrial repolarization and in intraatrial conduction properties. The underlying cellular mechanisms in humans are only poorly understood. We studied the effects of chronic AF on L-type calcium currents ($I_{Ca,L}$) and on sodium currents (I_{Na}) in humans.

Methods: Ionic currents were recorded in single atrial myocytes in the whole cell mode of the patch clamp technique. Patients in chronic atrial fibrillation (AF) (n = 8) were compared to those in normal sinus rhythm (SR) (n = 17).

Results: The presence of AF led to a strong reduction of $I_{Ca,L}$ densities at test potentials between −10 mV and +50 mV, i.e. at +10 mV, current densities were −6.97 ± 0.50 pA/pF (Mean ± SEM) in SR (n = 42) and −1.88 ± 0.19 pA/pF in AF (n = 18; $p < 0.001$ vs. SR). I_{Ca} voltage dependence was not altered by AF, peak current amplitudes occurred at +10 mV in both groups. Voltage dependence of activation and inactivation as well as recovery from inactivation of $I_{Ca,L}$ were not affected by AF. In AF, inactivation kinetics (biexponential fit) were slower than in SR. The fast inactivation constant τ_{fast} was 5.1 ± 0.6 ms in SR (n = 39) and 8.3 ± 0.9 ms in AF (n = 16; $p < 0.01$ vs. SR), whereas the slow time constant τ_{slow} was unaffected. I_{Na} current densities were identical in the 2 groups at all test potentials, i.e. at −40 mV: −50.2 ± 3.1 pA/pF in SR (n = 44) and −46.1 ± 4.5 pA/pF in AF (n = 25, p = ns). Voltage-dependent and kinetic properties of I_{Na} were also not altered by AF.

Conclusions: Electrical remodeling in human AF is associated with a marked decrease of $I_{Ca,L}$ densities and a slowing in the inactivation kinetics. A decreased calcium inward current in AF seems to contribute to accelerated repolarization and to the perpetuation of the arrhythmia. In contrast to the findings in animal models, I_{Na} is not affected in chronic human AF.

P1228 3-D endocardial spatial dispersion of atrial electrogram fragmentation during atrial fibrillation in the chronic goat model

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Local electrogram fragmentation has been previously shown to be associated with slow conduction, tissue anisotropy, conduction block, reentry and activation wave collision. To test the hypothesis that there is regional variation in the complexity of endocardial atrial activation during atrial fibrillation (AF) we have utilized a non-fluoroscopic electroanatomic mapping (NFM) system to map the 3-D spatial dispersion of the degree of local electrogram fragmentation and cycle-length (CL) histograms in the chronically paced goat model.

Methods and Results: Experiments were carried out in 10 goats with sustained AF (>24 h). By sampling a plurality of endocardial sites at which 60 sec of local atrial electrograms were recorded, the 3-D geometry of the chamber was reconstructed, with the electrophysiologic information color-coded and superimposed on the anatomy. A fragmentation index (FI), defined as the average number of deflections in the local bipolar electrogram for each atrial activation, was calculated for each site. Significant spatial variations were noted with the RA high and low septum associated with significantly higher FI values (3.2 ± 0.1 and 3.4 ± 0.1, $p < 0.01$)) than the rest of the atrium (2.3 ± 0.1 to 2.5 ± 0.2). In the LA, significantly higher FI values ($p < 0.01$) were noted at the posterior and septal aspects (3.5 ± 0.6 and 3.7 ± 0.2 respectively). Similarly the RA septum and posterior walls were associated with the shortest median CL (112 ± 3 and 114 ± 2 ms respectively) with longer median CLs observed at the anterolateral free wall (125 ± 3 ms) and near the SVC, IVC and isthmus regions (129 ± 4, 131 ± 2 and 132 ± 6 ms respectively). The LA was characterized by a more homogenous dispersion of CL histograms with the septal area displaying slightly shorter median CLs (118 ± 3 ms).

Conclusions: 1) Significant spatial dispersion of different electrophysiological parameters can be observed in this chronic model of AF and may result from a combination of anatomical and electrophysiological factors. 2) The septum is associated with the most complex atrial activation patterns (highest FI) as well as by the shortest median CLs suggesting a critical role of this area in the perpetuation of AF.

P1229 Regional patterns of atrial fibrillation spatial organization in the chronic goat model as quantified by the endocardial spatial correlation index

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Previous studies have shown that quantitative measurement of the degree of similarity between atrial activation sequences (using the cross-correlation function) recorded from a number of bipolar electrodes can be used to assess the global spatial organization of AF. To test the hypothesis that regional disparities in the spatial organization of AF exist, we examined possible regional differences in the endocardial spatial correlation index (SCI).

Methods and Results: 6 goats with sustained AF (>24 h) induced by chronic rapid atrial burst pacing were studied using a 3-D electroanatomical mapping system (Carto). A special quadripolar catheter (with a distance of 15 mm between the two bipoles) was used to record 15 seconds of atrial electrograms during AF. The signals extracted from the two bipolar electrodes were processed and then cross-correlated. This process was repeated at a plurality of endocardial sites in the RA. Significant regional variation was noted in all animals. The septum and posterior walls were characterized by the lowest SCI values (0.25 ± 0.01 and 0.35 ± 0.03 respectively, mean $\pm$ SEM). The anterolateral free wall and tricuspid-IVC isthmus displayed a more organized activity (SCI values of 0.47 ± 0.02 and 0.48 ± 0.02). The highest SCI values were noted at the SVC-atrial junction (0.66 ± 0.02) and IVC-atrial junction (0.55 ± 0.03).

Conclusions: 1) Significant regional differences were noted in the spatio-temporal organization of AF as measured by the SCI values. 2) The smooth RA (RA septum and posterior wall) is characterized by low SCI values indicating uncoupling of atrial activation sequences between the two bipoles due the presence of simultaneous multiple neighboring wavefronts. In contrast the anterolateral free wall is relatively protected from this turbulent activity (most probably due to the presence of the cristae terminalis) and is activated mainly by broad wavefronts (high SCI values). 3) The ability to assess regional disparities in the spatial organization of AF may increase our understanding regarding the mechanisms underlying AF and may possibly aid in designing custome-made curative strategies.

P1230 Efficacy and safeness oral loading dose propafenone in paroxysmal atrial fibrillation

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In 486 patients (pts) (226 M, 61 years) the efficacy and safety of a single oral loading dose of propafenone (PNF) (600 mg p.o. as a single dose) for converting recent onset (<48 hours) paroxysmal atrial fibrillation (AF) to sinus rhythm (SR) were assessed. All pts (lone AF, hypertension or mild organic heart disease) were in NYHA functional class I or II, but without signs or symptoms of heart failure and were hospitalised. They were randomly allocated to treatment with PNF or placebo. In case of persistent AF (>8 hours) they were DC cardioverted. A continuous Holter monitoring was recorded.

Results: With respect to placebo, PNF reduced conversion time to SR (7.8 vs 4.1 hrs, $p < 0.01$) and increased cardioversion rate both at 3 hours (19.3 vs 49%, $p < 0.01$) and at 8 hours (39 vs 77%, $p < 0.01$). However an higher percentage of adverse events was observed in the group of pts under PNF treatment (3.7 vs 2.5%, $p < 0.05$), but no major adverse events were observed. In PNF group minor side effects included slight transient hypotension (6 pts), junctional rhythm (2 pts) and QRS > 120 msec (3 pts). One case of atrial flutter with 1:1 AV conduction was observed but in the PI group.

Conclusion: A single oral loading dose of PNF is effective and safe in hospitalised pts with AF. Atrial flutter may be a common finding before conversion to SR, but without haemodynamic consequences. These observations can be the basis for a cost effective out of hospital therapeutic approach of pts with AF.

P1231 What are the limits for atrial fibrillation surgery in mitral patients?

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Background and Purpose: Different surgical approaches are available for the treatment of atrial fibrillation (AF). Some are complex, long and require surgical incisions on the posterior aspect of the heart. Radiofrequency (RF) catheter ablation has been used as an alternative to surgical incisions for creation of lesions in the atrial wall. We report our experience on electrosurgical treatment of AF using a new catheter conceived for intraoperative use.

Methods: Thirty-five Pts with mitral valve disease and AF were submitted to concommitant valve and AF surgery. AF was chronic in 27 Pts (77%) and paroxysmal in 8 (23%). Surgical approach was conventional sternotomy in 29 Pts, minithoracotomy in 5 and left thoracotomy in 1 Pt. AF surgery consisted of bilateral isolation of pulmonary veins (BIPV) using RF energy applied by a novel system specially designed for intraoperative use. It is a heptapolar catheter that allows 7 simultaneous applications of RF energy. Each set of applications aimed at a maximal duration of 60 sec and a maximal preset temperature of 70°C. Energy delivery (≤150 Watts) was controlled by thermosensors located on each electrode in order to optimize tissue warming. Mitral valve surgery consisted of valve replacement in 31 Pts, repair in 3 and leak suture in 1 Pt. Concommitant procedures were tricuspid valve repair in 9 Pts, atrial septal defect closure in 3 and LA volume reduction in 1 Pt.

Results: BIPV required two or three RF endocardial applications. Mean time dispended on the RF procedure was 7 ± 4 minutes. No mortality or myocardial infarction occurred and no bleeding was attributable to the RF procedure. At discharge, 21 Pts (60%) were off AF; 14 (40% of all Pts) of these presented sinus rhythm and bilateral atrial contraction. 4% had high atrial rhythm and bilateral atrial contraction, 8% were out of AF with the right atria contracting and 4% where out of AF with hemodynamically silent atria.

Conclusion: BIPV is a fast, safe and efficient procedure for electrosurgical treatment of AF in Pts submitted concommitantly to mitral valve surgery, precluding its use in other groups of Pts with less severe baseline characteristics.

P1232 Signal averaged P-wave energy increases after coronary bypass grafting in patients with postoperative atrial fibrillation

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Background: A number of investigations have demonstrated that analysis of the signal averaged P-wave (SAPW) *before* coronary bypass grafting (CBG) is of limited predictive value for *post-operative* atrial fibrillation (AF). Analysis of the *post-operative* SAPW may be more helpful. We have therefore investigated the characteristics of pre- and post-operative SAPW in pts undergoing first elective CBG.

Methods: SAPW were prospectively collected before and 6 hours after CBG in 181 pts (135 M, mean age 64 yrs). P-wave duration and energies contained in frequency bands from 40 and 80 to 150 Hz of the P-wave spectrum were calculated. Continuous electrocardiographic (ECG) monitoring was performed for 48 hrs after CBG with routine ECG recordings thereafter until hospital discharge.

Results: 54 (30%) of pts developed AF (group AF). Post-operative P-waves were significantly shorter compared to pre-operative values in both AF pts and those who remained in sinus rhythm (group SR). In SR pts no changes in P-wave energy occurred, but in AF pts a significant post-operative increase in high frequency P-wave energy was observed:

	Group AF		Group SR	
	Pre	Post	Pre	Post
Duration (ms)	148 (2)	140 (2)**	144 (1)	138 (1)**
P60	1.2 (0.1)	1.6 (0.17)*	1.2 (0.06)	1.4 (0.09)
P80	0.49 (0.05)	0.71 (0.09)*	0.52 (0.03)	0.60 (0.03)

P60, P80: Energy from 60 and 80 to 150 Hz. **$p < 0.001$, *$p < 0.05$ vs preoperative value

Conclusion: All patients demonstrate reductions in the SAPW duration after CBG, implying an increase in conduction velocity that would reduce vulnerability to AF. However, pts who develop AF exhibit an acute increase in P-wave energy that may correlate with a reduction in atrial refractoriness. Our data suggest that this provides the substrate for post-operative AF.

ATRIAL FIBRILLATION: HOW TO PREVENT OR PREDICT RECURRENCES

P1233 Incidence of sudden cardiac death after atrioventricular node ablation and pacing: long-term follow-up

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The incidence of sudden cardiac death (SCD) after atrioventricular (AV) node ablation and permanent pacing has been focused mainly in patients early after ablation, and is reported to range between 2% per year to 8% per year in patients with congestive heart failure. Few data are available regarding the risk of SCD late after the ablation procedures in pts with paroxismal or chronic atrial fibrillation (PAF, CAF).

Methods and Results: From May 1987 to January 1997, AV node ablation was performed in 585 severely symptomatic patients (mean age 66 ± 11 years) with high-rate, drug-resistant paroxismal (n = 308) or chronic AF (n = 277). Lone AF was present in 133 patients, while the remaining 452 patients suffered from dilated, ischemic or valvular heart disease. Patients underwent VVIR (454 patients) or DDDR (131 patients) pacemaker implantation, after AV node ablation. During a mean follow-up of 33.6 ± 24.2 months 80 deaths were recorded (13.7%): 40 non-cardiac, 23 non-sudden and 17 SCD (3%, 1.04% per year). The actuarial occurrence rates of SCD were 0.8%, 1.5%, 2.8% and 6% after 1, 2, 3 and 6 years respectively.

Pts with or without SCD were not statistically different in mean age (64.8 ± 0.2 vs 66.3 ± 11 ys, NS) while LVEF (34.2 ± 10.1 vs 46.6 ± 18.8, $p < 0.04$) and NYHA class (3.1 ± 1 vs 2.3 ± 0.9, $p < 0.02$) were significantly different between the 2 groups.

Conclusions: Data from our large cohort of patients indicate a fairly low incidence of sudden cardiac death at a long term follow-up after AV node ablation and pacing for drug-refractory, high-rate AF. The presence of clinical signs of heart failure and low LVEF before AV node ablation and pacing are good predictors of the incidence of SCD in these patients.

P1234 Multilinear radiofrequency ablation of the atria for the suppression of paroxysmal atrial fibrillation

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Background: For the treatment of paroxysmal atrial fibrillation (pAFib) only palliative ablation techniques are established, newly developed more curative techniques are presently under evaluation. A novel method for AFib suppression by atrial compartmentalization (COM) due to multilinear ablation (ML-RFA) is introduced. 11 patients (pts) with missing or minor cardiac disease and highly symptomatic, medically refractory pAFib underwent a well defined ML-RFA protocol in a prospective study using the 8-polar Revelation™ and the 2-polar large tip Cosio flutter ™catheter. During sinus rhythm 4 contineous lines from VCS to VCI, VCS to Tricuspid annulus anterior resp. posterior and along the isthmus were drawn. Primary endpoints were 1) increasing pacing threshold and reducing the amplitude of the local ecg and 2) improving symptoms and reducing the frequency of AFib attacks. The intended lines could be accomplished in all cases. A second ablation in the isthmus became necessary in 3 cases because of the onset of "new" atrial flutter, a left atrial linear resp. focal ablation in 4 cases because of recurrence of AFib. The pacing threshold increased from 1.45 ± 0.70 to 3.19 ± 1.07 V, i.e. by 121% ($p < 0.01$). The amplitude of the local A-wave decreased by 47 ± 5% ($p < 0.01$) from 1.62 ± 1.53 mV to 0.76 ± 1.12 mV (53 ± 6%). During short term FU (1–6 mo) the event free interval increased from 1.6 to 11.1 days ($p < 0.01$), symptoms improved markedly in 9/11 pts (81%) and no recurrence at all had 5 pts (45%). There was no severe complication.

Conclusion: Primary right atrial COM by MA-RFA is effective, safe and successful in nearly 50% of cases. In 1/3 of pts new atrial flutter or AFib requires additional isthmus resp. left atrial RFA. Final success rate amounts to 45% for suppression and 80% for symptoms relief.

P1235 Analysis of left atrial appendage doppler flow rate in atrial fibrillation and its relationship with duration of the arrhythmia and response to chemical cardioversion

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Background. Persistence of atrial fibrillation (AF) and lower response rate to cardioversion (CV) have been associated with shorter wavelengths of reentry pathways. A direct and close correlation between atrial electrical activity and left atrial appendage (LAA) Doppler flow has recently been demonstrated.

Purpose. To characterize LAA Doppler flow, in order to define the cycle length of emptying waves and hence LAA rate and its relationship with 1) duration of AF and 2) response to attempts at chemical CV.

Methods. Transesophageal echocardiographic (TEE) studies were performed in 38 pts (27 males, mean age 63 ± 11 years) in AF (mean duration 12 ± 15 days, unknown in 9 pts) awaiting CV. Propafenone (30 pts) or flecainide (8 pts) were administered i.v. at a dosage of 2 mg/kg body weight in 10 minutes, during continuous TEE monitoring. LAA rate was averaged in basal conditions and at the end of drug infusion over at least 5 consecutive cardiac cycles.

Results. LAA rate could not be determined in basal conditions in 2 pts and at the end of drug infusion in further 8 pts because of the presence of very low or passive flow profiles. A weak but significant correlation between LAA rate and duration of AF was found ($r = 0.45$, $p = 0.003$). CV was successful in 18 pts (47%). Baseline LAA rate was significantly lower in pts with successful CV (380 ± 42 vs 438 ± 37 beats/min, $p < 0.001$). At the end of drug infusion, there was a highly significant decrease in LAA rate (409 ± 39 vs 280 ± 42 beats/min, $p < 0.001$) but no significant difference in the magnitude of slowing between successful and unsuccessful CV.

Conclusion. Analysis of LAA Doppler flow rate is feasible in the vast majority of pts with AF. A lower LAA rate seems to indicate pts with AF of shorter duration and more prone to successful chemical CV.

P1236 Echocardiographic assessment of diastolic left ventricular function is a valuable tool for predicting the risk of early recurrence of atrial fibrillation after successful cardioversion

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Background: After successful cardioversion early recurrence of atrial fibrillation is documented frequently. The purpose of this study was to investigate whether left ventricular (LV) diastolic parameters are valuable to predict the risk of early atrial fibrillation after successful cardioversion.

Methods: In 58 consecutive patiens with atrial fibrillation (58 ± 6 years; 61% male; duration of atrial fibrillation > 28 days in 81%) who underwent successful cardioversion (electrical: 85%) to sinus rhythm, we performed an echocardiographic examination 24 hours after successful cardioversion. Following parameters of diastolic function were assessed: peak early (V_E) and peak late (V_A) diastolic flow velocity; early-to-late flow velocity ratio (V_E/V_A); acceleration (AT) and deceleration time (DT) of flow velocity in early diastole and isovolumetric relaxation time (IVRT). All patients were treated with anti-arrhythmic agents after cardioversion. Early recurrence was defined as documentation of atrial fibrillation during 30 days after cardioversion. Using multiple logistic regression, clinical and Doppler-echocardiographic parameters were tested for an association with recurrence of atrial fibrillation.

Results: 18 patients had recurrence of atrial fibrillation within 30 days after successful cardioversion. All patients (n = 11) with a restrictive diastolic filling pattern (V_E/V_A-ratio: 2.1 ± 0.8, DT: 158 ± 21 ms, IVRT: 51 ± 5 ms) and duration of atrial fibrillation > 28 days had early recurrence of atrial fibrillation. In 5 patients with restrictive diastolic filling pattern and atrial fibrillation < 28 days before successful cardioversion and 2 patients without restrictive filling pattern who had atrial fibrillation for more than 28 days also early recurrence of atrial fibrillation was documented. Multivariate analysis adjusted to clinical parameters as age, gender, presence of coronary artery disease and use of different antiarrhythmic agents after cardioversion demonstrated that just parameters of LV diastolic function were significantly associated with the recurrence of atrial fibrillation.

Conclusion: Assessment of LV diastolic function by Doppler-echocardiographic analysis of the diastolic transmitral flow 24 hours after successful cardioversion can predict the risk of early recurrence of atrial fibrillation. A restrictive diastolic filling pattern is associated with significantly increased risk of early recurrence of atrial fibrillation.

P1237 The value of Doppler derived mitral "a" wave in predicting maintenance of sinus rhythm after cardioversion

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The aim of this study was to assess the value of Doppler derived mitral "a" wave in patients with atrial fibrillation (AF) in predicting maintenance of sinus rhythm (SR) after cardioversion (CV).

One hundred and eighty-seven patients with nonvalvular AF (90 female, 97 male, mean age 65 ± 9) in whom SR had been restored with pharmacologically or with DC shock were enrolled in the study. Transthorasic echocardiography (TTE) is performed in all patients during the first 24 hours after CV. TTE variables evaluated included left ventricular ejection fraction (LVEF), left atrium diameter (LAD), and transmitral flow pattern. Patients were followed up for at least 1 year. The duration of the restored SR was less than 30 days in 20 patients, 31–90 days in 25 patients, 91–180 days in 43 patients, 181–365 days in 25 patients and more than 365 days in 74 patients.

Duration of SR was inversely correleted with age ($r = -0.97$, $p = 0.006$), duration of AF ($r = -0.93$, $p = 0.02$), and LA diameter ($r = 0.93$, $p = 0.02$). There was a direct correlation with the amplitude of the "a" wave, and the duration of maintenance of SR ($r = 0.96$, $p = 0.008$). The relation of age, AF duration and LAD to maintenance of SR was not influenced by the mode of CV, however mitral "a" wave was influenced by the mode of CV. There was a positive relation in the patients whom SR was restored pharmacologically ($r = 0.99$, $p < 0.00001$), but no relation in the patients DC shock was used for CV.

In conclusion, Doppler derived mitral "a" wave measured during the first 24 hours after CV may be used to predict 1 year outcome of CV.

P1238 Maintenance of sinus rhythm after cardioversion of chronic atrial fibrillation: sotalol versus bisoprolol

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Aim: Purpose of the study was to compare the efficacy and safety of sotalol and bisoprolol for maintenance of sinus rhythm (SR) after electrical cardioversion (CV) of atrial fibrillation (AF).

Methods: 128 patients entered the trial and were randomized equally to sotalol (80 mg bid) or bisoprolol (5 mg/day). Patients with contraindications to β-blockers or class III antiarrhythmics drugs and prior treatment with study drug for prevention of AF were excluded. Follow up clinical evaluation was performed one day, one months and thereafter in 3 months intervals up to one year. Rhythm was documented by 12-lead surface ECG.

Results: There were no differences in baseline clinical characteristics between both groups. After a follow up of 12 months 59% of all patients were still in SR. The proportion of patients (pts) remaining in SR on each drug was calculated for the two groups by Kaplan Meier method. 41% of patients on sotalol and 42% on bisoprolol developed AF during follow up (n.s.), 49 ± 87 and 38 ± 74 days respectively after CV. Sinus heart rate was significantly decreased ($p < 0.001$) in both groups (n.s. between groups). Uncorrected QT duration was prolonged by sotalol and significantly longer than the uncorrected QT interval in the bisoprolol group. Under treatment the corrected QT duration (Bazett formula) was equally prolonged in both groups ($p < 0.001$), whereas uncorrected QT duration at similar heart rate levels were prolonged in sotalol pts only (mean increase 30 ms; 95% confidence interval 21–40 ms, $p < 0.01$). Proaarhythmias occurred in none of the pts in the bisoprolol and in 2 pts (3.1%) in the sotalol group. Both adverse effects were torsade de pointes tachycardias.

Conclusion: This study demonstrats that sotalol and bisoprolol are equally effective in maintaining sinus rhythm. An obvious class III effect under low dose sotalol treatment could be shown. Our data indicate that, due to the proarrhythmic side effects of sotalol, bisoprolol seems to be advantageous in treatment for maintenance of SR after CV of AF.

P1239 Recent onset paroxysmal atrial fibrillation: spontaneous conversion and the role of high-dose intravenous amiodarone

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Objective: To compare the efficacy (conversion to sinus rhythm) of high dose amiodarone versus placebo, in patients with Paroxysmal atrial fibrillation (PAF).

Methods: One hundred patients with 2^{nd}–6^{th} episode of new onset PAF (lasting less than 48 hours) were randomized to receive placebo or high dose intravenous amiodarone (3 gr. over 24 hours).

Results: Spontaneous conversion (SC) to normal sinus rhythm (NSR) occurred in 64% of the patients in the placebo arm (mostly within 8 hours), and 92% of the amiodarone arm ($p = 0.0017$). Clinical EKG and echocardiographic parameters that were associated with reduced incidence of SC were: hypertension, ischemic heart disease, congestive heart failure, ST depression, left atrial enlargement, reduced ejection fraction, and moderate or severe mitral regurgitation. In patients without any of these markers SC to NSR occurred in nearly 90% of the patients.

Conclusions: 1) High dose amiodarone is superior to placebo in converting PAF to NSR. 2) Amiodarone most markedly improves conversion rates of patients with clinical and echocardiographic markers of reduced SC rates. 3) Anti-arrhythmic therapy with amiodarone, can be reserved for patients with markers associated with reduced incidence of SC, or for those failing SC within 8 h.

P1240 Verapamil could prevent atrial fibrillation recurrences if administred before conversion to sinus rhythm

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It has been shown that atrial "electrical remodeling" (ER) which takes place shortly after the onset of atrial fibrillation (AF) is partly responsible for the maintenance of this arrhythmia. Sparse studies in man speculate that calcium channel blockers could prevent ER. The aim of this study was to assess if Verapamil could prevent AF recurrences after electrical conversion (EC) and if the timing of treatment with Verapamil is determinant in this action. We included 68 pts. with persistent AF successfully converted to sinus rhythm. They were divided in two groups on the basis of their previous treatment: group A (34 pts.) was treated with Verapamil before EC in order to maintain the heart rate below 100/min and group B (34 pts.) was treated with Digoxin before EC. In order to minimize the experimental error, the groups were chosen equal and matched for the baseline characteristics. After EC each group was divided in two subgroups: one received Verapamil (17 pts.) and the other did not (17 pts.). Neither antiarrhythmics nor beta-blockers were permitted. During the follow-up period (45 days) the rhythm was checked daily and the AF recurrence rate was determined; the results were analyzed using McNemar's test to calculate Chi-square. After the follow-up period 16 pts. in group A (47%) and 10 pts. in group B (29%) remained in sinus rhythm ($p < 0.05$). There were no statistical differences between the AF recurrence rates in the subgroups with or without Verapamil after EC in both group A (10 pts. vs. 8 pts.), and in group B (13 pts. vs. 11 pts.). We conclude that administration of Verapamil prior but not after EC could prevent AF early recurrences and that it could be a proof of influencing ER.

P1241 The effectiveness of amiodarone in spontaneous conversion of atrial fibrillation and maintenance of sinus rhythm in patients with heart failure

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Patients and methods: In order to evaluate the effects of amiodarone and digitalis versus digitalis alone on AF in this study 54 patients with CHF (NYHA class II and III) and AF were followed up for six months. Twentysix of them were randomized to amiodarone and digitalis and 28 to digitalis alone. Both groups were comparable in clinical parameters and ejection fraction (Area Lenth – 43.56 ± 7.54% vs. 42.34 ± 5.67%, n.s.). Twelve-lead EKGs and 24-hour Holter monitoring were repeated at 2 weeks, 3 months and 6 months after the biginning of the study. At these enpoints, the average ventricular rate (VR) was also calculated.

Results: Of all patients involved in this study, four pts. (15.38%) of the amiodarone and digitalis and four pts.(14.39%) of the digitalis group, had intermittent AF on 24-hour Holter monitoring. Six of 26 patients on amiodarone and digitalis (23.08%) and none of 28 on digitalis converted to sinus rhythm during the study. The mean ventricular rate during AF over 24 hours was reduced by amiodarone at two weeks (23%, $P < 0.001$) and at 6 months (19%, $P < 0.001$). The difference was significant ($P < 0.005$).

Conclusions: In patients with CHF, amiodarone showed a significant potential to spontaneously convert patients with AF to sinus rhythm in comparison with patients who were treated only with digitalis. This drug prevented the development of new-onset AF and significantly reduced the VR in those patients with persistent AF.

MEDICAL MODULATION OF ATRIAL FIBRILLATION: HEART RATE AND THROMBOTIC RISK

P1242 Evidence for reduced electrical remodelling in patients with persistent atrial fibrillation taking calcium channel blockers

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Background: Experimental and clinical studies have demonstrated a progressive shortening of atrial refractoriness during atrial fibrillaton (AF). Calcium channel antagonists (ca) of the verapamil type have been suggested to prevent a reduction in the atrial refractory period. Since (1) there is a close inverse correlation between atrial refractory period and the rate of electrical atrial activation (f) and (2) f be accurately estimated from the surface ECG, it was hypothesized that patients taking ca have a lower f recorded on the surface ECG.

Methods: Holter ECG recordings were made in 20 patients (14 male, 6 female, mean age 58 ± 11 years) during persistent AF. One minute ECG segments were used for analysis at 4 PM, 10 PM, 4 AM and 10 AM. In those segments f was determined by subtracting averaged QRST complexes and then a Fourier analysis was applied to the resulting signal.

Results: Mean f of the 4 recordings per patient was 6.8 ± 0.6 Hz (range 5.0 to 7.8 Hz). Ten patients with long-term ca use (group I) had a mean f of 6.4 ± 0.6 Hz, significantly lower than the 7.1 ± 0.4 Hz ($p = 0.028$) recorded in 10 patients without ca treatment (group II). f was constant over time in both groups. During all measurements group I patients had a lower f than group II patients ($p = 0.028$). No other variable including age, gender, AF duration, underlying heart disease, echocardiographic parameters or concomitant digoxin treatment affected f.

Conclusion: In patients with persistent AF, fibrillatory frequency assessed by spectral analysis of the surface ECG is lower in patients taking calcium channel blockers of the verapamil type, suggesting a partially suppressed electrical remodeling process.

P1243 Stroke prevention practices in patients with atrial fibrillation and pacemaker therapy: evidence for underutilization of anticoagulation

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Background: Oral anticoagulation reduces the risk of thromboembolic events in patients (pts.) with atrial fibrillation (AF). However, there is evidence that anticoagulation is underutilized in a variety of clinical settings. The purpose of the study was to investigate anticoagulation rates in patients with AF and pacemaker therapy.

Methods: Between 11/98 and 12/98 all pts. of our pacemaker clinic were prospectively analyzed concerning heart rhythm, underlying disease, stroke risk factors, and antithrombotic medication.

Results: A total of 326 pts. with a mean age of 77.7 ± 9.6 years were analyzed. 52% were female and the mean pacing duration was 67.8 ± 53.4 months (1–225). 140 (43%) were diagnosed as being in AF, 153 (47%) were in sinus rhythm while 33 (10%) had other rhythms. While AF pts. had a mean age of 80.5 ± 7.1 years, pts. in sinus rhythm were 75.5 ± 11.4 years of age ($p = 0.014$). All pts. with AF had additional clinical risk factors for thromboembolic stroke. The ECG was insufficient to diagnose AF in 120 (86%) of the pts.. These pts. required temporary pacemaker reprogramming to low ventricular rates to diagnose the underlying rhythm. Of the pts. with AF 39 (28%) were on anticoagulation, 37% were on aspirin and the remainder did not receive any antithrombotic medication. Only 10.3% of the pts. not receiving oral anticoagulation had contraindications against this therapy.

Conclusions: The majority of AF pts. with pacemakers does not receive appropriate prophylaxis against thromboembolic stroke despite having no contraindications against anticoagulation. Therefore, cardiologists and electrophysiologists caring for pacemaker pts. should not only facilitate the diagnosis of AF but also encourage the referring physician to use anticoagulation in order to lower the stroke risk in this population.

P1244 Increased thrombogenesis and atrial fibrillation: effects of combination aspirin and warfarin therapy

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Atrial fibrillation (AF) is associated with an increased risk of thromboembolism and is known to have a hypercoagulable state. Aspirin and warfarin reduce the risk of stroke in patients with AF.

Methods. Prospective randomised study of chronic AF patients treated with warfarin 2 mg (group A, n = 23), aspirin 300 mg and warfarin 1 mg (group B, n = 21), and aspirin 300 mg and warfarin 2 mg (group C, n = 17). Effects on various haemostatic factors were looked at 2 weeks and 8 weeks, and subsequent full anticoagulation (for 8 weeks, INR 2–3).

Results. Patients with AF had higher baseline levels of D-dimer (533 ± 768 vs 173 ± 335 ng/ml), von Willebrand factor (vWF) (143 ± 37 vs 105 ± 30 IU/dL), plasminogen activator inhibitor 1 (PAI-1) (8.4 ± 7.5 vs 5.9 ± 3.6 ng/ml) and fibrinogen (3.1 ± 0.8 vs 3.1 ± 0.9 g/L) compared to age- and sex-matched controls ($P < 0.05$ for all).

		Baseline	2 weeks	8 weeks
Group A	vWF	144 ± 36	141 ± 40	148 ± 39
	D-dimer	625 ± 875	467 ± 451	482 ± 734
	Fibrinogen	3.0 ± 1.0	2.8 ± 1.0	2.5 ± 0.9
	PAI-1	8.3 ± 7.8	7.5 ± 4.8	8.8 ± 5.0
Group B	vWF	135 ± 33	136 ± 37	138 ± 36
	D-dimer	564 ± 840	247 ± 306	378 ± 1099
	Fibrinogen	3.0 ± 0.9	3.0 ± 0.7	2.5 ± 0.8
	PAI-1	9.7 ± 8.7	11.7 ± 9.0	14.1 ± 12.0
Group C	vWF	148 ± 42	154 ± 46	151 ± 33
	D-dimer	346 ± 447	385 ± 673	196 ± 187
	Fibrinogen	2.8 ± 0.7	2.9 ± 0.9	2.9 ± 0.8
	PAI-1	7.0 ± 4.7	10.8 ± 8.7	11.9 ± 11.3

P = NS (RMANOVA) *mean ± SD.

Both D-dimer and fibrinogen levels were significantly lower in dose-adjusted warfarin (INR 2–3) if compared to baseline levels in AF patients not on warfarin ($P < 0.05$).

Conclusion. Low-density warfarin and aspirin antithrombotic therapy results in improved reduction in haemostatic markers but the greatest reduction in thrombogenesis still was with full anticoagulation.

P1245 Atrial fibrillation and quality of life: do asymptomatic patients need treatment?

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Atrial fibrillation (AF) has been reported to be asymptomatic in 30% of patients (pts). Although AF is generally recognised to be associated with an increased morbidity and mortality, it is unknown to what extent asymptomatic AF affects quality of life (QL) and whether this condition needs treatment.

Methods: The aim of the study was to assess QL in 38 pts with the lowest quartile symptom scores from Bubien and Kay's Symptom Checklist (Group 1) and 118 pts from the remaining 3 quartiles (Group 2). Symptoms relevant for AF were selected, including palpitations, dyspnoea, exercise intolerance, dizziness, chest discomfort, and syncope. A control group comprised 50 healthy subjects.

Results: QL was significantly decreased in pts with AF, including those with and without symptoms, compared to control group ($p < 0.03$). Group 2 pts had significantly lower SF-36 scores than Group 1 pts ($p < 0.003$). Compared to controls, Group 1 pts had significantly decreased scores regarding vitality, mental health, and general health ($p < 0.03$). SF-36 scores are summarised in the table (data presented as mean ± SD, *$p < 0.03$ compared to controls).

SF-36 score in different groups

SF-36 score	Control	Group 1	Group 2	All AF
Role-Physical	88 ± 28	83 ± 26	35 ± 38*	48 ± 42*
Vitality	71 ± 14	63 ± 15*	42 ± 19*	49 ± 21*
Physical Fx	89 ± 19	89 ± 13	61 ± 26*	68 ± 27*
Social Fx	92 ± 14	87 ± 23	67 ± 27*	73 ± 27*
Mental Health	81 ± 11	75 ± 15*	65 ± 18*	69 ± 18*
Role-Emotional	92 ± 24	88 ± 22	58 ± 43*	65 ± 41*
Bodily Pain	77 ± 15	81 ± 14	65 ± 19*	69 ± 20*
General Health	78 ± 18	63 ± 17*	51 ± 21*	55 ± 21*

Conclusion: According to SF-36 scores, asymptomatic AF does not significantly deteriorate QL. However, several aspects of QL are lower in the asymptomatic patients compared to healthy subjects. Thus, consideration should be given to the treatment of this condition as sinus rhythm restoration may improve QL in some pts.

ECHO/DOPPLER AND ATRIAL FIBRILLATION

P1246 Long-term prognostic value of dobutamine stress echocardiography in patients with atrial fibrillation

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Aim of the study: To assess the long-term prognostic value of dobutamine stress echocardiography [DSE] for late cardiac events [CE] [cardiac death [CD] and MI] in pts with atrial fibrillation [AF].

Background: The diagnostic accuracy of DSE may be reduced in pts with AF due to unpredictable heart rate response.

Methods: Clinical data and DSE results were studied in pts undergoing DSE between 1989 and 1997. Sixty-nine pts had AF at the time of DSE and were matched [age, gender, rest wall motion abnormalities] with a control group in sinus rhythm. Presence and extent and of stress induced ischemia [NWMA] was scored for every pt. Follow-up was 37 months [range 6–96]. Data are presented as hazards ratio [HR] with 95% CI.

Results: Heart rate during DSE at rest, low-dose, and peak dose dobutamine in pts with AF and sinus rhythm was respectively: 76/72*; 82/78*; and 124/125 bpm [*$p < 0.05$]. Peak rate pressure product [peak heart rate × peak systolic blood pressure] in pts with AF and sinus rhythm was respectively 17602/17169 [$p = 0.4$]. CD occurred in 5 and MI in 2 pts. NWMA were highly predictive for late CE in pts with AF. There was no difference in prognostic value of NWMA in pts with AF or sinus rhythm for late CE HR: 8.0 [1.5–45] respectively HR 4.2 [3.1–5.6] [$p = 0.45$]. The number of ischemic segments was also predictive for late CE in pts with AF and sinus rhythm.

Conclusions: The prognostic accuracy of DSE for late cardiac events was not influenced by atrial fibrillation.

P1247 Changes in coronary blood flow and flow reserve after induction of atrial fibrillation

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The deleterious effects of atrial fibrillation (AF) on cardiac performance as well as the benefits from restoring sinus rhythm have been extensively studied, but the effect of AF on coronary blood flow remains unknown. The aim of this study was to assess the coronary blood flow changes with loss of atrial contraction in patients with a controlled heart rate to avoid the influence of rapid and irregular ventricular response.

Methods: Eight patients (5 men, mean age 57 ± 5 years) with a dual chamber pacemaker for complete atrioventricular block, no significant coronary artery disease and preserved ejection fraction were studied. During routine cardiac catheterization, coronary flow velocity were recorded using a 0.014" Doppler guide wire in the proximal left anterior descending coronary artery after intracoronary administration of 200 μg nitroglycerin. Time-averaged peak flow velocity (APV) was recorded at baseline (R) and after maximal vasodilatation (H) during atrioventricular sequential pacing at 100 bpm. Vasodilatation was achieved by intracoronary administration of 18 μg adenosine. The same measurements were repeated during ventricular pacing at the same heart rate, at least 5 minutes after induction of AF by programmed electrical stimulation. Intracardiac recordings were used to confirm the induction of AF. Coronary flow reserve (CFR) was calculated as the ratio of APV-H to APV-R.

Results: The values of the parameters measured during atrial pacing and AF are given in the table below.

Table

	APV-R cm/s	APV-H cm/s	CFR
Atrial paced rhythm.	19.1 ± 8.1	58.8 ± 25.6	3.1 ± 0.4
Atrial fibrillation.	16.2 ± 7.5*	57.5 ± 24.7	3.6 ± 0.5*
$p < 0.05$ vs. atrial paced rhythm			

Conclusions: In patients with well preserved ventricular function the induction of AF reduces baseline coronary blood flow without affecting hyperemic blood flow, leading to augmented CFR.

P1248 Role of direct measurement of left atrial volume on the result of electrosurgical treatment of atrial fibrillation

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Background and Purpose: Left atrial (LA) volume has been considered an important factor of success for atrial fibrillation (AF) treatment options. The aim of this study was to assess the influence of LA volume on the results of AF surgical therapy.

Methods: We studied 18 Pts submitted to simultaneous mitral valve and AF surgery. AF was chronic in 12 Pts and paroxysmal in 6 Pts. The surgical procedure for AF treatment was bilateral pulmonary veins isolation using radiobrequency energy. Before going on bypass, LA pressure was measured. After arresting the heart, a balloon was inserted in the LA and inflated with saline serum. LA volume was considered to be the volume of saline required to achieve the same mean LA pressure previously recorded during beating heart status. Pts were divided in two groups: group A – Pts with LA volume < 200 mL – and group B – Pts with LA volume ≥ 200 mL. At hospital discharge, cardiac rhythm and presence of atrial contraction were analysed for each Pt.

Results: Group A consisted of 11 Pts and group B of 7 Pts. In group A, 2 Pts were discharged in AF and 9 presented rhythm different to AF, whereas in group B, 6 Pts were discharged in AF and one presented rhythm different to AF ($p = 0.013$). Bilateral atrial contraction was present in 8 of the 9 group A Pts out of AF and in no group B Pt ($p = 0.004$).

Conclusion: In this population of Pts submitted to concommitant mitral and AF surgery using bilateral pulmonary veins isolation with radiofrequency energy, supression of AF and restoration of bilateral atrial contraction were achieved more frequently when LA volume was under 200 mL.

P1249 Recovery of left atrial function after conversion of non-rheumatic atrial fibrillation by echocardiographic automatic boundary detection

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In this study we evaluated left atrial (LA) function after chemical conversion of non-rheumatic atrial fibrillation (AF) using echocardiographic automatic boundary detection (ABD).

Methods: The study population consisted of 33 patients, 16 men, mean age 43 ± 11 years. Eighteen pts had brief duration AF (≤ 2 days, Group I) and 15 long duration AF (>3 weeks, Group II). All pts had normal left ventricular function. Changes in serial LA area wave forms were obtained from the apical 4-chamber view, using ABD with the LA as region of interest, on the first day and at 3, 7 and 30 days after conversion to sinus rhythm. LA end-systolic (ESA), mid-diastolic (MDA), end-diastolic (EDA) areas, diastolic emptying index (DEI = ESA − EDA/ESA) and atrial systolic emptying index (ASEI = MDA − EDA/MDA) were calculated.

Results: There were no differences in LA dimensions (40 ± 5.5 vs 41.5 ± 3 mm, p: NS) or in EF (59 ± 10 vs 61 ± 6, p: NS) between Groups I and II. In Group I there was a decrease in EDA (9.3 ± 1.5 vs 7.0 ± 1.3, $p < 0.005$), an increase in DEI (0.40 ± 0.004 vs 0.53 ± 0.005, $p < 0.001$) and ASEI (0.15 ± 0.001 vs 0.33 ± 0.004, $p < 0.001$) between the 1st and 3rd day, which persisted without significant change until day 30. In Group II, there was no significant change in EDA, DEI or ASEI between the 1st and the 3rd day. There was a decrease in EDA (9.3 ± 2 vs 8.1 ± 1, $p < 0.05$) an increase in DEI (0.36 ± 0.005 vs 0.42 ± 0.005, $p < 0.05$) and in ASEI (0.13 ± 0.001 vs 0.22 ± 0.001, $p < 0.05$) between the 3rd and 7th day which persisted until day 30. There were no significant differences in ESA or MDA in either group during the follow-up period.

Conclusions: Recovery of LA function is related to the duration of atrial fibrillation before restoration to sinus rhythm. Automatic boundary detection is a simple, noninvasive method for assessing the rate of recovery of LA function.

P1250 Comparison of left atrial appendage function in patients with idiopathic atrial fibrillation, valvular and non-valvular atrial fibrillation: impact on the thromboembolic risk

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Background: Patients with idiopathic atrial fibrillation (AF) have a lower thromboembolic risk than those patients with valvular and non-valvular AF. The aim of this study was to compare left atrial chamber and appendage function and the incidence of thrombi between those patient groups.

Methods: 130 patients with AF were investigated by transthoracic and multiplane transesophageal echocardiography The following parameters were measured: left atrial diameter (LAD), left ventricular ejection fraction (EF), incidence of left atrial thrombi and spontaneous echo contrast (SEC), maximal area of the left atrial appendage (LAA_F) and peak emptying velocity of the left atrial appendage (LAA_V). As controls served 30 patients in sinus rhythm (SR).

Results: 25 patients had idiopathic AF, 82 patients had non-valvular AF und 23 patients had valvular AF.

Comparison of patients with idiopathic, non-valvular and valvular AF

	Duration [weeks]	AF LAD [cm]	EF [%]	LAA_V [m/s]	LAA_F [m/s]	SEC [Grad]	Thrombi
SR	#3.6 ±	59 ± 0.4	0.6 ± 6	3.3 ± 0.18	0 1.3	0	
Idiopath. AF	159 ± 203*	4.1 ± 0.5*	54 ± 9*	0.52 ± 0.18*	4.3 ± 2*	0.4 ± 0.8*	0*
Non-valv. AF	463 ± 799	4.4 ± 0.6	49 ± 11	0.3 ± 0.13	5.4 ± 2.1	2.3 ± 1.4	11 [13%]
Valv. AF	2262 ± 2340	4.9 ± **	49 ± 0.7**	0.17 ± 14	6.4 ± 0.06**	3.2 ± 3.3**	6 [23%]** 1.1**

*p < 0.05 idiopathic AF versus non-valvular AF; **p < 0.05 valvular AF versus non-valvular AF

Conclusions: Patients with idiopathic AF have a lower incidence of left atrial thrombi and a better left atrial appendage function than those patients with an underlying heart disease. These data support the concept that patients with idiopathic AF have a lower thromboembolic risk than those patients with an underlying heart disease.

P1251 Comparison of TEE-detected risk markers for thromboembolism in patients with paroxysmal and permanent atrial fibrillation: a prospective study

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Paroxysmal (par.) atrial fibrillation (AF) has been associated with a lower risk of thrombo-embolic complications. However, the presence of atrial markers using transthoracic and transesophageal echocardiography (TEE) has not been yet evaluated.

Methods: We studied with transthoracic and TEE 104 consecutive patients with par. AF (duration < 48 hours, n = 33), in sinus rhythm at the time of TEE examination and permanent (perm.) AF, (n = 71) who had no recent embolic event. We evaluated history of embolic events (T.E.), right (RA) and left (LA) sizes, shortening fraction (SF, %), spontaneous echo contrast (SEC), thrombus, low LA appendage emptying velocities (LAA vel.).

Results: The main results are summarized in the table.

	Par. AF (n = 33)	Perm. AF (n = 71)	P
Age (years)	65 ± 16	71 ± 11	0.028
History of T.E.	5 (15%)	13 (18%)	0.906
SF (%)	35 ± 9	31 ± 10	0.053
LA area (cm^2)	21 ± 13	26 ± 6	0.008
LAA area (cm^2)	4.6 ± 2.2	5.8 ± 2.2	0.011
RA area (cm^2)	15 ± 10	20 ± 6	0.001
LAA SEC	5 (15%)	36 (51%)	0.001
LAA thrombus	0	4 (6%)	0.001
LAA vel. (cm/s)	36 ± 19	34 ± 18	0.605

Conclusion: TEE-detected atrial abnormalities are less frequent in patients with paroxysmal AF, despite the fact that history of T.E. was equally frequent.

P1252 Left atrial appendage outflow is augmented during atrial fibrillation compared to sinus rhythm: insights from a pig model of pacing-induced atrial fibrillation

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Maximal peak outward flow (V_{outmax}) of the left atrial appendage (LAA) is frequently measured to analyze its contractility. Decreased V_{outmax} of the LAA after cardioversion of atrial fibrillation (AF) is regarded as atrial stunning, without appreciating the hemodynamic effects of the atrial activation sequence. During sinus rhythm (SR) the main atrium is activated before the LAA thus creating a preload against whom the LAA has to contract. In contrast the chaotic activation pattern of AF prevents organised contraction in the main atrium, while the smaller LAA still contracts without preload, allowing higher V_{outmax}.

Methods: Transpericardial echocardiography (echo), using a 5.5 MHz echo probe was performed in five pigs (70–75 kg). Non-sustained AF (NSAF) was induced with burst pacing (20 Hz). Pulsed-wave doppler analysis of LAA-V_{out}, atrial E-wave (MV-E), A-wave (MV-A) and peak systolic and diastolic velocities of the left upper pulmonary vein (PV-sys and PV-dias) were recorded during AF and SR before and after NSAF episodes. Mean values were obtained in 3 consecutive cardiac cycles during SR, and 10 consecutive cycles during AF.

Results:

cm/s	LAA-V_{outmax}	PV-sys	PV-dias	MV-E	MV-A
SR pre AF	49 ± 6	60 ± 5	41 ± 7	63 ± 6	51 ± 4
AF	67 ± 14*	59 ± 11	38 ± 9	65 ± 13	24 ± 5*
SR post AF	48 ± 6	65 ± 11	47 ± 3	61 ± 5	61 ± 10

*p < 0.01 compared to SR

Compared to SR MV-A decreases, LAA-V_{outmax} increases significantly during NSAF. PV-sys, PV-dias and MV-E are not significantly affected. Values during SR before and after induction of NSAF do not change.

Conclusions: Altered electrical activation, resulting in decreased LAA afterload leads to an increased V_{outmax} at the onset of AF. Thus reduction of V_{outmax} after termination of AF may only represent the reversion of this phenomenon.

P1253 Exclusion of atrial thrombi by transesophageal echocardiography predicts low risk of embolic events after cardioversion of atrial fibrillation

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The place of transesophageal echocardiography (TEE) in the strategy to prevent embolic events after cardioversion of atrial fibrillation is still debated.

Methods: In a prospective study we used TEE in 127 patients to exclude thrombi in the left atrium and atrial appendage before cardioversion of atrial fibrillation. We detected spontaneous echo-contrast in 53 of these patients. The patient group consisted of 75 men and 52 women, mean age 68.1 ± 10.5 y, 57 of them having hypertension, 25 valvular heart disease, 21 coronary heart disease, 21 heart failure, 21 diabetes, 6 hyperthyreodism and 12 having no underlying cardiac disease.

Sinus rhythm was achieved in 103 patients by direct current cardioversion (n = 91, 239 ± 75 J) or by medical treatment (12) within 5.06 ± 7.20 days after TEE, during which period patients received either heparin (67), phenprocoumon (22), both (4) or no antithrombotic therapy (10). Mean atrial diameter was 44.8 mm in patients with successful and 46.3 mm in patients without successful cardioversion.

Results: Within 72 hours after establishing sinus rhythm none of the 103 successfully treated patiens developed any clinically symptomatic embolic event, all of them still having sinus rhythm. According to the method of HANLEY and LIPPMAN-HAND (JAMA 1983;249:1743) and assuming a significance of 0.05 our result of no embolic event in 103 patients can be extrapolated to a maximal risk of embolic events in a representative population of 2.9%, whereas the risk of embolic events in populations without antithrombotic therapy reaches from 3.4% to 7.1%.

Conclusion: We conclude, that if the existence of thrombi in the left atrium and left atrial appendage is excluded by TEE, antithrombotic therapy immediately before cardioversion of atrial fibrillation is sufficient without need of a longer period of anticoagulation.

Day 3

Monday, August 30, 1999

CATHETER ABLATION FOR VENTRICULAR TACHYCARDIA

1254 Catheter ablation of ventricular tachycardia in patients with structural heart disease using the localisa non-fluoroscopic localization system

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Ventricular tachycardia (VT) in patients (pts) with structural heart disease may originate from extended areas. We hypothesized an increased success rate of VT ablation in such pts may by area ablation using multiple adjacent radiofrequency (RF) applications. The aim of this study was to clinically evaluate the new real-time nonfluoroscopic 3D localization and visualization system (LocaLisa) in guiding catheter mapping and delivery of multiple adjacent RF pulses for ablation of complex VT substrates.

Methods: We treated 14 consecutive pts (age 59 ± 14 years), with 20 clinical VT morphologies: 10 pts with coronary artery disease (CAD, LVEF 0.30 ± 0.09), 1 pt with an inferobasal aneurysm without CAD, and 3 pts with arrhythmogenic right ventricular dysplasia (ARVD). All pts had symptomatic episodes (>1/week) of sustained monomorphic VT, mean cycle length 390 ± 96 ms. The ablation target site was determined using activation and entrainment mapping. The LocaLisa system was used to provide a real-time 3D image of the ablation catheter, to mark ablation target sites, and to deliver RF pulses at and around target sites, only in areas with low-voltage and fractionated signals. Ablation outcome was assessed using conventional pacing techniques, one week continuous telemetry monitoring, and follow-up.

Results: Multiple (23 ± 13) RF pulses (maximal power 50W, temperature 60°C) were delivered in an area of 7.1 ± 4.3 cm^2 using various brands of standard ablation catheters with 4 mm tip electrodes. After catheter ablation, 19 of 20 clinical VT morphologies were noninducible. In one ARVD pt with two VT morphologies, one VT was still inducible postablation. During a median follow-up of 7 (range 1–10) months, all pts remained free of VT recurrences. Functional class improved or remained stable. Average fluoroscopy time was: RAO, 28 ± 11 min; LAO, 19 ± 9 min.

Conclusions: These data suggest that the use of LocaLisa allows for appropriate catheter positioning for mapping and ablation of a complex VT substrate, while reducing fluoroscopy exposure.

1255 Radiofrequency catheter ablation of iterative or incessant postinfarction ventricular tachycardia: is it worthwhile?

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To better define the role of radiofrequency catheter ablation (RFCA) in pts with incessant or frequently recurrent postinfarction ventricular tachycardia (iVT), 124 pts referred to both Institution for drug-refractory well-tolerated PIVT were considered and a comparison between 97 pts with paroxysmal VT (pVT) and 27 pts with iVT has been performed. Between the two groups, no significant difference as to age, sex distribution and number of VT morphologies/pt was observed. In iVT group, there was an higher prevalence of pts with an ejection fraction (EF) < 30% (63% in iVT pts vs 23% in pVT pts; p = 0.01); there was no difference in VT cycle length (407 ± 81 in pVT pts vs 412 ± 83 ms in iVT pts). When appropriate, myocardial ischemia was corrected prior to ablation. The site of ablation was identified during VT on the basis of EP criteria and standard RF energy delivery was used. As to the acute ablation result, there was a trend towards an higher success rate in pts with iVT as compared to pts with pVT (78% vs 72%; p = 0.6), but there was also an higher complication rate (including 1 death) in iVT group (18% in iVT pts vs 4% in pVT; p = 0.023). During follow up, as to death for congestive heart failure (CHF), cumulative survival probability (CSP) at 5 years was 98% in pVT pts vs 62% in iVT pts with a 20 fold increased risk of dying from CHF in the iVT group (p = 0.0006); the type of arrhythmia is an independent risk factor, even when EF is considered. As to VT recurrence, there is no significant difference in CSP between the two groups (69% in pVT vs 56% in iVT) at 5 years.

In conclusion: RFCA in pts with iVT should be individually considered, taking into account that, as compared to pVT pts, the acute success rate may be slightly higher, but the procedure-related complication and mortality rate for CHF during follow-up are higher.

1256 Mapping of ventricular tachycardia: the steerable high-density sector basket catheter

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Identifying areas of slow conduction and early endocardial activity during ventricular tachycardia (VT) is mandatory for successfull radiofrequency catheter ablation (RFCA). The objective of this study was to evaluate the efficacy of a newly developed, steerable sector basket catheter during ablation of VT in pts.

Methods: Pts (n = 12, male, 63 ± 9 years) with drug refractory VT were studied during RFCA. The 8.5F steerable sector basket catheter with a 20-bipolar array was inserted percutaneously into the LV using the femoral approach. The 5 arms of the catheter are positioned close together, resulting in a spatial resolution of ± 1 cm. Color coded activation maps were reconstructed on-line using a computerized mapping system. After induction of VT and mapping of the region of interest, a standard ablation catheter was inserted and positioned within the region of interest.

Results: Sustained monomorphic VT (CL 322 ± 55 ms) was induced in all patients. During VT earliest endocardial activation was recorded 72 ± 19 ms prior to the onset of the QRS complex. Entrainment studies using the basket catheter electrodes to stimulate the heart were performed to localize the area of slow conduction during VT. Successful ablation of VT (non-inducible after ablation) was achieved in 83% of pts. No complications were observed.

Conclusion: The new steerable sector basket catheter facilitates RFCA of VT. Potentially fast and hemodynamically unstable VT can be mapped and treated using this approach.

1257 Radiofrequency catheter ablation of ventricular tachycardia in patients with coronary artery disease: relation between the inducibility of non-clinical tachycardias and clinical outcome after a long-term follow-up

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It has been suggested that inducible non clinical ventricular tachycardia (NCVT) after radiofrequency (RF) catheter ablation of ischemic VT are clinically significant, based on the analysis of stored electrograms from ICD implanted in such patients (P). However, this information is seriously limited by the inability to determine the VT morphology of VT detected and treated by ICDs. We analyzed VT recurrences in 27 P (23 men, aged 62 ± 10 years, left ventricular ejection fraction 34 ± 12%) with ischemic sustained monomorphic VT (SMVT) who underwent successful RF ablation of the clinical VT and were discharged without ICD. In 13 of them (Group A) no other SMVT were induced after a complete stimulation protocol before hospital discharge. In the remaining 14 P (Group B), 18 NCVT were induced. Nine NCVT (338 ± 65 ms cycle length) were haemodinamically well tolerated in 7 P and treated with RF (6 of them were successfully ablated in 5 P). Nine NCVT (242 ± 66 ms cycle length) in 9 P required prompt termination. Antiarrhythmic drug (AAD) regimen was not changed in group B P (12 were discharged on no AAD and 2 on amiodarone that had been taking before the ablation).

Results: During a mean follow-up of 28 ± 18 months, VT recurred in 6 P (22%). The table considers the morphology of the VT that recurred classified as identical to the clinical VT, to an NCVT that was induced or had a different morphology (other VT). One P of group A and 3 P of group B died during follow-up, (2 of them from heart failure, one on each group, 1 from asystole and 1 from no cardiac death).

	n	Clinical VT	NCVT	Other VT
Group A	13	3	-	0
Group B	14	1	0	2

Conclusions: Despite a significant incidence of VT recurrence in this P population no spontaneous VT had the morphology of the non clinical induced VT, suggesting a lack of clinical significance of these tachycardias.

1258 Acute and long-term results of the radiofrequency-catheter ablation for monomorphic and ventricular tachycardia in the chronic post-myocardial infarction state

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Background: We report on the short- and long-term results of RFA in patients (pts) who developed late after myocardial infarction drug refractory CRVT and try to identify predicting factors for ablation success.

Results: A total number of 45 pts (42 male, 3 female, age 66 ± 6 years, LVEF 32 ± 13%, localization of myocardial infarction: 50% anterior, 45% inferior, 5% posterolateral) received at least one, in 8 cases (18%) 2 and in 2 cases (4.4%) 3 RFA treatments. 4 pts underwent ablation with a "chilled" system. 23 pts showed only 1 morphology (morph), 16 pts 2 and 6 pts 3–4 morph. 7 pts presented with an incessant form of CRVT. The acute success rate amounted to 80% in the case of 1 morph, 57% in 2 morph and 33% in 3–4 morph ($p < 0.01$) and in the presence of the incessant form 86%. The cumulative recurrence rate during long-term follow-up (34 ± 20 months) was 29%. In total the ablation procedure was successful for 30 pts (67%). "Chilled" RFA led in 3/4 cases after 3 ± 2 RF applications to effective ablation (vs non chilled-RFA after 12 ± 9). After unsuccessful RFA 13 pts (29%) underwent implantation of a cardioverter/defibrillator and 4 pts (9%) an antitachycardiac surgery. Analyzing the mapping criteria, used for guiding the RFA, success rate was 86% in the presence of isolated middiastolic potentials followed by all other criteria showing together a success probability of 64% ($p < 0.05$). The rate of severe but reversible complications amounted to 8.7%, no pt died due to the procedure. During FU 8 pts died (20%). The cumulative survival rate after RFA was 87%, 80% and 73% at 1, 2 and 3 years.

Conclusion: RFA is relatively safe and for 2/3 of the pts a successful curative treatment modality for CRVT in the chronic post myocardial infarction state. The following factors predict a success rate of 80% or more: only one VT-morphology, incessant form and isolated middiastolic potentials. "Chilled" ablation might be more effective than conventional RF application.

1259 Ablation of ventricular tachycardia after Fallot repair: long-term experience on 11 cases

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From 1983 to 1998, 11 patients with drug resistant ventricular tachycardia (VT) after Fallot surgery were submitted to catheter ablation. Surgery had been done at the age of 1 to 11 years (mean value 6 ± 2), and VT had developed from 3 to 13 years later (mean 12 ± 4)

They had from 1 to 5 VT morphologies (median 2), with a left bundle branch block pattern in all, and a frontal axis from −60 to 110. VT cycle length was 258 ± 54 ms.

VT origin was found just under the pulmonary valves, anterior in 3 and septal in 3, on the anterior wall of the infundibulum in 5, on the septum in 1, and I lower on the anterior RV wall. Two patients had 2 different VT origin, respectively below the pulmonary valves, anterior and posterior, and high and low on the anterior right ventricular wall.

The 3 first patients (1983–1991) had fulguration (DC shock), the 6 next (1993–1996) had DC after failure of RF ablation with a 50 watt generator, and the last 3 had only RF with an 8 mm electrode and high power (80 watts) generator.

Ablation was done in one (7) or 2 sessions (4). The procedure lasted from 180 to 240 mn, with 21 to 52 mn of fluoroscopy.

All were successful. However one needed surgery on a second VT site. Ten patients have an uneventful follow-up, from 1 to 8 years without any therapy. The first patient died of ventricular fibrillation 10 years after ablation and persisting non sustained VT.

VT ablation is an effective cure for VT occurring on the surgical scar of Fallot repairs, usually needing higher energies than other ablative procedure.

CLINICAL USE OF IMPLANTABLE DEFIBRILLATORS

1260 The U.S. national survey of implantable cardioverter defibrillator recipients: examining the global and specific aspects of quality of life

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Background: The implantable cardioverter defibrillator (ICD) provides a marked survival benefit over antiarrhythmic medications for patients with life-threatening arrhythmias. The purpose of this study was to examine quality of life and define specific ICD concerns in a large, random, U.S. sample of ICD recipients.

Methods: 450 ICD recipients (82% male, mean age 65+12) responded to a mail-in survey regarding 22 specific ICD concerns and four global health outcomes. This sample was randomly drawn from a biomedical device company database.

Results: 448 patients responded, reporting "good to excellent" general health (316/447; 71%); "somewhat to much better" quality of life (201/448; 45%); and "somewhat to much better" emotional well-being (202/448; 45%) following ICD implantation. A small sample reported "fair-poor" general health (131/447; 29%), with fewer patients experiencing decrements in quality of life (42/447; 9%) and emotional well being (66/448; 15%) following ICD implantation. Younger recipients (<50 yrs. of age) reported significantly better general health ($X2 = 8.796$, $p < 0.05$) but poorer quality of life health ($X2 = 10.799$, $p < 0.05$) as compared to all older recipient age groups. The youngest recipient groups had significantly more difficulty with a range of psychosocial concerns. For example, worry was significantly higher for younger recipients compared to the older age groups (46% (<50 yrs. of age) & 39% (51–60) vs. 21% (61–70) & 18% (71–98)) ($p < 0.05$). Increased ICD shock experiences were associated with greater difficulty with generalized fear ($X2 = 29.273$, $p < 0.001$), fear of physical exertion ($X2 = 25.927$, $p < 0.001$), worry ($X2 = 21.594$, $p < 0.001$), and stress management ($X2 = 12.872$, $p < 0.001$).

Conclusion: These results suggest that most ICD recipients experience desirable quality of life outcomes but that young ICD patients and those who experience ICD shocks are at greater risk for psychosocial adjustment difficulties.

1261 Fast non-sustained ventricular tachycardias predict sudden cardiac death in patients following myocardial infarction

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The MADIT study has shown that electrophysiologic study (EPS) can be successfully applied to identify high-risk pts. following myocardial infarction (MI) that benefit from prophylactic implantation of a cardioverter/defibrillator (ICD). However, EPS is an invasive and non-standardized method that was applied to highly selected pts. late after MI. The purpose of the present study was to assess if a similar high-risk group could be defined prior to hospital discharge after an acute MI by using standard Holter ECG only.

Method: In a prospective study we analyzed arrhythmias on 24-h Holter ECG in 1202 post-MI pts. prior to hospital discharge (13 ± 4 days after acute MI). Pts.' mean age was 64 yrs., 69% were male, and 29% had an ejection fraction < 40%. During a median follow up of 25 months 20% (235) of pts. died: 4% (51) sudden cardiac death (SCD), 9% (102) non SCD, 3% (40) non cardiac death, and 3% (42) from unknown cause.

Results: Non-sustained ventricular tachycardias (nsVT) were observed in 11% (136/1202) of pts and fast nsVT (rate ≥ 150/min) in 3.7% (45/1202). The SCD rate was 14% for pts. with nsVT and 2.4% for pts. without ($p < 0.001$). Pts. with fast nsVT showed an even higher SCD rate of 22% ($p < 0.0001$). Fast nsVT was more predictive for SCD compared to all cause mortality (relative risk 6.3 vs. 3.0).

Conclusion: Pts. with fast nsVT in the first weeks following acute MI are at high risk of SCD. Whether these pts. will benefit from prophylactic implantation of a cardioverter/defibrillator is currently investigated in the IRIS (Immediate Risk-stratification Improves Survival) study.

1262 Efficacy of antitachycardia pacing in 160 patients with a history of ventricular fibrillation

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The efficacy of antitachycardia pacing (ATP) for the termination of ventricular tachycardias (VT's) was prospectively evaluated in 160 patients with implanted cardioverter defibrillators after survived sudden cardiac death due to ventricular fibrillation (VF). In all patients with a history of VF and no known VT's new tiered therapy ICD's were implanted and ATP was programmed on. Most of the patients had coronary artery disease (n = 90) or idiopathic cardiomyopathy (n = 48). The left ventricular function was reduced (EF = 38%). In only 37 of the 160 patients a VT was inducible at the baseline ventricular stimulation. Spontaneous ventricular arrhythmias were analyzed with the stored ECG and therapy history recorded by the ICD.

Results: During the follow-up of 31 (3–80) months 1857 spontaneous ventricular arrhythmias occurred in 97 (61%) patients. VF was seen 185 times and treated with primary shock delivery. ATP attempts were successful in terminating 1496 (90%) of 1672 spontaneous VT's. An acceleration of the arrhythmia due to ATP was seen in 5.7% of ATP attempts. VF was the only recurrent arrhythmia in 36 patients. Spontaneous VT's were seen in 27 patients and 34 patients had both, VT and VF recurrences. In 35 of 97 patients ATP was able to terminate 90–100% of all spontaneous VT's although the known history of arrhythmia was VF.

Conclusion: Patients with a history of ventricular fibrillation alone have more often recurrences of spontaneous VT's than VF (90% vs 10%). The efficacy of ATP (90%) for terminating VT's is high even in patients with a history of VF alone. Therefore we recommend that ATP be programmed for these patients, too.

1263 Higher incidence of inappropriate, but also appropriate implantable cardioverter-defibrillator therapy in survivors of cardiac arrest with atrial fibrillation

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Background and methods: Atrial fibrillation (AF) is a frequent arrhythmia, associated with increased morbidity and mortality in large population based studies. The effect of this arrhyhtmia on device-therapy in survivors of cardiac arrest with an implanted cardioverter/defibrillator (ICD) has not been studied systematically. In a prospective study all consecutive patients (pts) undergoing transvenous ICD-implantation at our institution between 1/1994 and 12/1998 were stratified for presence of AF at ICD-implantation, and incidence and adequacy of ICD-therapy was analyzed during follow-up.

Results: 205 patients (79% male; mean age 60 ± 11 years, ejection fraction 36 ± 13%; coronary artery disease 67%) were analyzed. At baseline, 46 pts (22%) presented with AF. During a mean follow-up of 20 ± 12 months 89 pts had adquate and 30 pts inadequate ICD-therapy as assessed by analysis of recorded electrograms. 10/46 pts (22%) with AF had at least one episode of inadequate ICD-therapy delivery compared to 20/159 (13%) in pts in sinus rhythm (SR) ($p < 0.05$). Adequate device therapy, however, was also significantly more frequently observed in pts presenting with AF (27/46 pts, 59%) compared to SR (62/159 pts, 39%; $p < 0.05$). Important clinical characteristics such as age, gender, and ejection fraction (EF) were similar in pts presenting with AF or SR. Multivariate analysis showed EF to be an independent predictor of adequate Tx in pts of both groups. Antiarrhythmic drug use with amiodarone and sotalol was also more frequent in AF-patients with 19/46 pts (46%) compared to 36/159 (23%) in SR-patients ($p < 0.02$).

Conclusion: ICD recipients with AF have a significantly higher incidence of inadequate, but also adequate device therapy despite higher use of antiarrhythmic agents in this subgroup of patients. These data are in agreement with the notion, that the presence of AF may identify a group of pts at particular high mortality risk.

1264 Value of programmed electrical stimulation to predict clinical outcome in survivors of cardiac arrest: subgroup analysis from the Cardiac Arrest Study Hamburg (CASH)

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CASH was designed to assess the 2-yr mortality of ICD therapy compared to treatment with either propafenone (PROP), amiodarone (AMIO) or metoprolol (METO) in survivors of cardiac arrest. Due to an excessive mortality in pts randomized to PROP, assignement to this group was prematurely terminated. Final analysis showed an improved 2-yr survival in 99 pts randomized to ICD (12.6%) as compared to that in 189 pts randomized to AMIO/METO (19.6%, 1-sided p = 0.047). Baseline programmed electrical stimulation (PES 1) was performed in all pts during hospitalization after the index event; pts randomized to drug treatment also underwent PES under the drug assigned (PES 2). The value of PES to predict clinical outcome was retrospectively assessed.

Results. PES 1 was performed in 97 ICD pts, in 92 AMIO pts and in 97 METO pts; inducibility of sustained VT or VF using a 3 extra-beats, 2-site PES protocol was observed in 47%, 49% and 44% of pts, respectively. 2-yr survival was at 89% higher in 135 noninducible (nonI) than it was at 75% ($p < 0.001$) in 152 inducible (I) pts. Of 82 AMIO and 84 METO pts undergoing PES 2, lower 2-yr survival rates (70% in 20 pts and 68% in 19 pts) were observed among those who still were I, compared to those suppressed (83% in 18 pts and 76% in 17 pts). Conversely, a 2-yr survival rate as high as 94% in 33 AMIO pts and 92% in in 39 METO pts was observed were nonI at both PES 1 and PES 2. Inducibility only at PES 2 (11 AMIO and 9 METO pts) was associated with a 91% and 100% 2-yr survival.

Conclusions. The present data suggest that PES is a valuable tool to select pts who most likely benefit of an ICD treatment among survivors of cardiac arrest. Prospective investigation is required to confirm this observation

1265 Baroreflex sensitivity contributes to the risk stratification of patients considered for a prophylactic implantable cardioverter defibrillator

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The growing use for primary prevention of the ICD, together with its high cost and invasive procedure, calls for accuracy in the identification of the patients (pts) who really need it. In the MADIT-II and SCD-HeFT studies risk stratification is based only on depressed ejection fraction (EF). The ATRAMI study has provided definitive evidence that alterations in the autonomic balance play an important role in cardiac mortality, and are of prognostic value independently of EF and ventricular arrhythmias. We have evaluated whether the presence of an autonomic imbalance defined by a depressed Baroreflex Sensitivity (BRS < 3 ms/mmHg) could improve the management strategy for the prophylactic use of ICD. In the ATRAMI population (1284 patients, age 57 ± 10 yrs, EF 49 ± 12%) the 2-year cardiac mortality of pts with EF < 35% (n = 180) differed significantly according to the presence (n = 33) or absence (n = 147) of nonsustained ventricular tachycardia (NSVT) at Holter recording (21.2 vs 8.2%, p = 0.027). In the presence of NSVT the mortality rates for BRS < or ≥3 ms/mmHg were 31% and 17% respectively (ns). By contrast, among patients without NSVT the 2-year mortality was markedly lower, only 4.6% vs 18% (χ^2 6.02, p = 0.014) according to a BRS ≥ 3 or <3 ms/mmHg. As patients with BRS ≥ 3 ms/mmHg account for 70% of patients without NSVT, the analysis of BRS (which has a Negative Predictive Accuracy of 95.4%) would allow to reduce by about 50% the number of implanted devices without any loss for the high risk pts.

In conclusion, among pts with EF < 35%, those without NSVT but depressed BRS have the same mortality (18 vs 21%) of those with NSVT; this enhances the identification of pts at high risk. Conversely, and perhaps more important, those without NSVT and BRS ≥ 3 ms/mmHg are at very low risk and may not need an ICD. Thus, the use of BRS can markedly improve the risk stratification strategy for the primary prevention of sudden cardiac death.

CATHETER ABLATION OF ATRIAL FIBRILLATION

1266 Electrophysiologic findings after open chest endocardial radiofrequency catheter ablation of atrial fibrillation during mitral valve surgery

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Open chest endocardial radiofrequency catheter ablation (RFA) of atrial fibrillation (AF) during mitral valve surgery (MVS) is a novel technique that combines catheter ablation with surgery to treat atrial AF. We used radiofrequency energy (RF) applied under direct vision through an ablation catheter during MVS to perform the long continuous lesions in the left atrium in patients (pts) with AF and mitral valve disease (MVD). The focus of this paper is to describe the electrophysiologic findings in the following days after the procedure and during the follow-up.

Methods: from February to November 1998 twelve pts (7 female and 5 male) underwent MVS and left atrial endocardial RF ablation in our Department. All had chronic AF (mean 13 months, range 4 to 18) and MVD needing surgery. Using a standard approach, under cardiopulmonary by-pass with bi-caval cannulation, warm cardioplegia was administered. Through left superior atriotomy (roof of the left atrium) RF was now applied encircling the two right and the two left PV, using an ablation catheter Medtronic or Cordis Webster 7F 2-5-2 with distal tip of 4 mm modified and fluid irrigated to provide a pen-like device. The energy was continually delivered at 30 Watts from a power generator (Medtronic Atacr) with a median procedure time of 10 mins. All the pts were studied through the epicardic wires in the following days after the operation and with electrophysiologic endocavitary study (EPS) after 3 months.

Results: the postoperative course was smooth in all pts. The extra corporal circulation and the aortic cross clamp time were minimally increased. At the echo check before discharging from the hospital and after 3 months all the pts with sinus rhythm (SR) showed recovery of atrial contractility. At the end of the operation all the pts had restoration of SR. At discharge all pts were in SR and without AA. All 5 pts with AF recurrence underwent DC shock with acute recovery of SR. Amiodarone therapy (A) was administered in all AF recurrences. 83% of the pts now continue to remain in SR after a medium follow-up of 6 months and 17% are in chronic AF. In the EPS immediatly after the procedure in all the pts we documented a delayed left atrial activity at SR and during right ventricular pacing. In 3 pts with recurrence of AF we performed EPS during AF and during SR after DC shock. In the right atrium we recorded the AF waves while through the coronary sinus catheter we observed a regular left atrial rhythm dissociated from the right atrium.

Conclusion: the combination of the open chest RF ablation during MVS, is an attractive option associated with excellent early procedure outcome at low risk and with stable electrophysiologic findings during the follow-up. Pts with MVD and AF, who require concomitant MVS, seem to be good candidates for this combined approach.

1267 Linear radiofrequency ablation in the right atrium for drug refractory paroxysmal atrial fibrillation: clinical results from a prospective multicenter study

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In order to test the use of a catheter (REVELATION, Cardima, Fremont, CA, USA) specifically designed for creating linear lesions, 43 patients (12 female, mean age 54 ± 10) with highly symptomatic (16 ± 23 episodes/month), paroxysmal, lone atrial fibrillation (AF) underwent radiofrequency (RF) ablation in 6 European centers. Patients were refractory to 2–6 antiarrhythmic medications before ablation, and had paroxysms for 4 months to 40 years with a frequency of 2–150 episodes/month. Symptoms were documented to be due to AF with Holter and/or an Event Recorder. Three lines of lesions were created in the right atrium using the 3.3 Fr REVELATION microcatheter which contains 8 coiled electrodes, each 3 mm long with 2 mm interelectrode spacing. RF lesions were placed between: 1. Inferior Vena Cava (IVC) and Superior Vena Cava (SVC) posterolaterally, 2. SVC and Tricuspid Annulus (TA) anteriorly, and, 3. SVC and TA posteriorly. Ablation along the IVC-TA isthmus was also performed with conventional catheter and technique. Patients were anticoagulated with heparin during the procedure and with antivitamin K post-ablation. After the procedure, patients were kept on the arrtiarrhythmic drug regimen previously ineffective, and monitored with Holter ECG and/or Event Recorder.

Results: In the 34 patients with 1 month follow up data available, the number of symptomatic AF episodes decreased from 16 ± 23/month to 4 ± 6/month post-ablation, and from 17 ± 15 to 3 ± 4 in the 25 patients with 3 month follow up. At least 50% reduction in AF episodes was demonstrated in 23 patients (68%), 80% reduction in 19 patients (56%), including 12 patients (35%) without any recurrence. No procedure related death or major complications occurred in any of the patients.

Conclusions: Linear ablation in the right atrium is safe using the REVELATION microcatheter. Short and medium term clinical benefit was confirmed in most patients with drug refractory, paroxysmal AF.

1268 In vitro and vivo results with the new ATLAS basket catheter for linear radiofrequency ablation of atrial fibrillation

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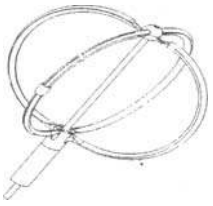
Purpose: To assess the efficacy of the ATLAS catheter for transvenous linear radiofrequency ablation (RFA) of atrial fibrillation (AF).

Methods/Results: The ATLAS basket catheter for linear RFA of AF was designed with 4 expandable struts and a movable electrode for temperature-controlled RFA. In vitro studies were carried out on muscle tissue in saline solution. Additionally, linear transvenous RFA of AF was attempted in a dog model of chronic AF. Size, morphology and location of the lesion in the right and left atrium (RA, LA) were analyzed. In dogs with discontinuous endocardial lesions, epicardial RFA along the endocardial lesion line was added in order to assess the biological effect of each distinct lesion line. In vitro, continuous lesions of 20 mm in length, 6 mm in width and, depending on temperature and settings, up to 4 mm in depth were achieved at low energy setting (4 ± 2 watts, 65 ± 5 C). In 3 dogs (24–31 kg) with chronic AF (≥ 2 months), 2 RA and 2 LA lesions via left upper pulmonary or transseptal approach were created, which terminated chronic AF in all 3 animals. EP-studies in sinus rhythm demonstrated continuous electric wave propagation throughout both atria, attempts to re-induce AF were not successful in 2 dogs, whereas atrial flutter was sustained in 1 dog. Postmortem examination of the hearts revealed, that the majority of lesions were discontinuous and non-transmural, in particular, in the trabecular parts of the atria.



Conclusion: Our study demonstrates that creation of transvenous linear lesions with the ATLAS catheter is both feasible and successful in abolishing chronic AF despite the fact, that the majority of lesions are non-transmural and discontinuous.

1269 Efficacy to perform atrial linear radiofrequency lesions: an experimental histologic comparison

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Catheter ablation of atrial flutter and atrial fibrillation requires the radiofrequency (RF) application of linear lesions. In the sheep model we investigated the efficacy of three different multipolar ablation catheters.

Methods: In 22 sheep a multipolar ablation catheter was inserted via the internal jugular vein into the right atrium and placed in the posteroseptal, posterior and lateral region. In 11 sheep a sheath guided 3.3-F catheter with 8 electrodes of 3-mm length with 2 mm interelectrode spacing was used (Cardima). For linear bipolar radiofrequency (RF) energy application the electrodes were connected consecutively in pairs (10–20 watts, 60 seconds). In 7 sheep a steerable 7-F catheter with four 6-mm electrodes (EPT) and in 4 sheep a steerable 7-F catheter with four 5-mm electrodes (Bard) was placed to perform temperature controlled unipolar RF applications (target T 70° C, 60 seconds). All sheep were heparinised (5000 IE bolus i.v.). The histology was achieved 6–10 days later.

Results:

	7-F	3.3-F	p
Depth [mm]	3.3 ± 1.8	0.8 ± 0.9	<0.001
Width [mm]	6.1 ± 3.4	2.9 ± 2.6	<0.001
Length [mm]	16.1 ± 10.0	10.8 ± 9.4	0.03

There were no differences in the lesion extension related to the ablation site.

Conclusion: In order to achieve transmural linear lesions by catheter ablation in the right atrium, the usage of a 7-F steerable catheter working in unipolar temperature control mode is more promising compared to a sheath guided 3.3-F catheter without T° control ability.

1270 A novel microcatheter approach to the ablation of atrial fibrillation: safety and feasibility in 43 patients

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The placement of linear lesions is considered an effective treatment strategy for the Ablation of atrial fibrillation (AF). The purpose of this multi-center prospective study was to assess the performance of a new multi-electrode radiofrequency (RF) ablation catheter designed to achieve continuous linear lesions. Feasibility and safety of this novel procedure was evaluated in 43 patients with highly symptomatic paroxysmal lone AF. A 3.3 Fr microcatheter (REVELATIONTM, Cardima) which contains 8 coiled electrodes, each 3 mm long with 2 mm interelectrode spacing, was used in the right atrium to deliver multiple 60 second impedance-controlled RF pulses under constant power of 10–25 Watts. The energy was delivered in sinus rhythm sequentially from two adjacent electrodes as anode and a large back plate as cathode. One to two withdrawals of the catheter were required to complete the following four lines: A) IVC to SVC posterolaterally, B) SVC to TA anteriorly, C) SVC to TA posteriorly, and D) IVC to TA along the isthmus. The isthmus line was created with a conventional catheter and technique. The presence of sinoatrial and AV nodal conduction disturbances were evaluated. Assessment of linear lesions was based upon changes of electrograms (egm) amplitude and stimulation threshold.

Results: Impedance rises (>200 W) were only observed at power settings >15 W. There was no thrombus formation or any damage to the catheter. Mean procedure and fluoroscopy times (± sd) required to complete the procedure were 206 ± 65 and 40 ± 20 minutes, respectively. Three ablation EGM amplitude decreased significantly from 1.6 ± 0.20 to 0.6 ± 0.06 mA post ablation, from 1.4 ± 0.08 to 0.8 ± 0.06 mA, to 2.1 ± 3.6 to 1.6 ± 0.51 mA ($p < 0.001$ for paired values comparing pre-vs-post ablation). Pacing threshold values rose significantly when comparing pre-vs-post ablation values from 2.4 ± 0.22 to 6.6 ± 0.41 mV, from 3.7 ± 0.47 to 5.9 ± 0.54, from 2.4 ± 3.8 to 7.8 ± 0.70, for lines A, B and C respectively ($p < 0.001$ for pair values comparing pre-vs-post ablation).

Conclusions: These results indicate linear RF ablation in the right atrium is technically feasible and safe using the REVELATION Microcatheter.

1271 Clinical follow-up after linear left atrial radiofrequency lesions to treat atrial fibrillation

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Using the CARTO (Biosense Ltd.) electroanatomical mapping technique, we performed a right atrial (RA) ablation procedure in 14 pts (11 m, 3 f) with idiopathic atrial fibrillation (AF). Postablation, AF recurred daily in all pts and a left atrial (LA) ablation procedure was subsequently performed. Three linear lesions were created: between the ostia of superior lateral and septal pulmonary veins ("roof line"); from the anterior aspect of the mitral annulus (MA) to the center of the roof line ("anterior line"); and from the center of the roof line to the posterior aspect of the MA, with an intentional gap of 1–2 cm left in its inferior part. The anterior line was omitted in the first 4 pts. Creation of the pattern of ablation lines required 47 ± 18 radiofrequency current applications. LA sessions lasted for 8.7 ± 1.9 hours, median fluoroscopy time was 25.5 minutes. During a median follow-up of 112 days and continued antiarrhythmic medication, 7 pts (50%) were predominantly in sinus rhythm, interrupted occasionally by atrial ectopy. All but one of these pts developed incessant atrial tachycardia (AT) at least once during follow-up, suggestive of an unintended conduction gap in a lesion; termination of AT was achieved by overdrive pacing from the coronary sinus. Four other pts had a marked decrease in number and/or duration of AF episodes, accompanied by symptomatic improvement. The final 3 pts exhibited an unchanged number and duration of AF episodes. Of the 4 pts without an anterior line, none reverted to sinus rhythm.

Conclusions: LA linear lesions including an anterior line supplementing previously created RA ablation lines leads to predominant sinus rhythm in 50% of pts. The occurrence of AT may be attributed to conduction gaps in the applied lesions. This underlines the necessity to validate ablation lines for completeness.

SMOKING: RISKS, MECHANISMS AND STOPPING

1294 Smoking habits and cardiovascular risk in middle-aged inhabitants of Tartu and Stockholm in the SWESTONIA study

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Coronary heart disease mortality per 100 000 inhabitants among 50–54 year old Estonian males and females is about 500 and 100, respectively, which exceeds corresponding Swedish mortality rates approximately 5 times. Smoking is generally recognised as the major cardiovascular risk factor. The aim of the present study was to compare smoking habits and other cardiovascular risk factors in 35 year old and 55 year old population of the city of Tartu (Estonia) and Stockholm (Sweden).

Methods: From the population registers four random groups of the 35 year old and 55 year old subjects were invited both from Tartu and Stockholm. Altogether, 545 subjects (274 from Estonia and 271 from Sweden) filled in a questionnaire (including questions concerning smoking habits), had a physical examination (including blood pressure measurement) and donated blood for analysis. The list laboratory parameters studied consisted of serum total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, lipoprotein (a), apolipoproteins and glucose.

Results: In Tartu, 45% of 35-year old females and 51% of 35-year old males are regular smokers in comparison with 26% in Swedish females and 15% in males. This huge difference is stastistically highly significant ($P < 0.05$ for females and $P < 0.001$ for males). The smoking rate did not differ between 55-year old Estonian (16%) and Swedish (18%) females. However, Estonian 55-year old men were smoking much more frequently (58%; $P < 0.001$) when compared to Swedes (20%). Clearly higher systolic blood pressure was found in Estonian 35-year old men (133 vs. 126 mmHg; $P < 0.01$). No major difference was found in laboratory cardiovascular risk factors studied. Less Estonians believe that lifestyle matters for the risk of cardiovascular disease.

Conclusion: Much higher mortality rates from coronary heart disease in Estonian inhabitants are likely to be ascribed to 3-fold higher rate of smoking, higher blood pressure and less believe that lifestyle matters for the risk of cardiovascular disease.

1295 Antioxidant ascorbic acid attenuates the endothelial dysfunction after acute cigarette smoking

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Endothelial dysfunction has been reported in systemic arteries after acute smoking and it is a persisting phenomenon lasting 60–90 min. In chronic smokers endothelial dysfunction is mediated by increased oxidative stress and is reversed by antioxidants; it is not known whether oxidative stress has a potential role in mediating endothelial dysfunction after acute smoking.

Methods. In a randomized, crossover, double blind study endothelial dependent dilatation of the brachial artery (flow-mediated dilatation, FMD) was assessed in 12 healthy volunteers 30.7 ± 7.8 years) before and immediately, 30, 60, 90 and 120 min after smoking. All subjects were examined on 2 occasions; on Day 1 all subjects received 2 g of ascorbic acid per os 2 hours before smoking and Day 2 all participants received placebo.

Results. Heart rate, blood pressure were not different in two treatment groups in all stages of the study. FMD was similar in two groups before smoking. In the group of ascorbic acid FMD was reduced immediately after smoking, remained depressed 30 min after smoking ($p < 0.05$) and returned to baseline 60 min after smoking (ns). In the group of placebo FMD was reduced immediately after smoking, remained depressed 30, 60 and 90 min after smoking ($p < 0.05$) and returned to baseline values 120 min after smoking (ns); thus the time of impaired endothelial function after smoking was reduced from 90 to 30 min by the use of ascorbic acid.

Conclusions. The administration of ascorbic acid ameliorates the deleterious effect of acute smoking on endothelial function, indicating that increased oxidative stress may be an important mechanism for the endothelial dysfunction after short term smoking.

1296 Short-term mortality of habitual cigarette smokers after acute myocardial infarction: the "smoker's paradox" in a statewide study

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Cigarette smokers paradoxically present improved outcome after acute myocardial infarction (MI). We evaluated the relation between cigarette smoking and in-hospital mortality of MI in the Greek population, which is a low coronary risk population with exceptionally increased use of tobacco products.

Methods: The study population was obtained from the Greek multicenter study for MI and consisted of 7433 consecutive pts with MI (5755 men and 1678 women, mean age 60 ± 14 and 69 ± 13 years respectively) who were hospitalized in 76 hospitals throughout Greece, from May 1993 to May 1994.

Results: Smokers had lower mean age (59 ± 12 vs 70 ± 11 years) and decreased unadjusted in-hospital mortality rates (7.4% vs 14.5%, $p < 0.001$) compared to non-smokers. However, in a logistic regression model with age and gender included as covariates, smoking was not significantly related to prognosis ($p = 0.671$) and the smoker to non-smoker relative risk was 1.053 (0.828–1.339). When diabetes, hypertension, fibrinolytic therapy and the existence of previous MI were added in the model, smoking was still not significantly associated with in-hospital mortality ($p = 0.627$, relative risk 1.065, limits 0.828 to 1.369). The univariate analysis of smokers' clinical characteristics is presented below:

Proportion of cigarette smokers in the subgroups of the studied patients

				p value
Males	80.7%	Females	23.2%	<0.001
Diabetics	56.0%	Non-diabetics	73.8%	<0.001
Hypercholesterolemics	68.6%	Normocholesterolemics	70.1%	0.243
Hypertensives	60.8%	Normotensives	76.6%	<0.001
Positive heredity	75.1%	Negative heredity	67.6%	<0.001
Previous MI	68.3%	No previous MI	69.8%	0.367
Thrombolyzed pts	77.0%	Non-thrombolized pts	63.1%	<0.001

Conclusion: Unadjusted mortality rates are significantly lower in smokers but age accounted for much of their improved outcome. When a number of additional clinical variables were taken into consideration, no significant influence of habitual smoking on early outcome after acute MI was observed.

1297 Related factors with a lower mortality in smokers after an acute myocardial infarction: a subanalysis of the TIM study

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Objectives: Smokers that develop an acute myocardial infarction (AMI) have a lower mortality during the acute phase of the infarction than non-smokers. Recently, it has been suggested that this fact can be attributable to a higher thrombosis incidence on small plaques in smokers that develop an AMI, due to the systemic thrombogenic action of smoking. Therefore, fibrinolysis would be more efficient to reduce mortality in smokers than in non smokers.

Material and methods: The TIM study (Triflusal in Acute myocardial infarction) is an international, multicenter, double-blind, randomized, sequential clinical trial that compares Triflusal versus Aspirin in the prevention of vascular complications (death, non-fatal reinfarction and non-fatal cerebrovascular event) in patients (P) with AMI. The total of 2124 P that were included in the study constitute the basis for this analysis.

Results: On day 35th after the infarction, 148 P had died (7.0%). Mortality was significantly lower in smokers than in non-smokers (3.6% vs 11.0%, $P < 0.001$). Fibrinolysis, given to 70.8% of patients, was associated with a significant mortality reduction both in overall population (5.3% vs 11.0%, $p < 0.001$) and in non-smokers (8.1% vs 16.6%, $p < 0.001$). However, reduction of mortality by fibrinolysis in smokers was not significant (3.3 vs 4.5%, NS). Smoker population was significantly younger, with less females, lower incidence of hypertension, diabetes, obesity, previous angina, MI, heart failure and stroke. A multivariant analysis adjusting by age, sex, and prior MI showed that these risk factors influence mortality and reduces the apparent association between smoking status and mortality.

Conclusion: Although our study shows a lower mortality in smoker patients that suffer an AMI, the reduction in mortality does not seem due to a higher efficacy of thrombolysis in this population. In fact, after performing a multivariant analysis, we can infer that smoking causes the first AMI in younger patients who have less associated risk factors. In consequence, their mortality in acute phase is lower.

1298 Demographical, clinical and psychological characteristics related to long-term smoking cessation in post-myocardial infarction patients

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Aim: To evaluate which characteristics are related to long-term smoking cessation in 1472 post myocardial infarction (MI) patients.

Methods: Smoking habits of 520 (35%) patients, who were smoking during the year before admission for a myocardial, were related to baseline demographical or clinical characteristics. Furthermore, survivors were asked to fill in a set of questionnaires with items on smoking and psychological questions.

Results: At averagely 3.8% years follow-up, 405 (80%) of the 520 smokers were still alive, while of the non-smokers 573 (60%) had survived. This so-called 'Smoker's Paradox' is primarily explained by the difference in mean age: smokers had their MI 10 years earlier (59 vs. 69 years). In 319 (79%) of the smokers, smoking habits were followed: 167 (52%) patients were persistent smokers. No differences in baseline demographical or clinical characteristics could be found between quitters and persistent smokers. 247 (77%) baseline smokers completed a set of questionnaires: 33% patients had stopped smoking within 30 days of the AMI. Persistent smokers had a higher number of smokers in the environment, especially children, family and friends. Quitters were significantly more encouraged, particularly by partner and colleagues, but also their cardiologist. Furthermore, smokers had higher levels of depression, anxiety; fatigue and somatisation at follow-up.

Conclusion: The better survival of the smokers could largely be explained by their younger age. About 50% of the patients continued smoking 4 years after their myocardial infarction. Persistent smokers had more smokers in their environment and received less encouragement to stop. Furthermore, they had a less favourable psychological profile. In order to offer support for smoking cessation, patients' symptoms as depression and anxiety should be taken into account. Furthermore, it is preferred to involve partner and other close family members to encourage smoking cessation.

1299 Effects of cigarette smoking on proinflammatory cytokines and platelet activation in patients with stable angina

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Cigarette smoking is associated with significant endothelial dysfunction. Injured endothelium releases macrophage colony stimulating factor (MCSF) which induces macrophage activation and consequently, causes the release of vasoactive substances, interleukin 6 (IL6), platelet chemoattractants and tissue factor. We investigated the effects of smoking on cytokines, platelet activation and thrombin generation in patients with stable angina (SA) We also examined whether these effects are reversed by aspirin treatment.

Methods: We measured prothrombin fragments (PF1 + 2, nmole/l) MCSF, IL6 (pg/ml) plasma levels and 24 h urine excretion of 11-dehydrothromboxane B2 (DTXB2, ng/mg creatinine) in 60 patients with SA and in 24 matched controls. Thirty four patients (56%) and 13 controls (54%) were smokers (p = NS). Patients had angiographically documented disease and were given ASA 300 mg, o.d. or placebo for 3 weeks in a double blind, cross-over trial.

Results: PF1 + 2, MCSF and IL6 were increased in patients with SA compared to controls (table, $p < 0.05$). Smoker patients had higher MCSF, platelet (PLT) count ($\times 10^3$) and DTXB2 compared to non-smokers ($p < 0.01$). Aspirin reduced MCSF, IL6, DTXB2 and PF1 + 2 ($p < 0.05$). MCSF levels remained higher in smokers than non-smokers after aspirin administration ($p < 0.05$). Conversely, DTXB2 levels became similar between smokers, non-smokers and controls High MCSF was related to high DHTXB2 before and after aspirin administration ($r = 0.40$ and $r = 0.50$, $p < 0.01$)

	All	Smokers	Non-smokers	ASA	Controls
MCSF	1076 ± 613	1095 ± 716	610 ± 390	950 ± 567	479 ± 287
DTXB2	4.4 ± 2.8	4.7. ± 3.4	2.6 ± 2.0	2.2 ± 2.1	3 ± 3.3
IL6	4.2 ± 1.3	4.7 ± 3.0	4.6 ± 2.4	3.5 ± 0.8	2.0 ± 0.9
PF1 + 2	2.26 ± 1.8	1.9 ± 1.5	2.0 ± 1.4	1.73 ± 1.2	0.93 ± 0.5
PLT	230 ± 59	245 ± 55	194 ± 51		190 ± 50

Conclusion: Smoking is related to increased MCSF production and platelet activation in SA but not to thrombin generation. Aspirin reduces cytokine production, thrombin generation and eliminates smoking-induced but not cytokine-induced platelet activation.

EPIDEMIOLOGY AND PREVENTION: FATS, ALCOHOL AND MAGNESIUM

1300 Beneficial effect of alcohol on the elastic properties of the aorta

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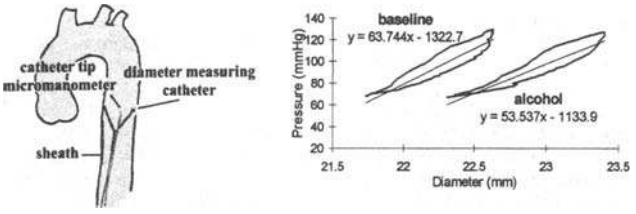
Moderate alcohol consumption has a cardioprotective effect. However, the underlying mechanisms have not been fully elucidated and its direct vascular effects are not well understood. To assess the effect of alcohol on the elastic properties of the aorta (Ao), serial pressure-diameter loops (right fig.) were obtained from the simultaneous recordings of Ao diameter and pressure in 10 patients before and after i.v. administration of ethanol (0.5 gr/kg). Ao diameters were measured by an ultrasonic dimension intravascular catheter developed in our institution (*Ann Intern Med 1998; 128: 426–34*) and Ao pressures by a Millar micromanometer (left fig.).

Results: Ao distensibility (= 2 [pulsatile change in Ao diameter]/[diastolic Ao diameter] × [pulse presssure]) was significantly increased after ethanol administration (2.1 ± 1.0 vs. 2.6 ± 1.1 10^{-6} cm^2 dyn^{-1}, P < 0.001) denoting improvement of aortic elastic properties. Moreover, the shifting of the loop to a new hypothetical line of elasticity (right fig.) indicated an active (direct) effect of ethanol on the intrinsic elastic properties of the Ao.



This improvement of Ao elastic properties may contribute to the protective effects of moderate alcohol consumption on the cardiovascular system.

1301 Oral magnesium treatment inhibits platelet-dependent thrombosis in patients with coronary artery disease

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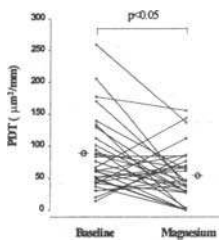
The role of magnesium (Mg) treatment in CAD is controversial. To determine whether oral Mg treatment inhibits platelet-dependent thrombosis (PDT), we conducted a randomized prospective, double-blind, cross-over, placebo controlled study in 36 stable CAD patients (32 men, 4 women, mean age 68 ± 9 years) on aspirin. Patients received either Mg oxide tablets 1,200 mg/day or placebo for 3 months followed by a 4-week washout period, and the crossover treatment for 3 months. PDT was evaluated by exposing porcine aortic media to the flowing non-anticoagulated venous blood for 5 minutes at a shear rate of 800 sec^{-1} using ex-vivo chamber model. PDT was measured by computerized morphometry and expressed as 2 m^2/mm of the aortic surface.

Results: Median PDT (θ) was significantly reduced by 35% (Figure) in patients who received Mg versus placebo. There were no significant differences in platelet aggregation, serum lipids, fibrinogen, platelet count or serum Mg levels between the two treatment groups.



Conclusion: PDT is significantly reduced by Mg treatment in stable CAD patients. This effect is additive to that of aspirin, suggesting a potential mechanism whereby Mg may beneficially alter outcomes in CAD patients.

1302 Combined effects of plasma lipids on 10-year risk of ischaemic heart disease: the Caerphilly collaborative studies

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We have previously shown triglyceride levels to be an important predictor of subsequent risk of ischaemic heart disease (IHD) in men by 5 years of follow-up. Few studies have examined the combined effects of HDL cholesterol (HDL-C), triglyceride (T-G) and total cholesterol (T-C) on subsequent risk of IHD. We examine the combined effect of plasma lipids on risk of IHD by 10 years of follow-up of 4362 British men aged from 45 to 63 years at baseline in two study populations; 533 major IHD events occurred in this population. By 10 years T-C and HDL-C were each contributing independently to risk of IHD but the association with T-G was no longer statistically significant. High, intermediate and low levels of each lipid were defined using the tertiles of the distributions. Men were then grouped into the 27 (= 33^3) possible combinations.

Incidence of IHD by 10 years follow-up was 5% among men in the risk factor combination with lowest expected risk 23% among men in the highest. The number of IHD events observed in each combination was compared with the number predicted from a logistic regression model which included terms for the three lipid variables each in three categories. Additional potential confounding variables (age, study area, pre-existing IHD, smoking, diastolic blood pressure and body mass index) were included in the model. There was no evidence of significant deviation between the observed and predicted numbers of IHD events when the three lipid levels were included in the model; in particular there was no need to include interaction terms between the lipid variables in the model to attain a satisfactory fit.

We conclude that groups of men with a high risk combination of lipid factors exist within this population, but that the joint effect of adverse levels of all three lipids is no greater than the effect predicted by the logistic model from the separate contributions of the three individual lipids.

1303 The role of triglyceride-rich lipoproteins in predicting coronary artery disease

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Accumulating evidence indicates that triglyceride (TG)-rich lipoproteins, such as VLDL, IDL or chylomicron remnants, are more related to the progression of coronary artery disease (CAD) than TG. Levels of lipoprotein lipids, apolipoproteins [apolipoprotein (apo) A-I, apo B, apo E, apo C-III] and of lipoprotein particles [Lp(a), LpA-I, LpB:E, LpB:C-III] were measured in 672 men enrolled in a case-control study. All patients were referred for coronary angiography and the control group consisted of randomly selected men from the general population [360 men with CAD (55 ± 7 years) and 312 controls (53 ± 7 years, p < 0.01)]. The patients with CAD had a higher proportion of CAD risk factors than controls. There were no significant differences in LDL-cholesterol (3.75 ± 1.06 vs 3.82 ± 0.96 mmol/L), apo B (130 ± 30 vs 130 ± 27 mg/dL) or LpA-I (43 ± 23 vs 41 ± 17 mg/dL) levels between cases and controls. CAD cases had lower (p < 0.001) HDL-cholesterol (1.19 ± 0.34 vs 1.55 ± 0.47 mmol/L) and apo A-I (138 ± 23 vs 156 ± 24 mg/dL) levels than controls. CAD cases had higher (p < 0.001) TG (1.74 ± 1.25 vs 1.48 ± 1.02 mmol/L), Lp(a) (55 ± 61 vs 25 ± 31 mg/dL), apo E (7.22 ± 5.42 vs 5.13 ± 1.90 mg/dL), apo C-III (3.46 ± 1.55 vs 2.77 ± 1.10 mg/dL), Lp B:E (3.16 ± 5.05 vs 0.77 ± 0.90 mg/dL), Lp B:C-III (1.80 ± 1.43 vs 1.35 ± 0.71 mg/dL) levels than controls. Logistic regression analyses were carried out after adjustment for confounding factors. Models of equivalent predictive power were achieved by the combination of HDL cholesterol [Odds ratio (OR): 0.08, p < 0.001], Lp(a) [OR: 1.76, p < 0.001] and apo E [OR: 6.46, p < 0.001] or apo C-III [OR: 5.20, p < 0.001] or LpB:E [OR: 4.24, p < 0.001] or LpB:C-III [OR: 1.36, p = 0.07]. TG were not an independent risk factor. In conclusion, both HDL-cholesterol, Lp(a) and TG-rich lipoprotein particles contributed independently to the discrimination between cases and controls. Furthermore, our study suggests that TG metabolism related apolipoproteins or lipoprotein particles may be more specific parameters of CAD than lipids currently measured.

1304 Air force/Texas Coronary Atherosclerosis Prevention Study: invasive procedures and extent of disease

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Background: In AFCAPS/TexCAPS, a randomized, double-blind placebo-controlled primary prevention trial of 6605 men and women without clinical evidence of atherosclerotic disease, treatment with lovastatin 20–40 mg daily reduced first acute major coronary events: fatal or nonfatal MI, unstable angina or sudden cardiac death, by 37% ($p < 0.001$).

Methods: Time to first surgical (CABG) or catheter-based (PTCA) revascularization was a pre-specified secondary endpoint. Exploratory analyses included all with diagnostic coronary angiography regardless of endpoint status. Coronary lesions were categorized by percent stenosis, number and distribution. LV dysfunction was assessed by ejection fraction, presence of mitral insufficiency and wall motion abnormalities.

Results: Treatment with lovastatin reduced the risk of revascularization by 33% (106 vs. 157) [p = 0.001, RR 0.67, 95% CI 0.52, 0.85] and reduced CABG [58 (1.8%) vs. 74 (2.2%)], PTCA [48 (1.5%) vs. 83 (2.5%)] and first diagnostic coronary angiography [188 (5.7%) vs. 238 (7.2%)]. There were fewer patients with significant CHD (worst lesion > 50%) treated with lovastatin [139 (4.2%) vs. 200 (6.1%)]. The extent of LV dysfunction was independent of treatment group.

Conclusion: Treatment with lovastatin reduced total, surgical and catheter based revascularizations, diagnostic angiography and presence of significant CHD. Among those with significant lesions, there was a similar degree of LV dysfunction in both groups.

1305 The acute coronary syndrome and cholesterol dynamics: an association with peak cardiac troponin I levels

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A fall in serum cholesterol immediately following myocardial infarction has been previously reported, although controversy exists over the timing and magnitude of such events. To assess the variability, we looked at changes in total cholesterol immediately following admission with chest pain.

Method: Lipid profiles were measured on admission and on the second morning after admission, in non-selected consecutive patients presenting to the chest pain triage unit of a large general hospital. In addition, troponin I (Bayer Diagnostics) levels were measured daily for three days following admission.

Results: Patients (n = 212) were grouped by primary clinical diagnosis and the changes in serum cholesterol (mmol/l) calculated (n, mean change in cholesterol, maximum drop, maximum rise, p [paired t-test]): Myocardial infarction (59, −0.49, −2.6, +0.9, <0.0001): Unstable angina (67, −0.01, −1.5, +2.5, 0.897): Other cardiac (49, −0.17, −1.6, +1.2, 0.057): Non-cardiac (37, −0.17, −2.0, +1.3, 0.096). A statistically significant change in cholesterol was shown only for the myocardial infarction group. In patients who demonstrated a net rise in cholesterol, the mean peak troponin I level was 6.65 ng/ml compared to 23.4 ng/ml in those with a net fall in cholesterol ($p < 0.05$; t-test).

In conclusion: The data shows that there are potentially clinically significant variations of serum cholesterol within the first 48 hours following admission in all patient groups. Important therapeutic decisions with regards to the introduction of lipid lowering drugs (and assessment of the effectiveness of such interventions) are often based on the results of serum cholesterol levels measured during admission. To minimise the potential error, we recommend that all patients should only have lipid profiles performed on an admission sample. Use of results from subsequent samples, even within the first 48 hours, can lead to clinically significant misclassification, or misinterpretation of an apparent lack of response to subsequent hypolipidaemic therapy. Peak cardiac troponin I levels have been previously shown to be correlated with infarct size. Patients exhibiting a fall in cholesterol in this study statistically had higher peak troponin I levels. The interpretation of cholesterol values in patients with more extensive infarction may require even more caution.

NEUROHUMORAL ASPECTS OF CARDIOVASCULAR REMODELLING

1314 Adrenergic and reflex abnormalities in obesity-related hypertension

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Hypertension (H) is characterized by sympathetic hyperactivity and we have previously shown that this is the case also in obesity (O), even in absence of H. It is unsettled, however, whether the concomitant presence of H and O further enhances the abnormalities characterizing the above mentioned diseases.

Methods: In 13 normotensive lean control subjects (C, age: 33.1 ± 2.3 yrs, body mass index, BMI: 22.6 ± 0.7 kg/m^2, mean ± SEM), 10 untreated essential lean H (BMI: 24.2 ± 0.8 kg/m^2,), 10 normotensive O (BMI: 36.1 ± 1.1 kg/m^2) and 11 untreated HO (BMI: 37.2 ± 1.6 kg/m^2), all age-matched with C, we measured beat-to-beat mean arterial pressure (MAP, Finapres), heart rate (HR, EKG) and postganglionic muscle sympathetic nerve traffic (microneurography at a peroneal nerve) at rest and during baroreflex stimulation and deactivation via stepwise i.v. infusions of phenylephrine (PHE) and nitroprusside (NTP).

Results: MAP was higher in H and in HO (112.9 ± 1.9 and 109.4 ± 2.3 mmHg respectively, $p < 0.01$ for both) than in C and in O (89.3 ± 1.8 and 91.6 ± 1.6 mmHg), while HR was significantly increased only in OH. MSNA values were significantly higher in H and in O than in C (44.9 ± 3.7 and 50.0 ± 3.1 vs. 31.6 ± 2.6 bs/100 hb respectively, $p < 0.01$ for both), a further increase being detected in OH (57.4 ± 4.8 bs/100 hb, $p < 0.05$). In C the mean BP increase induced by PHE caused a reflex reduction in HR (−18.7 ± 1.6 b/min) and in MSNA (−78.5 ± 12% i.a.), while the mean BP fall induced by NTP caused opposite effects (HR: +20.9 ± 2.2 b/min; MSNA: +103.4 ± 19% i.a.). While in H only baroreflex modulation of HR was impaired (−48.4 ± 8%, $p < 0.01$ vs. C), in O both HR and MSNA changes were attenuated (−37.1 ± 5 and −42.9 ± 7% respectively, $p < 0.01$ for both), a further attenuation being observed in OH (−59.4 ± 9 and −61.3 ± 7% for HR and MSNA, $p < 0.05$ vs. O).

Conclusions: These data provide the first evidence that the concomitant presence of O and H triggers a sympathetic activation greater for magnitude than that found in these pathological conditions. This is accompanied by a marked impairment in baroreflex control of both vagal and sympathetic components, which is greater for magnitude than that observed in O and H.

1315 Depressed baroreflex sensitivity is associated with angiotensin II type 1 receptor gene polymorphism C1166 in adults free of clinical heart disease

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Aging, hypertension and genetic variation have been associated with decreased baroreflex sensitivity (BRS). Angiotensin II (ATII) can modify BRS through direct central and humoral effects which are mediated mostly by type 1 receptor (AT1R) at the cellular level. The cytosine (C) allele of A1166C (A = adenosine) polymorphism in the untranslated region of the AT1R gene has been associated with hypertension and left ventricular hypertrophy.

A random sample of population (n = 83, 39 men) born in 1954 was studied. All subjects were free of heart disease and hypertension. A prospective 2-month collection of life-style data included recording of daily ethanol and cigarette consumption, leisure-time physical activity and 1-week salt intake. The means of 3 blood pressure (BP) measurements during this period were used in the analysis. BRS was evaluated from the overshoot phase of the Valsalva maneuver, and AT1R polymorphism by restriction enzyme digestion of PCR products. Multiple regression analysis was used to assess the effect of genotype with other variables on BRS. Variables with skewed data distribution were logarithmically transformed prior to analyses.

AC + CC genotypes were compared together (n = 23) with AA homozygotes (n = 60). The groups did not differ regarding BP and heart rate: the mean systolic BP was 122(12) vs 126(15) mmHg; diastolic BP, 70(11) vs 71(15) mmHg; and heart rate, 66(9) vs 67(10) bpm. However, BRS was significantly smaller in the presence of C allele with a median of 11.4 (5.4–16.9) in the AC + CC group vs 13.5 (2.7–47.3) ms/mmHg in the AA group (P = 0.030). This association was independent of sex, body mass index and all life-style traits.

We conclude that the A1166C polymorphism of the AT1R gene predicts interindividual variation in BRS in healthy individuals. As low BRS is an established risk factor for cardiovascular morbidity and mortality this observation merits further study.

1316 Sympathetic nerve traffic and baroreflex control of circulation in systodiastolic and isolated systolic hypertension of the elderly

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Previous studies have shown that young and middle-age essential hypertensives are characterized by a sympathetic overactivity coupled with an impaired baroreflex heart rate control. It is unkown, however, whether this is also the case for systodiastolic (SDH) and isolated systolic hypertension (ISH) of the elderly.

Methods: In 9 healthy normotensive subjects (age: 67.8 ± 2.0 yrs, mean ± SEM), in 8 SDH and 8 ISH, both untreated and age-matched with C, we measured beat-to-beat arterial blood pressure (BP, Finapres), heart rate (HR, EKG) and efferent postganglionic muscle sympathetic nerve activity (MSNA microneurography at a peroneal nerve) at rest and during baroreflex stimulation and deactivation induced by stepwise i.v. infusions of phenylephrine (PHE) and nitroprusside (NTP) respectively.

Results: Resting systolic and diastolic BP values were 127.8 ± 5.8/78.9 ± 2.9 mmHg in C, 163.9 ± 4.1/98.4 ± 1.3 mmHg in SDH and 174.8 ± 3.3/85.9 ± 2.3 in ISH. While HR was similar in the 3 groups, MSNA values were significantly greater in SH than in C (66.4 ± 6.5 vs 50.6 ± 4.4 bs/100 heart beats respectively, $p < 0.05$), a further increase characterizing SDH (78.7 ± 6.3 bs/100 heart beats, $p < 0.01$ vs C). In C the mean BP increase induced by PHE caused a reflex reduction in HR (−6.3 ± 0.7 b/min) and in MSNA (−64.2 ± 6.6.% i.a.), while the mean BP fall induced by NTP caused opposite effects (HR: +6.9 ± 1.2 b/min; SNA: +89.6 ± 17.0% i.a.). For similar BP changes, in SDH and ISH reflex changes in HR were markedly and significantly ($p < 0.01$) attenuated as compared to C (−43.2 ± 7.0 and −34.3 ± 8.0% respectively). In contrast reflex modulation of MSNA was superimposable.

Conclusions: These data provide evidence that sympathetic activation is a phenomenon which 1) characterizes not only the hypertensive state of young and middle-age patients but also hypertension of the elderly, 2) is not peculiar to SDH but can be detected also in ISH and 3) is accompanied by an impairment in baroreflex cardiovascular control, which, however, is limited to its vagal component.

1317 Baroreflex sensitivity predicts unexpected death in chronic heart failure

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Accurate identification of patients at greatest risk of sudden death remains elusive. We hypothesised that abnormalities of autonomic dysfunction would predict sudden death in CHF.

Established clinical variables were determined in 199 patients with stable CHF remote from myocardial infarction: age (59 ± 9 years), aetiology of CHF (ischaemic n = 163, nonischaemic n = 36), NYHA status (2.7 ± 0.8), maximal oxygen consumption (VO_2max 16.9 ± 4.9 ml/kg/min). Investigational variables included: heart rate variability from 24 hour tapes (HRV, median SDNN 118 msec), baroreflex sensitivity by phenylephrine bolus injection (BRS median 5.4 msec/mmHg), signal averaged ECG (25 positive) and QT dispersion (median 94 msec).

Events were categorised by established standards using information from death certificates, autopsy findings and hospital and GP case records. Patients who died of a documented ventricular arrhythmia, or who did not survive a community resuscitation attempt were classed as sudden cardiac death. Patients who died at home with no recent (>4 weeks) documented change in cardiac status were also classed as sudden cardiac death, unless an obvious alternative aetiology was documented. Mean duration of follow-up was 971 ± 378 days. There were 54 all cause deaths, 47 cardiac deaths and 24 unexpected deaths.

A Cox-proportional hazards analysis was performed with age, NYHA class, aetiology of CHF and LVEF as forced variables and multivariate analysis of VO_2max, HRV measures and BRS.Variables were dichotomised above and below median values.

Cox hazards ratios

	Hazard Ratio	95% CI	p value
Age	0.95	± 0.05	0.09
NYHA	1.75	± 0.97	0.25
Cause	7.13	± 2.10	0.09
LVEF	2.04	± 1.05	0.17
IVCD	2.60	± 0.89	0.03
BRS	5.71	± 1.24	0.005

Cox hazards ratios (above/below median)

BRS was the only additional co-variate which predicted both cardiac and sudden death (see table). In patients with severe LV dysfunction (EF < 20%), BRS retained this prognostic power. BRS testing identifies patients most likely to die sudden, unexpected deaths in CHF.

1318 Hypertrophic remodelling in subcutaneous small arteries of normotensive and hypertensive patients with non-insulin-dependent diabetes mellitus

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Objective Vascular structure is influenced by several neurohumoral growth factors, including insulin levels. It is not known whether patients with non insulin dependent diabetes mellitus (NIDDM), who are characterised by high levels of circulating insulin, present structural alterations in small resistance arteries. Therefore, we have investigated structural characteristics of subcutaneous small arteries in 12 normotensive subjects (NT), in 18 patients with essential hypertension (EH), in 15 patients with NIDDM, and in 15 patients with NIDDM and essential hypertension (NIDDM + EH).

Design and Methods All subjects were submitted to a biopsy of subcutaneous fat. A blood sample was taken in order to evaluate the circulating levels of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (ELISA)

Small resistance arteries were dissected and mounted on a micromyograph (Mulvany's technique). The normalized internal diameter (ID), the media/lumen ratio (M/L) as well as the remodeling index (RI) and the growth index (GI) were calculated (Heagerty and coll, Hypertension 1993).

Results The results are summarised in the table:

	NT (n = 12)	EH (n = 18)	NIDDM (n = 15)	NIDDM + EH (n = 15)
SAP (mm Hg)	128 ± 8	161 ± 7***	130 ± 10	157 ± 15***
DAP (mm Hg)	79 ± 7	98 ± 7***	80 ± 3	96 ± 9***
M/L (%)	5 ± 1	9.3 ± 2.3***	10.0 ± 2.4***	11.2 ± 1.5$^{***\#}$
ID (μm)	299 ± 53	226 ± 67*	245 ± 56*	2220 ± 47***
RI e GI	–	92%, 6%	75%, 46%	86%, 40%
ICAM-1 (ng/ml)	205 ± 26.4	271 ± 26.0***	333 ± 87.6$^{***\#}$	318 ± 71.2$^{***\#}$
VCAM-1 (ng/ml)	520 ± 105	670 ± 194*	892 ± 114$^{***\#}$	852 ± 177$^{***\#}$

($^{*}p < 0.05$, $^{***}p < 0.001$ vs. NT, $^{\#}p < 0.05$ vs.

NIDDM and EH; SAP and DAP: systolic and diastolic arterial pressure). M/L and ID were significantly different in EH, NIDDM and NIDDM + EH compared with NT. Moreover, NIDDM + EH had a significantly higher M/L compared with EH and NIDDM. EH showed the presence of eutrophic remodelling, while NIDDM and NIDDM-EH presented a 40–46% cell growth (hypertrophic remodelling). Plasma ICAM-1 and VCAM-1 concentratons were higher in EH, NIDDM and NIDDM + EH than in NT. Moreover, NIDDM and NIDDM + EH showed higher levels of adhesion molecules than EH.

Conclusions Our data suggest that diabetes mellitus and essential hypertension have a synergistic effect on vascular structure. This may represent an important mechanism underlying the increase of cardiovascular events observed in the presence of the two risk factors.

1319 Agonist-induced downregulation of the β_2-adrenoceptor is modulated by the amino-acid at position 16 but not by the amino-acid at position 27 in essential hypertension

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Two common polymorphisms resulting in the amino-acid substitutions Arginine 16→Glycine and Glutamine 27→Glutamate, occur in the N-terminus of the β_2-adrenoceptor. *In-vitro* functional studies revealed that the Arginine 16→Glycine variant underwent increased agonist-promoted downregulation but that the Glutamine27→Glutamate variant was resistant to downregulation. Importantly, the combination of both mutants resulted in downregulation equal to that for the Arginine 16→Glycine variant alone. Changes in agonist-promoted regulation may alter vascular reactivity affecting blood pressure and recently the Arginine 16→Glycine variant has been associated with essential hypertension in an African Caribbean population. Previous studies have examined these functionally opposing variants individually, with conflicting results. We wished to assess the relationship between them in essential hypertension.

Methods: We genotyped 211 patients with essential hypertension for both variants using a fluorogenic 5′ nuclease assay. This assay utilises PCR and the 5′ exonuclease activity of Taq polymerase to cleave a fluorescent dye from an allele specific probe. For each variant two probes were used, one specific for each allele and labelled with a different fluorescent dye facilitating allelic discrimination. The accuracy of this technique was assessed by fluorescent sequencing of DNA from a random sample of 50 patients.

Results: The sequencing data confirmed the results of the fluorogenic assay in all 50 patients. The genotype frequency for the first variant was; Arg16/Arg16: 10%, Arg16/Gly16: 55%, Gly16/Gly16: 35% and the second was Gln27/Gln27: 34%, Gln27/Glu27: 50%, Glu27/Glu27: 16%. Although all genotypes were common, the Glu27/Glu27 variant only occurred in association with the Gly16/Gly16. Furthermore in no cases that were Arg16/Arg16 was the Glu27 allele found. Therefore the Glu27 allele appears to occur only in the presence of the Gly16 allele in this population.

Conclusions: Two groups have previously suggested that the Glu27 allele results in resistance to downregulation of the β_2-adrenoceptor in man. Our results demonstrate that the Glu27 allele only occurs with Gly16, which functionally dominates it. We therefore conclude that, at least in subjects with essential hypertension, the Glu27 allele does not determine the degree of downregulation of the β_2-adrenoceptor.

PHARMACOLOGIC ALTERATIONS OF ENDOTHELIAL FUNCTION

1320 Effects of estrogen and simvastatin on markers of inflammation in hypercholesterolemic postmenopausal women

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Background: Atherosclerosis in humans associated with inflammation. Therapies that increase nitric oxide (NO) bioactivity may reduce synthesis if proinflammatory proteins within the vessel wall by inhibiting transcriptional activation of target genes.

Methods: As estrogen and statin lipid-lowering therapies improve vascular NO bioactivity, we administered conjugated equine estrogen (CEE) 0.625 mg, simvastatin 10 mg, or the combination daily for 6 weeks to 28 hypercholestrolemic (low-density lipoprotein 165 ± 36 mg/dL; mean ± SD) postmenopausal women in a randomized, double-blind, double-crossover study. We measured brachial artery flow-mediated dilation (FMD) following forearm ischemia as a bioassay of endothelial NO, and serum levels of E-selectin, intercellular adhesion molecule (ICAM-1), and vascular cell adhesion molecule (VCAM-1).

Results: Equivalent improvement in FMD (P = 0.600 by ANOVA) was seen with each therapy: CEE 4.0 ± 2.6 to 10.2 ± 3.9%, simvastatin 4.3 ± 0.4 to 10.0 ± 3.9%, CEE/simvastatin 4.6 ± 2.0 to 9.8 ± 2.6% (all P < 0.001 vs respective baselines). However, only therapies including CEE significantly reduced levels of cell adhesion molecules. CEE reduced levels of E-selectin, ICAM-1, and VCAM-1 by −17 ± 14%**, −3 ± 22%, and −14 ± 21%*, respectively. Simvastatin reduced levels of E-selectin, ICAM-1, and VCAM-1 by 6 ± 3%, 5 ± 27%, and −3 ± 26%, respectively. CEE/simvastatin reduced levels of E-selectin, ICAM-1, and VCAM-1 by −18 ± 16%**, −8 ± 15%*, and −11 ± 19%*, respectively. Data (mean ± SD) = %change from respective pretreatment values; *P < 0.01; **P < 0.001.

Conclusion: Thus, therapies that improve NO bioactivity in postmenopausal women may not have comparable effects on markers of inflammation, and suggest a primary mechanism of estrogen.

1321 A six-month statin therapy reduces endothelial ICAM-1 levels in 30 patients with very early stages of coronary atherosclerosis

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Background: Increased expression and endothelial release of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) play a key role in initiation and progression of atherosclerosis under the impact of risk factors. Aim of our study was to measure ICAM-1 levels in patients with mild-to-moderate LDL-hypercholesterolemia, angina pectoris, reduced coronary flow reserve (CFR) and minimally affected coronary vessels before and after 6 months of intensive lipid lowering with statins (20–40 mg simvastatin n = 28, others n = 2), previously not receiving lipid lowering drugs.

Methods: In 30 patients CFR was determined from dipyridamole (0.56 mg/kg) flow/basal flow ratio with dynamic positron emission tomography (PET) and N-13-ammonia as flow tracer. Coronary angiogram was performed due to exertional or atypical angina revealing minimal changes in terms of wall irregularities or minimal stenosis (≤30%). Baseline data: 20 males, 10 females; mean age: 58 ± 8 years. After 6 months lipid lowering therapy with statins, supported by fat- and cholesterol-reduced diet, soluble ICAM-1 levels were measured by solid phase sandwich enzyme linked immuno sorbent assay (ELISA) in venous blood.

Results: (mean ± SD) CFR: 2.3 ± 0.7, LDL: 176 ± 47 mg/dl at baseline. After 6-month follow-up LDL decreased to 103 38 mg/dl ($p < 0.01$), ICAM-1 levels decreased from 95 ± 65 to 66 ± 44 ng/ml ($p < 0.05$). The clinical course showed a regression of anginal symptoms in the majority of patients ($p < 0.01$).

Conclusions: An intensive lipid lowering therapy induces a significant reduction of ICAM-1 levels after ≈6 months in patients with hypercholesterolemia and early stages of coronary atherosclerosis, possibly demonstrated for the first time. Measurement of ICAM-1 could serve as a new atherosclerosis response marker in the control of coronary risk factors.

1322 Influence of oestrogen replacement therapy on endothelial function

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Several studies have suggested that estrogen supplementation may improve the vascular dysfunction by promoting endotelium-dependent vasodilatation exerting a cardioprotective effect in postmenopausal women. Three groups of menopausal women (basal estradiol level below 50 pg/ml) were included into the study:

(a) the first group (n = 22: n = 18 after natural menopause and n = 4 after total hysterectomy with bilateral salpingoophorectomy) received transdermal 17 β-estradiol therapy (Estraderm MX 50, Novartis)
(b) the second group (n = 6 after natural menopause) received simvastatin (Zocor, MSD, 20 mg/day)
(c) the third group (n = 12 after natural menopause) remained without pharmacotherapy

At the beginning, after 3 and 6 months of the study the nitric oxide (NOx), and endothelin-1 (ET-1) plasma levels were measured before, during and after standard exercise test (according the Bruce's protocol) whereas $VEGF_{165}$ was measured only before exercise test at the some time points. NOx concentration was analysed in serum by modified Griess method, ET-1 was determined with RIA kit (Amersham) and $VEGF_{165}$ with ELISA Kit (R & D Systems).

The simvastatin as well as 17β-estradiol therapy resulted in an increase of NOx release during maximal exercise (by above 50%) and in decrease of basal ET-1 level after 6 month therapy. Thus the NOx/ET-1 ratio was significantly increased at maximal exercise and after exercise by 71% and 85% respectively. The improved blood perfusion was also documented by the decrease of plasma $VEGF_{165}$ level after 6 months of both kind of therapy but not in control group, since ischemia is the main activator of VEGF gene induction.

In summary transdermal therapy with estrogen as well as oral one with simvastatin equipotentially modulate the endothelium-dependent regulation of blood redistribution during effort and protect tissue against ischemia.

1323 Effects of atorvastatin and vitamin C on endothelial function of hypercholesterolemic patients

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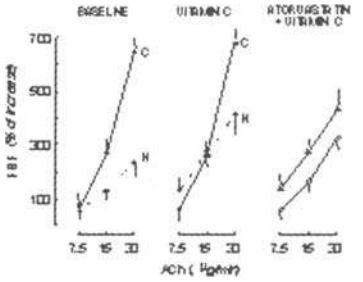
Endothelial dysfunction has been reported in presence of different risk factors such as hypertension, smoking, diabetes and hypercholesterolemia. We tested in 18 hypercholesterolemics (H) (10 M/8 W, age = 40 ± 6 yrs), the effects of 1-month of atorvastatin alone (10 mg/day) on impaired endothelium-dependent vasodilation and during coadministration of vitamin C (24 mg/min). Twelve normal volunteers (7 M/5 F, age = 39 ± 5 yrs) were also enrolled as control group (C). The responses of the forearm blood flow (FBF) to acetylcholine (ACh) (7.5, 15 and 30 mcg/ min), sodium nitroprusside (SNP) (0.8, 1.6, 3.2 mcg/min) and L-NMMA (2, 4, 8 mmol/ min) were evaluated at baseline and after 1 month of atorvastatin treatment by strain-gauge plethysmography. At baseline, the response to ACh was significantly attenuated in H vs C: at the highest dose (30 mcg/min), FBF was 27.0 ± 3.4 vs 11.5 ± 1.9 mL. 100 mL tissue^{-1} min^{-1} respectively ($p < 0.0001$). No significant differences were found between groups during SNP infusion. The atorvastatin significantly improved ACh-stimulated FBF: at highest dose the FBF increased to 14.9 ± 1.5 mL. 100 mL tissue^{-1} min^{-1} ($p < 0.0001$). Similarly, the L-NMMA endothelial effects were significantly potentiated by atorvastatin treatment. Vitamin C increased ACh-vasodilation in the same way before and after atorvastatin treatment.



In conclusions, the endothelial dysfunction in H is due to oxidative stress, and atorvastatin rapidly improves impaired endothelial vasodilation by lipid-lowering action and, probably, by pleiotropic effects.

1324 Endothelin selectively induces functional and morphological coronary alterations in cardiac transplant recipients

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Endothelin (ET) opposes the effects of NO and plays a significant role as a modulator of coronary vascular reactivity in the early stages of arteriosclerosis. We have previously detected that coronary endothelial dysfunction after HTx is associated with increased myocardial ET mRNA expression. However, the impact of early ET and eNOS-activation on development of functional and morphological coronary alterations during follow-up is unknown.

Methods: We investigated the impact of myocardial ET and eNOS-gene (RT-PCR) expression as well as ET and nitrite/nitrate-plasma levels (aorta and coronary sinus; RIA, Griess) on development of morphological and functional coronary changes in 42 cardiac transplant recipients (CTr) early (1 month) and 12 months after HTx. Epicardial (QCA) and microvascular (ic Doppler) endothelium-dependent (acetylcholine) and endothelium-independent (adenosine) vasomotor-function was studied sequentially. IVUS was performed to determine intimal hyperplasia.

Results: Significant ET uptake by the heart (aortic-coronary sinus plasma level > 1 fmol/ml) was noticed early and during follow-up in the majority of CTr ($p < 0.001$). Endothelium-dependent flow increase during follow-up was inversely correlated to early aortic ET-levels ($r = -0.38$; $p < 0.05$). CTr with newly developed intimal thickening and epicardial endothelial dysfunction during follow-up had an increased ET mRNA expression score at baseline compared to patients with no functional and morphological changes over time (2.8 ± 1.0 versus 1.7 ± 0.8; $p < 0.03$). Importantly, eNOS-mRNA expression and nitrate/nitrite levels at baseline were comparable in CTr with and without development of intimal thickening and/or endothelial dysfunction during follow-up.

Conclusion: Coronary endothelial vasomotor dysfunction as well as morphological coronary alterations during follow-up after HTx are at least in part induced by early myocardial activation of the ET-pathway.

1325 L-arginine administration improves insulin-mediated endothelial dysfunction in patients with syndrome X

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Patients (pts) with angina pectoris, positive exercise test and smooth coronary arteries (syndrome X-SX) have been shown to be insulin (I) resistant. We assessed whether I sensitivity could be improved by the administration of L-arginine, the natural precursor of nitric oxide (NO). Nine SX pts and 13 matched controls (C) were recruited. All SX pts underwent 120 min L-arginine (A) (0.125 g/min) and saline (S) infusions in random order, while C underwent only S infusion. In all cases, after the first 60 min of infusion, a 0.1 U/kg i.v. insulin bolus was administered and blood glucose (G) levels were maintained at basal values by means of a variable G (20%) infusion rate (GIR). At baseline, I, G, NO_2/NO_3, triglycerides, free fatty acid blood levels, systolic-diastolic blood pressure (SBP-DBP) and forearm blood flow (FBF) were similar in SX and C. In SX pts, A induced a reduction in SBP ($p < 0.01$) and DBP ($p < 0.01$) and an increase of FBF (3.11 ± 0.23 vs 2.34 ± 0.16 ml/100 ml/min, $p < 0.05$) reaching values similar to those observed in C (3.2 ± 0.31 ml/100 ml/min). while I and G levels were unchanged. Conversely, no changes were observed during S in both groups. After I, there was an increase in ΔAUC (0–30) of NO_2/NO_3 during A compared to S (60.8 ± 19.2 vs 14.8 ± 31.8 μmol/L, $p < 0.05$) in SX, even though levels remained well below those found in C during S (168.8 ± 52.5 μmol/L, $p < 0.01$). In SX during A, GIR was 32% higher than during S (282 ± 27 vs 213 ± 23 mg/kg, $p < 0.05$), but these levels were inferior to those observed in C (390 ± 32, $p < 0.01$ vs A and S of SX).

In conclusion, L-arginine mediated increase of NO production improves I sensitivity in SX pts. Endothelial dysfunction may concur in the pathogenesis of I resistance in these pts.

LEFT VENTRICULAR REMODELLING AND HUMORAL REGULATION IN ACUTE MYOCARDIAL INFARCTION

1326 Influence on left ventricular remodelling after a first myocardial infarction of a randomly allocated ACE-inhibition, β-blocker or ACE-inhibition + β-blocker therapy

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The R.I.M.A. (Rimodellamento Infarto Miocardico Acuto) study was designed to assess the relative effect of ACE-inhibition (ACE), β-blocker (BB) therapy or their combination on left ventricular (LV) remodeling process in patients (pts) with a first, uncomplicated myocardial infarction (MI). Two hundred-fifty consecutive pts were randomly allocated to receive for >3 months captopril (up to 75 mg/day, Group A), metoprolol (up to 200 mg/day, Group B) or both (Group C) within 24 hours from the onset of symptoms. Of these, 130 pts (Group A = 46, Group B = 47, Group C = 37) were free of cardiac events or revascularization procedures at 6 months from MI: all underwent 2D echo at the admission, 3 and 6 months from MI. LV diastolic areas and volumes (modified Simpson rule) were blindly calculated and averaged by the same operator in the core laboratory from the apical 2- and 4-chambers views. The wall motion score index (WMSI) was calculated on a 16 segments model (score 1 to 4).

Results: Baseline LV areas, volumes, ejection fraction and WMSI were comparable in the three groups. The relative increase of diastolic LV areas at 3 months (Group A: 2.1 ± 11.6%, Group B: 5.5 ± 10.6%, Group C: 9.0 ± 15.5%, $p = 0.047$; Bonferroni: $p < 0.05$ Group A vs C) and at 6 months (Group A: 2.2 ± 15.1%, Group B: 7.3 ± 11.8%, Group C: 12.8 ± 18.1%, $p = 0.02$; Bonferroni: $p < 0.05$ Group A vs C) was comparable in Groups A and B; a significantly major increase of LV areas was observed in Group C in comparison with Group A. In the subgroups of pts with anterior MI similar differences were observed, but the statistical significance was not achieved being the sample inadequate.

Conclusions: The early BB treatment was as effective as ACE in preventing LV dilatation after uncomplicated MI, but their combination resulted in a more pronounced LV remodeling process in comparison with ACE alone.

1327 Effects of β-blocker compared to angiotensin converting inhibitor on left ventricular remodelling in acute myocardial infarction: a randomized study

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Background: Angiotensin converting enzyme (ACE) inhibitor attenuates left ventricular (LV) remodeling after acute myocardial infarction (AMI), but it is still unclear whether beta blocker therapy affects LV remodeling. We assessed the effects of beta blocker therapy compared with ACE inhibitor therapy on LV remodeling after AMI.

Methods: Sixty patients with AMI who underwent reperfusion therapy within 4 hours were randomly assigned to 2 treatment groups: imidapril (ACE inhibitor: group I, 20 patients) or bisoprolol (beta blocker: group B, 20 patients), or to a control group (group C, 20 patients). Each treatment was started within 24 hours. Cardiac catheterizations were performed on admission and after 1 and 3 months after admission. LV function and regional LV function were determined by the area-length method and the center-line method.

Results: Baseline clinical, procedural, and hemodynamic characteristics on admission were similar in the 3 groups. All patients had documented patency of infarct-related artery during 3 months. Mean pulmonary wedge pressure (PCWP), right atrial pressure (RA), and LV end-diastolic pressure (LVEDP) after 1 month were higher in group B than group I and group C (PCWP: 11 ± 6 vs 7 ± 3 vs 8 ± 3 mmHg, RA: 6 ± 2 vs 4 ± 2 vs 4 ± 2 mmHg, LVEDP: 16 ± 7 vs 12 ± 6 vs 13 ± 7 mmHg, $p < 0.01$). LV end-diastolic volume index (EDVI) increased in group B throughout the 3-month period ($p < 0.05$), whereas EDVI in group I decreased ($p < 0.05$). The changes in EDVI in group B were greater than those of group I and group C (group B: 6 ± 2, group I: −6 ± 2, group C: −3 ± 2 mL/m^2, $p < 0.05$). The changes in regional wall motion of the infarct zone in group B were smaller than those in group I and group C (group B: 0.38 ± 0.12, group I: 0.78 ± 0.15, group C: 0.67 ± 0.13, $p < 0.05$).

Conclusion: It is suggested that treatment of AMI with beta blocker further increase the preload and cannot prevent LV remodeling. Conversely, early treatment with ACE inhibitor attenuated LV remodeling.

1328 Left ventricular shape distortion after first myocardial infarction is related to the extent of initial ischaemic damage and to the recovery of viable myocardium but not to infarct site

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Ventricular cavity geometry is an important determinant of LV function and patients' exercise capacity. Distortion of LV geometry and progressive deterioration in LV function are known sequelae after acute myocardial infarction (AMI). The aim of our study was to characterize the time course and determinants of LV geometry changes after a first, uncomplicated AMI. Therefore, 2D echoes were obtained in 567 pts at 36 ± 8 hrs (S1), 12 ± 5 days (S2), at 6 weeks (S3), and at 6 months (S4) after AMI to assess LV size (Simpson's biplane volumes), shape (Lama's sphericity index) and function (ejection fraction), and percentage of LV that was akinetic or dyskinetic (%WMA, 16-segment model)

	S1 (n = 587)	S2 (n = 587)	S3 (n = 577)	S4 (n = 567)	F Value	p
ED volume (ml)	144 ± 38	150 ± 42	152 ± 45	155 ± 47	21.2	<0.0001
ES volume (ml)	76 ± 27	80 ± 31	82 ± 35	83 ± 37	14.0	<0.0001
ED sphericity	0.42 ± 0.09	0.43 ± 0.09	0.45 ± 0.10	0.45 ± 0.10	26.6	<0.0001
ES sphericity	0.33 ± 0.10	0.34 ± 0.10	0.36 ± 0.10	0.37 ± 0.10	29.3	<0.0001
EF (%)	48 ± 7	48 ± 8	47 ± 9	48 ± 8	1.0	NS
%WMA	26 ± 43	23 ± 15	21 ± 15	19 ± 1	62.6	<0.0001

ED = end diastolic; ES = end systolic; p values = repeated measures ANOVA.

Multivariate stepwise regression analysis of clinical, including AMI location, and echo data showed that %WMA at S1, change in %WMA from S1 to S4, and change in LV volume from S1 to S4 were the only independent determinants of LV shape at S4 ($p < 0.0001$).

Thus, after AMI, progressive LV dilation is associated to increasing LV shape distortion. Six-month LV shape changes are directly related to extent of initial ischemic damage and changes in LV volumes, and inversely related to extent of recovery of viable myocardium, but it is not related to site of AMI.

1329 Increased plasma cardiotrophin-1 following an acute myocardial infarction and its relationship to left ventricular systolic dysfunction

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Augmented ventricular gene expression of Cardiotrophin-1 (CT-1), a member of the interleukin-6 related cytokines that act via the gp130 signalling pathway, following myocardial infarction (MI) in rats is thought to be involved in the process of ventricular remodelling.

Method: To clarify the role of CT-1 following MI we compared plasma CT-1 in 40 patients(30 males and 19 anterior infarcts) and 30 controls (17 males). A competitive immunoluminometric assay using a methyl acridinium ester to label the peptide and an in-house polyclonal antibody to amino acids 105–120 of the CT-1 sequence was developed. Serial blood samples were obtained at 4 time points following admission between day 0–2, 3–5, 6–8 and at the 6 week outpatient appointment. Echocardiogram was performed before discharge (WMI1) and at the outpatient visit (WMI2).

Results: Patient CT-1 levels were significantly elevated at all time points compared to controls ($p < 0.0001$). Median values of CT-1 (in fmol/ml) of the patients at the 4 time points were 53.35 [range 17–428.5], 47.2 [19–2228.5], 52 [19.9–780.5] and 70.30 [16.9–223.6] Vs. 27.7 [7.6–42.1] for the controls. In the high risk patient group with anterior infarcts WMI1 and WMI2 correlated with log CT-1 levels in the first 48 hours ($r = -0.48$ & -0.57 respectively, for both $p < 0.05$).

Conclusion: This is the first quantitative assessment of CT-1 in humans. Furthermore this is the first demonstration of significant elevation of CT-1 levels following an MI. The study suggests the intriguing possibility that CT-1 may discriminate patients who will be at risk of an adverse outcome.

1330 Differential effects of reperfusion on vasoactive neurohormone levels in patients with acute myocardial infarction treated with direct angioplasty

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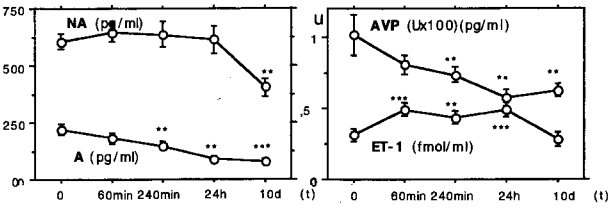
Activation of neurohumoral systems plays an important role in the extension of myocardial infarct size in myocardial injury during acute myocardial infarction (AMI). Although neurohumoral activation is known to persist in complicated AMI, no data are available on changes of hormone levels in AMI pts undergoing reperfusion therapy.

Methods: We analysed 63 consecutive pts with AMI, who had successful reperfusion (TIMI 2 and 3) by direct angioplasty. Arterial plasma levels of adrenaline (A), noradrenaline (NA), endothelin-1 (ET-1), arginine vasopressin (AVP) were determined before, 60, 240 min, 24 h and 10 days after reperfusion.

Results: Two different patterns of hormonal changes were found: A, Na and AVP levels (mean ± SEM) slowly decreased from high initial values, whereas, ET-1 levels initially rised after reperfusion, followed by a subsequent decrease at 10 d.



Neurohormone patterns. *,**,***$p < 0.05, < 0.01, < 0.001$ compared to 0 min levels.

Conclusion: Primary angioplasty in the acute phase of AMI is associated with rapid normalization of most vasoactive neurohormone levels. A different pattern of ET-1 may reflect reperfusion-dependent activation mechanisms and rise the opportunity for therapeutic interventions. Early normalization of neurohumoral activation should be considered as a marker for effective treatment of AMI.

1331 The clinical implication of circulating levels of angiogenin in acute myocardial infarction patients

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Angiogenesis, the formation of new blood vessels, plays a central role in a variety of physiological and pathological processes. Angiogenin (ANG), a potent modulator of Angiogenesis, has been found to be activated in peripheral occlusive arteriopathy. The aim of our study was to clarify the importance of ANG activation in acute myocardial infarction (AMI) patients.

Methods: 29 patients with first attack of AMI, and no previous history of any other disease, were examined for plasma levels of ANG, measured by ELISA, and compared to corresponding levels of 20 Normal controls (NC) with mean values: 207.31 ± 14.8 ng/ml. All pts were divided in 2 sex and age-matched groups. Group A: pts with limited AMI, EF > 45% and normal LV function. Group B: pts with extensive AMI, EF < 45% and subsequent heart failure. Plasma samples were collected at the time of hospital admission (0 hours) and 6 h, 12 h, 18 h, 24 h, 48 h, 3 days, 4 d, 5 d, 7 d, 15 d, 30 d thereafter. All pts received thrombolysis.

Results are expressed as mean values ± SEM in ng/ml as follows:

Pts	0 h	6 h	12 h	18 h	24 h	48 h	3 d	4 d	5 d	7 d	15 d	30 d
A (14)	346 ± 47.4 *	278 ± 19.7 *	262 ± 2.04	260 ± 14.3	261 ± 19.5	299 ± 17.3 *	333 ± 21.8 *	329 ± 24.4 *	330 ± 23.6 *	343 ± 28.3 *	349 ± 29.2 *	355 ± 30.1 *
B (15)	293 ± 21.2 *	292 ± 14.2 *	273 ± 15.4	248 ± 16.8	232 ± 16.2	309 ± 25.7	301 ± 17.1	292 ± 15.3	287 ± 14.1	272 ± 21.5	243 ± 15.3	229 ± 14.8

p < 0.05 compared to corresponding values of: a) NC (*) (Wilcoxon test).

Conclusions: Both groups exhibit initial high ANG plasma levels statistically compared to NC. This increase is followed by a gradual decrease, probably as a result of thrombolysis, that is reversed in both groups. However this late rebound of ANG 48 h after AMI is significant and remains only in group B and may imply that the process of angiogenesis is enhanced, thus preserving LV function and exerting a cardioprotective potential. On the other side angiogenesis seems to be in a much lesser extent in pts with large infarct size, thus resulting in LV decompensation. These data support the rationale for using specific pharmacologic interventions that could modify the progression of ventricular remodeling following AMI particularly in pts whose disease is not amenable to direct revascularisation.

ACUTE CORONARY SYNDROMES: PROGNOSIS

1332 Long-term outcome in patients with unstable angina pectoris compared to patients with non-Q-wave myocardial infarctions: results from a 10-year follow up

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Purpose.The aim of the present study was to asses the long term outcome in patients with unstable angina pectoris (UAP) compared to patients with non-Q wave myocardial infarctions (NQAMI).

Methods: 3941 patients (2627 men and 1314 women) with UAP or NQAMI admitted to the coronary care unit at Östra hospital, Gothenburg between 1988 and 1997 were followed until the end of 1997. Infarct and unstable angina diagnoses were based on clinical presentation, ECG and CK-MB mass concentration (= 15 μkat/l for infarct).

Results: The average age was 66.0 years for UAP patients vs 70.7 years for NQAMI patients (p < 0.001). By multivariate analysis including prior myocardial infarction, age, sex, diabetes mellitus, prior revascularization, smoking and hypertension, the development of a NQAMI compared to UAP was independently associated with higher mortality (RR = 1.7 p < 0.0001). However most part of the difference in outcome was accounted for by a higher mortality in the early phase among the infarct patients, in particular the first 30 days. After 2 years the mortality rate was similar in booth groups (see Table).

Table: Cumulative survival

Follow up time	Unstable angina pat	Non-Q infarct patients
30 days	98.3 (97.6–98.9)%	86.8 (85.4–88.1)%
1 year	92.7 (91.3–94.0)%	76.7 (75.0–78.4)%
2 years	88.2 (86.5–89.9)%	70.2 (68.3–72.1)%
4 years	79.8 (77.4–82.0)%	59.4 (57.3–61.5)%
6 years	71.7 (68.8–74.6)%	50.1 (47.8–52.5)%
10 years	52.6 (44.9–60.4)%	35.5 (31.4–39.5)%

Conclusion: Patients with unstable coronary syndromes suffer a poor long term outcome. Mortality is higher for those with non-Q myocardial infarction during the first 2–3 years after which the yearly risk for death is similar to that of unstable angina patients.

1333 The risk of adverse outcome in patients with acute coronary syndromes without ST-segment elevation is mainly determined by baseline clinical factors

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Background Appropriate treatment policies should include a satisfactory estimation of the patient's baseline clinical risk. So far, however, risk-modelling in acute chest pain patients without ST-segment elevation is underexposed.

Methods To evaluate the relationship between baseline characteristics and the 30-day occurrence of mortality or non-fatal myocardial infarction, we analysed data collected on the 10,948 ischemic chest pain patients without persistent ST-elevation, which enrolled the PURSUIT trial. Risk modelling was performed by multivariable logistic regression and validation by bootstrapping techniques. Variables examined included demographics, history, hemodynamic condition, symptom duration and treatment assignment.

Results There were 3.6% deaths and 11.4% non-fatal myocardial (re)infarctions in PURSUIT. Over 20 significant contributors were determined, both to mortality alone and the combined outcome. The most important predictors of mortality are presented in the table, together with the relative contribution to the mortality model. Variables that were predictive for mortality alone generally were so for the combined outcome. However, the strength of the relation between predictors and combined outcome was less than for mortality alone (c-index 0.67 vs. 0.80). Furthermore, differences were observed in the ranking order by the degree of risk stratification. Still, in both models, age, heart rate and enrollment diagnosis contained about 45% of the total prognostic information available in the examined variables.

Characteristic	Contribution	Characteristic	Contribution
Age	24%	ST-depression	4%
Heart rate	10%	Heart failure	3%
MI at enrollment	8%	Weight	3%
Blood pressure	5%	Angina class	3%

Conclusions The occurrence of adverse cardiac events after an episode of ischemic chest pain is affected by multiple factors, which are often not treatment related. These determinants should be considered in the clinical decision process.

1334 New Q-wave development following acute myocardial infarction does not predict increased short or long-term mortality

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Background: ECG changes in acute myocardial infarction (MI) have been used to assess relative risk of future complications. New Q-wave development has been associated with greater myocardial damage than non-Q-wave MI but it is not clear if long-term mortality is affected.

Hypothesis: New Q-wave development is associated with increased short and long-term mortality following acute MI.

Methods: We analyzed 815 patients from Rochester, MN admitted to the Mayo Clinic CCU. 389 (47.7%) developed Q-waves following the MI and 426 (52.3%) did not develop Q-waves.

Results:

Survival by New vs. No New Development of Q-Waves

Survival Summary	New Q-Wave Development (N = 389)	No New Q-Wave Development (N = 426)	Log-Rank Statistic	P value
Est. % Surv & 95% CI at:				
• 30 days	95.8% (93.9, 97.9)	97.6% (96.2, 99.1)	1.13	0.29
• 6 months	92.3% (89.7, 95.0)	93.5% (91.1, 95.9)		
• 1 year	90.6% (87.7, 93.6)	90.8% (88.1, 93.7)		
• 2 years	86.6% (83.0, 90.3)	85.1% (81.6, 88.8)		
• 5 years	75.5% (70.5, 80.5)	70.1% (64.8, 75.7)		
Adjusting for ECG classification, age & gender	Adjusting for ECG classification, age & gender	Adjusting for ECG classification, age & gender	0.06[a]	0.81

[a]Chi-square statistic resulting from the likelihood ratio test

Conclusions: No significant differences in short and long-term mortality were observed, even after adjustment for ST segment pattern at presentation, age and gender. The development of a Q-wave MI ECG pattern does not suggest a high risk subset of patients who require different risk stratification efforts consistent with non-Q-wave MI patients.

1335 Improving prognosis amongst 178,000 patients hospitalised with acute myocardial infarction between 1981 and 1995

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Background: Though many new therapies have been shown to improve prognosis after myocardial infarction (MI), in clinical trials, the *population* impact of these treatments is unknown. We report trends in survival for all patients hospitalised with acute MI in Scotland over a 15 year period.

Methods: Scotland (population 5.1 million) has a national Morbidity Record Database holding comprehensive, high quality data, which links all hospitalisations and deaths. A Scottish wide, retrospective, cohort study of all 178,077 individual MI patients admitted between 1981–1995 was carried out. Mortality up to 10 years was calculated with Cox-modelling for the effects of age, sex, socioeconomic deprivation, co-morbidity and year of treatment.

Results: Over the whole period of study, one months, one year, 5 year and 10 year case fatality rates were 24, 33, 50 and 65 years. The principal factors independently influencing prognosis were age and prior morbidity. Both short (1 month) and longer term (1–5 years) *adjusted* case fatality rates fell by about half between 1981 and 1995.

Conclusions: Modern treatment appears to have dramatically improved the short and long-term survival of patients hospitalised with acute MI.

1336 History of angina and early prognosis of myocardial infarction

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Background: It has been suggested that previous angina may result in a lower number of complications after acute myocardial infarction (MI).

Objective: To assess whether first-MI patients with prior angina develop less complications than those without such a history.

Methods: All first-MI patients aged less than 75, consecutively admitted to the hospitals participating in the pilot phase of the IBERICA study. Twenty-eight-day survival and complications were assessed. Patients were divided in two groups according to the presence of history of angina before 48 hours of the index event.

Results: Among the 1996 patients recruited, 841 had had previous angina. Mean age was 60.6 (59.9 in non-angina patients and 61.4 in the rest), and 20.0% were women (19.4 and 20.1, respectively). Previous-angina patients had similar mortality (10.0% and 11.5%, respectively) and proportion of life-threatening arrhythmias (14.2% and 13.3%), atrio-ventricular block (5.6% and 5.0%), stroke (1.1% and 1.2%), mecanical complications (2.1% and 1.5%) but higher incidence of acute pulmonary oedema or cardiogenic shock (13.8% and 17.5%, $p = 0.03$), reinfarction (2.0% and 4.0%, $p = 0.007$) and angina post-MI (11.5% and 22.7%, $p < 0.0005$).

Conclusions: Although 28-day mortality rate was similar, first-MI patients with previous angina had worse prognosis than the rest, particularly, they show higher angina post-MI, severe left ventricular dysfunction and reinfarction rates.

1337 Comparison of PTCA to medical therapy in patients with silent ischaemia after myocardial infarction: results of the Swiss Interventional Study on Silent Ischaemia (SWISSI II)

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Background: Silent ischemia (SI) post myocardial infarction (MI) adversely affects outcome. We studied the influence of PTCA or antiischemic drug therapy (Rx) on survival free of death, MI, or unstable angina (UA)and exercise capacity and left ventricular ejection fraction.

Methods: 201 patients (pts; 1 or 2 vessel disease) with SI (stress echo, MIBI or radionuclide ventriculography) were randomized after angiography (<3 months from MI) to PTCA of MI and ischemia related vessel(s) (n = 96) or aggressive drug therapy (Rx (n = 105): bisoprolol, amlodipine, molsidomine alone or in combination; acetylsalicylic acid was used in all pts)aiming at elimination of exercise induced ischemia.

Results: Both groups did not differ at baseline. Event free survival (median follow up (FU) 4.1 years) was not different in both groups (probability of survival 0.52 vs 0.752 Rx vs PTCA) at 7 years). Endpoints (Rx/PTCA) were: death 3/2, MI 15/8, UA 18/13). During FU, ejection fraction decreased more in Rx pts (from 59.7 ± 11.8 to 49.2 ± 9.4%) than PTCA pts (from 53.8 ± 9.9 to 53.7 ± 8.9%) suggesting less ventricular impairment in the PTCA group despite similar event rates. Also, PTCA pts increased their exercise capacity (from 140 ± 31 to 169 ± 40 watts, $p < 0.001$) while it remained unchanged in Rx pts (146 ± 33 vs 148 ± 38 watts, n.s.), had less ST-segment depression (0.033 ± 0.054 vs 0.064 ± 0.065 mV, $p < 0.001$) and received less frequently antiischemic therapy (bisoprolol: 13 vs 95; amlodipine: 6 vs 56; molsidomine:1 vs 61; $p < 0.001$).

Conclusions: PTCA of SI post MI did not significantly influence the rate of ischemic events as compared to drug therapy. However, revascularization by PTCA preserved left ventricular ejection fraction, improved exercise capacity and reduced the need for antiischemic drug therapy during long-term follow up.

NEW DEVELOPMENTS IN THE MANAGEMENT OF PROSTHETIC VALVE THROMBOSIS

1338 Incidence and predictors of prosthetic thrombosis on mitral bileaflet prosthesis during the postoperative period

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The post-operative period after mitral valve replacement (MVR) is at particularly high risk for prosthetic thrombosis (PT). Besides occlusive thrombosis, transoesophageal echocardiography (TEE) after MVR may reveal non-occlusive PT. The aim of this study was to assess the incidence and predictive factors of PT after MVR with a bileaflet prosthesis.

Between 1988 and 1996, 331 consecutive patients (pts) underwent MVR with a bileaflet prosthesis (Saint-Jude 192, Sorin 74, Carbomedics 30, Duromedics 9, ATS 26). Mean age was 56 ± 13 yrs; 58 pts had previous embolism (18%) and 180 (54%) were in atrial fibrillation. Anticoagulant therapy used heparin and vit. K blockers without systematic use of anti-agregant therapy. TEE was performed 15 ± 6 days after surgery in 319 pts (96%).

Occlusive and non-occlusive thrombi were differentiated according to the motion of the leaflets on TEE and fluoroscopy. TEE revealed PT in 57 pts (18%): occlusive thrombi in 6 pts (2%) and non-occlusive thrombi in 51 (16%).

Multivariate logistic regression identified 5 independent predictors of PT: previous myocardial infarction ($p = 0.03$), the type of prosthesis (Sorin vs. others $p < 0.001$), post-operative atrial fibrillation ($p = 0.007$), spontaneous left atrial echo contrast ($p = 0.002$), and the presence of fibrin strands ($p = 0.008$).

In conclusion 1) PT frequently occurs early after MVR with bileaflet prosthesis. 2) Predictors are mainly related to blood stasis. 3) Identification of patients at high risk for thromboembolism may be useful to offer them a more aggressive post-operative anticoagulant therapy.

1339 Diagnostic work-up in patients with suspected prosthetic heart valve thrombosis: is echocardiography always justified?

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The aim of the study was to evaluate and compare the diagnostic efficacy of cine-fluoroscopy (CF), transthoracic (TTE) and transesophageal echocardiography (TTE) in pts with clinically suspected prosthetic heart valve thrombosis (PVT).

Methods: Eighty-two consecutive pts with single mechanical prostheses were submitted to CF, TTE and TEE. Criteria for PVT were: leaflet(s) motion restriction at CF, increased Doppler gradients at TTE and evidence of thrombi at TEE.

Results: Patients were divided in 4 groups according to CF and TTE results. Group 1 (n = 24) had +CF and TTE; TEE showed prosthetic thrombosis in all, suggesting that CF and TTE, when both +, always identify PVT so as to defer TEE. Group 2 (n = 12) had +CF and −TTE. TEE showed PVT in 4/12 (33%): all were pts with bileaflet mitral valves and slight restriction of leaflet motion at CF. This suggest that in pts with hemodynamically non critical PVT a correct diagnosis may be missed by TTE alone: CF should be always carried out in these cases. The remaining 8 pts of this group were carriyng monocuspid prostheses and had −TEE for thrombus and pannus; the abnormal leaflet motion at CF was therefore thought to be functional (valve adaptive changes). Group 3 (n = 18) had −CF and +TTE. All had small size aortic prostheses, very high Doppler gradients and no symptoms. TEE ruled out PVT in all cases outlining the diagnostic role of CF in this subset of pts. TEE should be programmed if symptoms are present and they are not due to other cardiac or extracardiac sources. Group 4 (n = 28) had −CF and TTE. TEE confirmed these results by showing no thrombi in 24/28 (86%), suggesting that, when both −, CF/TTE confidently rule out PVT in most pts. However, in 4/28 (all with mitral prostheses, chronic atrial fibrillation and embolism in 3/4) TEE showed "non-obstructive" PVT. Thus, TEE should be performed in selected cases despite −CF and TTE results. Sensitivity and specificty were 87%, and 84% for CF and 75% and 64% for TTE. Both tests correctly identified PVT in 70/82 (85%) of pts. TEE was actually required in 15% of the cases.

Conclusions: PVT has a multiform clinical and non-invasive presentation. CF and TTE are quick, effective and complementary diagnostic tools to diagnose PVT in most pts. Transesophageal echocardiography remains the goldstandard technique in selected cases.

1340 Thrombolysis in stuck bileaflet heart valves: experience in 25 episodes

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Thrombosis is a serious complication of prosthetic heart valves. A re-do operation carries a substantial risk. Current therapeutic recommendations are partially based on older valve models and inclusion of patients with high-risk thrombi. We present our experience with thrombolysis in bileaflet heart valves.

Thirteen patients (M/F = 3/10, age 54.0 ± 16.1, range 32–75) experienced 25 episodes of valve thrombosis over a 28-month period. The valves involved were mitral (13 episodes), tricuspid (11 episodes), and both valves (1 episode). In only 7 episodes (28%) admission INR was >2.5. The diagnosis was raised in all cases clinically and by TTE, and confirmed in all by fluoroscopy (n = 24) and/or TEE (n = 17). One leaflet was involved in 11 episodes, and both leaflets were affected in the others. There was no evidence of a mobile or large (>5 mm) thrombus.

A total of 36 courses of thrombolysis were administered, with streptokinase, urokinase or tPA (11, 8 and 17 courses, respectively). In 11/13 patients (84.6%) a re-do operation was avoided. A full resolution was achieved in 21/25 episodes (84%). Treatment failed in 2 cases [5 courses (13.9%)]. Five courses (13.9%) were interrupted due to adverse reactions. Minor bleeding occurred in 5 courses (13.9%), allergic reaction in 4 (11.1%), and in 5 courses (14.7%) there were transient, vague neurologic complaints, without subjective findings. TPA was more effective than the other agents. A completely occluded leaflet was associated with the lowest success rate [only 6/16 (37.5%) completely successful courses in 10 patients]. Two patients with thrombosed mitral valve, who failed to respond to thrombolysis, were referred to a re-do operation. One died due to pump failure, and the other had a complicated course. Six patients had one or more relapses within 5.2+3.7 months (1–12) from the previous episode, and were given thrombolysis successfully.

In patients with stuck bileaflet valves without large visible clots, thrombolysis offers a valid alternative to surgery, with high success rate and minimal complications. Despite a high recurrence rate, repeated thrombolysis is highly successful.

1341 The utility of transoesophageal echocardiography guidance of thrombolytic therapy in prosthetic mitral valve thrombus

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Purpose: The aim of the study is to assess the utility of transesophageal echocardiography (TEE) for guiding thrombolytic therapy in prosthetic mitral valve thrombus.

Method: The study cohort consists of 29 consecutive cases of prosthetic mitral valve thrombus diagnosed from January 1995 to May 1998 and managed according to data obtained from TEE. Three patients with pedunculated thrombus and 5 patients in NYHA functional class (FC) I–II were triaged to surgical treatment. The patients who refused surgery or in NYHA FC III–IV and had unpedunculated thrombus were selected for thrombolytic therapy.

Results: Twenty-one cases (7 male, mean age 47 ± 8 years) were given streptokinase as thrombolytic therapy. The mean duration from surgery was 36 ± 23 months, and the mean duration from onset of symptoms was 9.2 ± 14.3 months. Anticoagulant use was inadequate in 16 (76.2%) patients and adequate in 5 (23.8%) cases. Fourteen cases (66%) were NYHA FC IV, 4 (19%) in FC III and 3 (15%) in FC II. The cardiac rhythm of 10 (47.6%) patients were atrial fibrillation. In the first 24 hours of thrombolytic therapy mitral valve peak and mean gradient decreased from 25.6 ± 4 and 13.8 ± 2.5 mmHg to 11.7 ± 5.3 and 7.1 ± 3.1 mmHg respectively ($p < 0.0001$). Four cases with inadequate response to thrombolysis were treated for an additional 24 hours. The second, third day and 1 month peak and mean transmitral gradients were 10.4 ± 5.8 and 5.9 ± 3.1, 10.3 ± 5.4 and 5.3 ± 3.0, and 9.3 ± 3.2 and 4.4 ± 1.7 mmHg respectively ($p > 0.05$). The mitral valve area increased from 1.0 ± 0.1 cm2 to 2.3 ± 0.7 cm2 at the end of the first month ($p < 0.0001$). Early full success in thrombolysis was achieved in 17 (81%) cases. Three cases (14.3%) had partial success and one case (4.7%) was referred to surgical therapy on the third day because of failure of thrombolysis. Two minor skin bleeds (9.4%) not requiring transfusion was attributed to thrombolytic therapy. One case of successful thrombolysis had a non-fatal stroke after therapy and one case was referred to surgery for recurrent prosthetic mitral valve thrombus at the sixth month of follow-up. Mortality was nil in the surgically treated patients.

Conclusion: It was concluded that TEE guidance for choosing patients for thrombolytic therapy in prosthetic mitral valve thrombus is safe and effective.

1342 Effects of picotamide on thrombus formation and clinical outcomes in patients with mechanical heart valves: a double-blind, randomized, placebo-controlled trial

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Adding aspirin to warfarin may benefit patients with mechanical heart valves, but the risk of bleeding is increased. In this study we investigated the effects of the dual thromboxane synthase inhibitor/thromboxane A2 receptor antagonist picotamide on thrombus formation and clinical events in patients with mechanical heart valves.

Methods: 39 patients aged 18–75 years were randomly treated with picotamide or placebo over 4 months according to a double-blind protocol. Thrombus formation was investigated ex-vivo in a perfusion chamber (Badimon) allowing native blood to flow at low (212 sec^{-1}) and high (1690 sec^{-1}) shear rate. Thrombotic burden was measured by computerized morphometry of the deposition on porcine arterial segments (mild or deep vascular injury). Clinical events, INR values (target INR 2.5–3.5), bleeding time, β-thromboglobulin, platelet factor 4 and prothrombin fragment 1+2 were also obtained.

Results: Picotamide was extremely well tolerated over 4 months (no excess of major or minor bleeding compared with placebo, no interference with INR values, no changes in haematocrit values, no prolongation of the bleeding time). Duplicate measurements of thrombus deposition yielded a good correlation ($r = 0.688$, $p < 0.0001$). Picotamide decreased the ex-vivo thrombus formation on deep vascular injury at high shear rate (picotamide: 2834 ± 1247 vs 1552 ± 879 micron^2/mm, $p < 0.0001$; placebo 1492 ± 731 vs 1655 ± 890 micron^2/mm, p = NS) but not at low shear or in presence of mild injury. Systemic markers of thrombosis were not affected by the treatment.

In conclusion, thromboxane A2 blockade by picotamide may decrease thrombus formation at high shear rate (typically occurring near hinges or pivots of mechanical heart valves), apparently without side-effects. A large-scale trial may be warranted.

1343 Oral anticoagulant therapy (OAT)following heart valve replacement (HVR): comparison of a daily fixed 2.5 mg with a 5 mg, INR-adjusted, dose

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We have previously observed that patients starting OAT following HVR are more sensitive to warfarin (W) than non surgical patients. They also require an initially lower target INR (2.0, range 1.5–2.6) because of a higher risk of bleeding until pericardial wires are removed. In a randomized trial, we compared a fixed, lower dose of W (2.5 mg) with the standard treatment during the first 5 days of OAT in HVR patients.

Methods: The study was carried out at the Hamilton Civic Hospitals, Canada and at the University Hospital of Varese, Italy. Patients were randomized to receive a loading 5 mg dose of W then adjusted to a target INR of 2.0 (range 1.5–2.6) or a fixed 2.5 mg dose. INRs were measured daily, but fixed dose was only modified on day (D) 3 if the INR was <1.5 or >3.0.

Results: Of the 245 patients enrolled (123 in the 5 mg group and 122 in the 2.5 mg), 197 were eligible (113 and 84 respectively) and 48 excluded (10 and 38 respectively) because the protocol was not respected without an evident clinical reason. Daily management of the study was left to the same physicians or registered nurses usually in charge of the patients in order to not interefere with the routinary activity in the wards. The 2 groups were well matched according to age, gender, height, weight, body mass index, concomitant treatments, and type of valves implanted. The proportion of INRs > 2.6 during the study period was reduced from 42.5% in the 5 mg group to 26.2% ($p < 0.05$) in the 2.5 mg group, and the proportion of INRs > 3.0 on D3 from 23.9% to 9.5% ($p < 0.05$) respectively. In the 2.5 mg group, 35.7% of patients had a D3 INR < 1.5 and had the dose increased (vs 3.5%, $p < 0.001$), but in the 5 mg group 95.6% had the initial dose reduced, 49.6% had the dose withheld for at least 1 day, and the mean dose during the 5 days of study was 3.08 mg. Average time to achieve therapeutic range was higher in the 2.5 mg group (2.72 vs 1.98, $p < 0.0001$), but the approach to the targeted INR was more regular (D2: 1.66 vs 2.27, D3: 1.91 vs 2.46, D5: 1.99 vs 2.21, $p < 0.0001$). There were no bleeding nor thromboembolic complications in both groups.

Discussion: Starting OAT with a lower dose of W in HVR patients reduces the rates of excessive anticoagulation, and gives a more stable achievement of the therapeutic target by reducing the number of dose adjustments. In the fixed dose group, 44% of the patients never required a dose adjustment, and 42% had 1 adjustment on D3. Nevertheless, because of the large individual variability in W response, a daily monitoring of the INR is still recommended.

NEW ASPECTS OF AORTIC DISSECTION

1344 Accuracy of transthoracic echocardiography imaging for the diagnosis of acute aorta dissection

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Objectives: We sought to determine the diagnostic accuracy of transthoracic echocardiography (TTE) in patients (pts) survived an acute aortic dissection (AD).

Methods: We studied 36 consecutive pts (mean age 54 ± 10 years old) with the diagnosis of acute (AD) confirmed by transesophageal echocardiography (TEE) performed just on their admission. Out of 36 pts 18 (50%) had a De Bakey type I, 10 a type II and 8 type III. Subsequently a TTE performed from investigator unaware of the results of TEE(during patient's preparation for surgery).

Results: We found the following abnormalities with either method.

– Pericardial effusion (TTE: n = 6/17% – TEE: n = 6/17%).
– Aortic regurgitation (TTE: n = 17/47% – TEE: n = 17/47%).
– Aortic dilatation (TTE: n = 30/83% – TEE: n = 33/92%).
– False lumen and intimal flap (TTE: n = 21/58% – TEE: n = 36/100%).
– Thrombus and echocontrast in the false lumen (TTE: n = 0/0% – TEE: n = 11/31%).

Conclusions: Our results show that the TTE has 100% diagnostic agreement with TEE for pericardial effusion and aortic regurgitation and ninety per cent for aortic dilatation. The TTE can manifest the false lumen and intimal flap for 58% of the cases. Therefore the diagnosis of acute AD become suspected approximately for 90% of the cases (aortic dilatation, pericardial effusion, aortic regurgitation). The diagnosis becomes odds-on for 58% with the manifestation of false lumen-intimal flap. Farther experience with the TTE for the diagnosis of AD will increase the diagnostic accuracy of this method.

1345 Aortic root replacement with preservation of the aortic valve – five years experience

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Background:

Reimplantation of the native, structurally intact aortic valve within a Dacron tube graft in patients with aortic root aneurysm corrects annular ectasia as well as dilatation of sinotubular junction. Durability of this valve repair with respect to increased mechanical stress on valve cusps is discussed controversially and yet unknown.

Methods and Results: From 7/93 to 1/99 replacement of the ascending aorta with repair of the aortic valve was performed in 81 patients (56 male, 25 female; 50 ± 19 years). Twenty-two patients (27%) had a Marfan syndrome and 12 patients (15%) had an aortic dissection type Stanford A (6 acute, 6 chronic). In 20 patients (25%), concomitant replacement of the aortic arch was necessary. In 6 patients (7%) an additional Trusler valvuloplasty was performed to achieve perfect cusp coaptation. Clinical and echocardiographic follow-up was performed in 6–12 months intervals for a cumulative study period of 140 patient years.

There were no operative deaths. Two patient (3%) died 5 and 20 months postoperatively. One additional patient experienced a TIA within the first post-operative week. Three patients (4%) with progressive aortic insufficiency (AI) required aortic valve replacement after 9, 11, and 14 months. All other patients have no or mild aortic insufficiency. The repair now remains stable for up to 70 months (mean: 22 ± 20 months). Other valve related complications did not occur.

Conclusions: Our results demonstrate that this type of aortic valve repair achieves excellent results in selected patients. Perfect coaptation of valve cusps during the repair with no or only trace AI at initial echocardiography seems to be essential for durability.

1346 Predictive factors of thoracic aorta enlargement in type B aortic dissection follow-up

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Progressive enlargement of descending aorta is one of the complications in the type B aortic dissection follow-up. This study aimed to determine which factors could by related to this enlargement. 74 type B aortic dissection were prospectively studied. Those with Marfan's syndrome or difficult hypertension control were excluded. The remaining 43 patients were followed for more than 3 years (4.7 ± 1.4; range 3–9 y.). Prior to hospital discharge, a TEE was performed in each patient. All had at least a yearly a TEE, MRI or CT.

Results: Descending aorta diameter (DAD) prior to hospital discharge was 42.4 ± 6.5 mm (range: 32–61 mm). 7 patients (16%) had diameter >55 mm. 15 patients had a proximal entry tear, 24 a non-proximal tear and in 4 tear was not detected. Entry-tear was >7 mm in 19 patients and <7 mm in 20. Entry site flow was unidirectional in 7, bidirectional with similar velocities (SD) in 13 and bidirectional with a false-to-true flow predominantly (Sd) in 29. False lumen thrombosis was partial in 12 and total in 4.

On follow-up DAD increased 2.4 ± 2.6 mm per year, range 0–10 mm/y. In 16 patients (37%) DAD did not increase in 16 (37%), it increased mild to moderately (1–4 mm/y) 18 (42%) and increased importantly (> 4 mm/y) 9 (21%). 7 of the 9 cases (78%) with significant enlargement had an entry tear >7 mm with SD flow. In contrast, in patients who did not suffer aortic enlargement, entry tear was >7 mm in only 6 (37%); none had SD flow, 7 had Sd flow and 5 unidirectional flow. No significant differences related to initial DAD (43 ± 7.4 vs 43 ± 5.1 mm) or to partial or total thrombosis (33% vs 50%) were observed.

Conclusions: Some type B aortic dissections (20%) have significant progressive diameter enlargement during follow-up. A wide entry tear with inflow and outflow of similar velocities is related to significant increase DAD. Small size entry tear or a unidirectional entry tear flowlare signs of good prognosis.

1347 Endovascular treatment of complicated aortic dissection

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Purpose: To evaluate the acute results and midterm follow-up of percutaneous treatment of visceral and lower limb ischaemia resulting from aortic dissection.

Materials and Methods: Between March 1997 and December 1998, we treated 9 patients (6 men, 3 women) with visceral or lower limb ischaemia secondary to acute aortic dissection (4 Type A, 5 Type B) using direct stenting (n = 4) alone, or in combination with a novel fenestration technique (n = 5)that requires neither endovascular echo guidance nor the use of needle perforation. Fenestration was performed through a single introducer sheath using 2 guidewires to create a longitudinal tear between the true and false lulen. Presenting symptoms and signs included anuria (3), severe hypertension (4), mesenteric ischaemia (3), acute lower limb ischaemia (2), and severe abdominal pain (4). Echodoppler and or helical CT showed stenosis or compression of the renal arteries (10), superior mesenteric artery (4), coeliac axis (3), inferior mesenteric artery (2), or the supra-aortic vessels (1).

Results: After arteriography, 4 patients (2 with mesenteric ischaemia, 1 with renal ischaemia, 1 with lower limb ischaemia) underwent direct stenting of the involved vessels with a good initial result. The other 5 patients, with extensive compression of the true lumen by the dissection had ischaemia involving multiple vessels; they were all successfully treated by fenestration with subsequent renal stent implantation in 2 patients. At follow-up (range 3–16 months), 3 patients were dead (2 deaths were due to extension of the dissection, 1 of undetermined aetiology); the remainder were well with no signs or symptoms of residual ischaemia.

Conclusions: Endovascular treatment has an important role in the management of complications resulting from aortic dissection. While localised compression or ischaemia can be treated by stenting the vessel involved, fenestration with spot stenting is an effective alternative when multiple vascular territories are compromised by the dissection.

1348 Follow-up of aortic aneurysms treated by stent graft implantation using magnetic resonance imaging

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Purpose: To report our preliminary experience with magnetic resonance imaging in the follow-up of aortic aneurysms treated by stent graft implantation.

Materials and Methods: Between November 1997 and December 1998, 27 patients underwent stent graft implantation (Vanguard, Boston Scientific) as treatment for abdominal aortic aneuryms. Follow-up MRI studies (Vision 1.5T, Siemens) were performed at 1-month (n = 24), 6-month (n = 12), and 12-month (n = 3). The examination included T1-and T2-weighted TSE sequences, a turbo-MRA sequence, and an axial T1-weighted TSE sequence after injection of gadolinium. Helical CTA (Somaton Plus 4) was perfomed at 6 months (n = 12) and 12 months (n = 3), and where a leak was suspected on MRI. Imaging was perfomed in the arterial and late phase.

Results: MRI was performed in all but 3 patients (1 allergic to gadolinium, 1 technical problem, 1 patient lost to follow-up). On the 1-month examinisation (n = 24), thrombuys was observed as a heterogeneous signal on T1- and T2-weighted TSE sequences in 23/24 patients. Gadolinium uptake was observed in 8 of these 23 patients; no uyptake was seen in the patient in whom the signal was homogeneous. A significant leak was also seen on CT in 5 of these 8 patients. Arteriography showed leakage in all 8 patients; all were treated by embolisation. MRI at 6 months found a heterogeneous T2 signal and gadolinium uptake in 4/12 patients, suggestive of a lead that was confirmed on arteriography. Abnormal CT findings were present in 2 of these 4 patients. Overall, 12/24 patients had MRI findings suggestive of leakage, evidenced by abnormal uptake of gadolinium on the early (1 month) scans or by persistence of a heterogeneous T2 signal on the 6 month scan. No leaks were seen at 12-month follow-up.

Conclusions: MRI appears to be mre sensitive than helical CT angiography in the detection of leaks after stent graft implantation for abdominal aortic aneurysms.

1349 Coronary reimplantation by the Cabrol technique: medium-term clinical follow-up

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The Cabrol technique for the coronary reimplantation is employed in the replacement of the ascending aorta. The mid-term evolution of these patients is controversial. Our objective was to revise the mid-term clinical evolution and coronary permeability in patients submitted to the Cabrol technique in our centre.

Methods: The study included 14 patients, 13 male and 1 female, mean age 51 ± 12 years. Surgery was indicated for aortic insufficiency associated with annulo-aortic ectasia in 12 patients, and ascending aorta aneurysm in 2 patients None of the patients demonstrated coronary lesions in preoperative coronary arteriography. Chronic oral anticoagulation treatment was initiated in all patients following surgery. Follow-up included clinical examinations and echocardiograph, magnetic resonance (MR) in the 8 surviving patients, and coronary angiography in 4 patients where occlusion of one of the two coronary anastomosis was suspected.

Results: One patient died postoperatively from cardiogenic shock. At follow-up, of the 13 remaining patients, 5 had died (38% mortality at follow-up, 43% global mortality), two of them from inferior myocardial infarct. The single patient submitted to autopsy showed obstruction of the right coronary anastomosis. Of the 8 surviving patients, 3 developed obstruction of the right coronary anastomosis, and one of the left, which were demonstrated through both MR and angiography. In the 4 remaining patients, MR revealed permeability of the coronary systems. Survival free of coronary occlusion was 28% at 4.3 ± 2.9 years, and 26.4% at 7.5 years when applying the Kaplan-Meier survival analysis.

Conclusions: These results suggest that obstruction of the right coronary anastomosis is a frequent complication at follow-up after the coronary reimplantation by the Cabrol technique.

APOPTOSIS

1359 Involvement of apoptosis, Bcl-2 family and P53 in the morphogenesis of the trabecular and compact regions of ventricular wall during cardiogenesis

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Although apoptosis is an important feature of normal development and organogenesis, little is known about apoptosis in the developing heart. The molecular regulation of apoptosis via several factors is an area of intensive investigation. We evaluated the role and localisation of apoptosis and apoptosis related genes in the developing ventricular wall of fetal mice hearts by using apoptosis specific labeling (ISEL), Immunocytochemistry and both light and electron microscopy. Fetal mice hearts of 11, 12, 13, 14 and 16 days of gestation were used. Three embryos of each day were fixed in 4% paraformaldehyde, dehydrated and embedded in paraffin. Ten sections (4–5 m) of each embryo were in situ labeled for detection of apoptosis using proteinase-K method, in which digoxigenin attaches to the N-terminal of fragmented DNA and anti-digoxigenin antibody reacts with attached digoxigenin. Fragmented DNA is stained with NBT/BCIP. Ultrastructural identification of apoptotic cells was done by using Jeol JEM-100SX transmission electron microscope. Bcl-2, Bax and P53 were detected immunocytochemically in the corresponding sections of the ventricular wall. The proportions of apoptotic cells of all cells in the ventricular wall differed between the trabeculted and compact regions and between days of gestation (p = 0.0001, 0.0033) respectively, ANOVA for repeated measures). In the looped heart on days 11, 12, 13 of gestation, the proportions of apoptotic cells in the trabeculated (non-trabeculated) regions were 3.2 ± 1.3% (4.4 ± 2%), 2.1 ± 1.1% (2.9 ± 1.8%), 3.6 ± 1.7% (2.8 ± 1.4%) (mean ± SD) respectively. After formation of the four chambers, on days 14 and 16 of gestation, the proportions of apoptotic cells were 2.8 ± 1% (3.3 ± 1.2%), 0.4 ± 0.2% (0.6 ± 0.3%) (mean ± SD) respectively. Electron microscopy confirmed the typical features of apoptotic cells. Bl-2, Bax and P53 expression was observed during early and late embryonic development at the same period when apoptosis took place in different cell types. We conclude that apoptosis is active phenomenon both the trabeculated and non-trabeculated parts of the ventricular wall in the developing mouse heart of days 11, 12, 13, 14 and 16 of gestation. The expression of bcl-2, Bax and P53 may indicate additional role in the differentiation process. This is a very active period of ventricular growth. Thus, apoptosis and its regulation are tightly integrated components in the morphogenesis of the ventricular wall of the mammalian heart.

1360 17β-Oestradiol reduces caspase-3 activity: a mechanism for the anti-apoptotic effect of oestrogen in cardiac myocytes

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Introduction: Cardiac myocyte apoptosis as a mechanism leading to heart failure is currently under discussion. One of the key events in apoptosis is the activation of caspase-3 which finally leads to death of the cell. We have previously shown that cardiac myocytes contain functional estrogen receptors and thereby identified the heart as a target for estrogen. It is known that estrogen has an anti-apoptotic effect in breast carcinoma and therefore we have asked the question whether estrogen can reduce cardiac myocyte apoptosis.

Methods and Results: Isolated rat cardiac myocytes were treated with physiological concentrations of 17β-estradiol (E2, 10 nM) for 24 hours followed by induction of apoptosis by 100nM staurosporine. Morphological assessment, TUNEL assay and cell nuclei fragmentation analysis by Hoechst dye staining showed a reduction of the number of apoptotic cells by E2. To investigate the underlying mechanism involved, we have observed a 45 ± 6% reduction of caspase-3 activation by E2. Western blot analyses of the anti-apoptotic proteins Bcl-2 and Bcl-XL and the pro-apoptotic BAX protein revealed no change in the amount of these proteins.

Discussion: The prevention of cardiac myocyte apoptosis may be one of the cardioprotective effects of estrogen.Identification of the exact underlying mechanism may therefore be an important starting point for developing new treatment strategies for heart disease.

1361 Occurrence of apoptosis in specific cell types in isolated perfused rat hearts exposed to ischaemia and reperfusion

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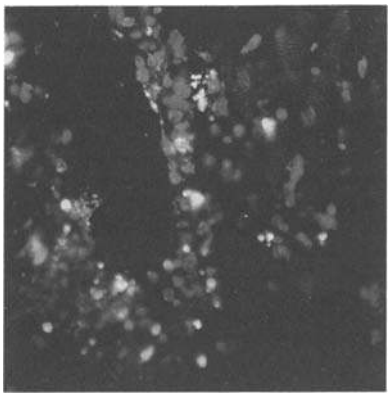
Apoptosis is a particular type of cell death implicated in the aetiology of ischaemia/reperfusion injury.

The apoptotic process has been seen to affect cardiac myocytes of ischaemic/reperfused hearts, occurring primarily during reperfusion. Nonetheless, the occurrence of apoptosis in specific cell types, with particular reference to the earliest stages of reperfusion, has still to be clarified.

Materials and Methods: Isolated Langendorff perfused rat hearts were randomly divided into three groups: control group (n = 6), subjected to 60′ of perfusion; ischaemic group (n = 6) exposed to 35′ of regional ischaemia and ischaemic/reperfused group (n = 6), exposed to 35′ of regional ischaemia followed by 5′ of reperfusion. Hearts were cross-sectioned into slices which were fixed in 4% formaldehyde and embedded in paraffin. Serial 5 microns sections were cut, dewaxed and incubated with trypsin. After the employment of TUNEL assay, sections were labelled with anti-desmin antibody, in order to accurately address apoptosis in specific cell types and counterstained with propidium iodide (PI).

Results: Apoptosis was seen only in sections from hearts subjected to ischaemia and reperfusion. In ischaemic/reperfused hearts the number of TUNEL positive cells was significantly higher in endothelial cells (24 ± 3%) than in cardiac myocytes (4 ± 1%). In the same sections the most common pattern of TUNEL staining was represented by rings of positive cells within the wall of vessels of different sizes. Amongst these, the largest may be surrounded by a few positive cardiac myocytes easily recognisable by the red desmin-banding of the cellular body (figure).



Conclusions: The data show that cells within vessel walls are the predominant cell type affected by apoptosis in the very early stage of reperfusion.

1362 Chronic hypoxia induces apoptosis in cardiac myocytes: a possible role for the apoptotic markers Bcl-2 and Bax

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Although ischemia and myocardial infarction can trigger apoptosis in cardiac myocytes, the effect of prolonged hypoxia/ischemia as well as the molecular mechanisms are not well established. Studies in different cell types have proposed a possible anti-apoptotic role of the Bcl-2 protein in hypoxia-induced apoptosis. Here we demonstrate the effect of chronic hypoxia on the expression of the anti-apoptotic Bcl-2 and the proapoptotic Bax protein in hearts from rats exposed to chronic hypoxia.

Methods: Adult rats were exposed to hypoxia (n = 4) or normoxia (n = 4) for 3 weeks. Hearts from hypoxic rats showed an increased rate of apoptosis as demonstrated by increased DNA fragmentation compared to hearts from normoxic animals. Bcl-2 protein expression was significantly decreased ($p < 0.05$), whereas Bax expression was increased, up to 3 fold, ($p < 0.05$) in myocardium from animals exposed to chronic hypoxia (n = 4) compared to normoxia (n = 4). As previously demonstrated, overexpression of p53 can induce apoptosis in cardiac myocytes possibly via modulation of Bcl-2 and Bax expression. Our results demonstrate an increased p53 expression, about 2-fold, in hearts from hypoxic rats compared to normoxic rats.

Conclusion: These results demonstrate for the first time in vivo an increased apoptosis rate in hearts from rats exposed to *chronic* hypoxia compared to normoxia, accompanied by a significant decrease of Bcl-2 and an increase of Bax protein expression in hypoxic hearts. These results suggest a possible role of these markers in hypoxia induced cell death, most likely dependent of p53. Additional studies are needed in vivo and in vitro to further elucidate the role and regulatory mechanisms of Bcl-2 and Bax protein expression in hypoxia induced apoptosis in cardiac myocytes.

1363 Prolonged effect of cardiomyocyte apoptosis on ventricular remodelling after myocardial infarction in rats

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Apoptotic cardiomyocyte death (CA) occurs in acute myocardial infarction (AMI) and in heart failure both in experimental animals and in man. To clarify the role of CA in the post-AMI remodelling process, we studied the amount and site of CA during 12 weeks after experimental AMI in rats.

Methods: AMI was produced by ligating the proximal LAD coronary artery in adult male Wistar rats. Sham-operated animals were used as controls. Rats were sacrificed and myocardial samples obtained at 24 hrs and at 1, 4 and 12 weeks post AMI. In histological sections, the infarcted area was demarcated and apoptotic cardiomyocytes quantified (TUNEL assay) in the areas adjacent to infarction and in the remote non-infarcted tissue. To measure left ventricular (LV) end-diastolic dimension (LVDD) and ejection fraction (EF), echocardiography was performed at baseline, at 24 hrs and at 1 and 4 weeks after LAD ligation.

Results: Sham-operated animals showed no statistically significant change in LVDD or EF during the study. Also CA was low (0.04 ± 0.02%, mean ± SD) and remained stable during the study. At 24 hrs, TUNEL positivity was observed in up to 8.5% of total cardiomyocytes in the infarcted areas. In the remote non-infarcted areas, CA was already elevated at 24 hrs (0.09 ± 0.04%, $p < 0.05$ vs. sham) and remained increased at 1 week (0.11 ± 0.09%, $p < 0.05$). However, at 4 and 12 weeks CA in the remote myocardium did not differ from control samples. In contrast, CA was more frequent in the peri-infarct zone: 0.34 ± 0.18% at 1 week, decreasing thereafter gradually but remaining at 0.13 ± 0.04% ($p < 0.05$) even after 12 weeks. By echocardiography, mean LVDD increased gradually from 24 hrs to 1 week (+3.8% vs. baseline) and to 4 weeks (+11.1% vs. baseline) whereas mean EF showed no significant change during the study.

Conclusions: Post-AMI LV remodelling, assessed as progressive increase of LVDD, parallelled the occurrence of cardiomyocyte apoptosis in both the remote and peri-infarct areas up to 1 week after experimental AMI in rats. In contrast, prolonged and remarkable increase of CA was observed only in viable areas adjacent to the infarct scar as long as 12 weeks post AMI. This probably contributed significantly to the extended LV dilatation and remodelling after coronary artery occlusion.

1364 Simvastatin modulates nitric oxide synthase expression and myocytic apoptosis induction after acute ischaemia in isolated rat hearts

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Previous studies have suggested that Simvastatin (S), an inhibitor of B-hydroxy-B-methylglutaryl-coenzyme A (HMG-CoA), may exert an endothelial-protective and anti-ischemic effects via nitric oxide (NO) mediated mechanism. The aim of this study was to evaluate the effects of acute S administration on endothelial and inducible NO-synthase (e-NOS and i-NOS) mRNA expression and myocytic apoptosis after ischemia-reperfusion (I/R).

Isolated working rat hearts were used (Neely's technique) and submitted to 15 min. global ischemia and 190 min. reperfusion. To detect myocytic apoptosis we used DNA agarose gel electrophoresis and TUNEL technique; e-NOS and i-NOS expression were evaluated by multiplex RT-PCR; glyceraldheyde-3-phosphate deydrogenase (G-3PDH) was used as internal standard. The e-NOS and i-NOS mRNA were expressed as G-3PDH/e-NOS and G-3PDH/i-NOS densiometric ratio.

Hearts were divided into four groups: A) hearts excised and used as histological controls; B) hearts submitted to I/R; C) hearts treated with actinomycin D, an inhibitor of genic transcription (1.5 mg/kg); perfused with 25 μM S, subjected to I/R; D) hearts perfused with S 25 μM and submitted to I/R.

In group B we evidenced a significant myocytic apoptotic damage, reduced in C and D groups. In B group an increase in G-3PDH/e-NOS ratio vs A group was detected; in D group a reduction in G-3PDH/e-NOS ratio vs B group occurred; no significant changes were observed between C and D groups. G-3PDH/i-NOS ratio was significantly increased in D group respect to A and B groups.

Our data point out that S acutely modulates NO-synthase mRNA expression (induction of e-NOS mRNA expression and inhibition of i-NOS post-ischemic over-expression) by a post-transcriptional mechanism and reduces myocytic apoptosis.

TRANSGENIC MODELS

1365 Kinetics, toxicities, and efficacies of new transfection reagents: increased cellular uptake of antisense-oligonucleotides encapsulated into GS 2888 Cytofectin®

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Transfection of cells with viral vectors or antisense oligonucleotides (ASO) is of major interest for both experimental studies, as well as therapeutical options. In restenosis, growth of human arterial smooth muscle cells (haSMC) is stimulated by the paracrine PDGF release of human arterial endothelial cells (haEC) and the autocrine secretion of TGF-β1. Transfection with ASO against the mRNA of PDGF and TGF-β1 might be an interesting therapeutical concept but requires sufficient transfection efficacy.

Methods: Viability of haSMC and haEC 24, 48, or 72 h after transfection with the liposomes Lipofectin® (LF), GS 2888 Cytofectin® (CF), and DAC-30® and the dendrimer Superfect® (SF) for 1, 2, 3, 4, 5 h was examined in MTT-tests. Uptake studies were performed with FITC-labeled mismatch control-oligos and specific ASO with or without incorporation into transfection reagents. Effects of ASO on PDGF-AB and TGF-β1 protein production was studied in conditioned media by ELISA and Western blotting, effects on mRNA-expression were examined by non-radioactive Northern blotting.

Results: In contrast to SF > 3 μg/ml, DAC-30 and CF showed no significant toxic effects on haSMC. Addition of LF to serum-containing medium caused cell detachment. At haEC, SF and CF showed the less toxic effects. Fluorescence microscopy of FITC-labeled ASO demonstrated no remarkable intracellular incorporation of naked ASO. In contrast, transfection with CF- or SF-encapsulated ASO showed a strong cytoplasmic labeling after 1–2 h and a nuclear labeling after 4–6 h. With DAC-30, just a slight cytoplasmic labeling after 6 h was found. Interestingly, SF caused a 10-fold stimulation of PDGF-AB secretion by haEC independently of the ASO-effects. Thus, CF-encapsulated ASO (0.05–2.0 μg/ml) were used in order to inhibit PDGF-AB secretion of haEC and TGF-β1 release by haSMC. ELISA, Western and Northern blots showed a significant inhibition of PDGF-AB and TGF-β1 expression with a 50% inhibition at 0.5 μg/ml after 3–5 h transfection. High ASO-doses > 2 μg/ml and transfection periods > 5 h caused toxic effects. Mismatch control-oligos did not influence PDGF-AB and TGF-β1 expression.

Conclusions: New transfection reagents, such as SF or CF showed an improved transfection efficacy and less toxicity than the 'classical' liposom LF. Depending on the structure and cell type, an unspecific activation of cells may occur. CF was found to be superior to other transfection reagents at haSMC *and* haEC and thus offers a promising therapeutic concept with encapsulated antisense oligonucleotides e.g. against growth factors.

1366 Delivering adenoviral vectors to rabbit myocardium: effect of dose and method of delivery on efficiency and micro-infarction

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In vivo adenoviral mediated gene transfer through the coronary circulation may prove valuable in models of gene therapy and for functional experiments on cardiac tissue following infection.

In adult New Zealand white rabbits we have compared a minimally invasive selective right coronary injection technique with an aortic cross-clamp technique at open thoracotomy. We used replication deficient adenoviral vectors encoding a beta-galactosidase reporter gene. Animals were sacrificed 5 days after viral introduction for tissue histochemistry and the proportion of positively staining cardiomyocytes calculated by point counting.

Right coronary injections were performed using 1 ml of vector at a concentration of 5×10^9 plaque forming units (pfu)/ml (n = 6) and in a separate group, 1 ml of 1×10^{10} pfu/ml (n = 8). In the low dose group beta-galactosidase reporter gene expression was localised morphologically to perivascular cardiac myocytes and non-myocytes in the right ventricles of 5 animals. In these animals 2.6% (range 1.2%–4.3%) of right ventricular (RV) cardiomyocytes stained positively for the reporter gene product. The heart of one animal displayed areas of lymphocyte infiltration with associated cardiomyocyte cell death (micro-infarction). In the high dose group, reporter gene expression was found in the hearts of 7 animals. In these animals 4.3% (range 0.2%–11%) of RV free wall cardiomyocytes and 10% (range 0.2%–31%) of RV trabecular cardiomyocytes stained positively for the reporter gene product. However, all of these animals displayed areas of micro-infarction. In each animal the left ventricular free wall served as a non-infused control. Animals infused with an adenoviral vector encoding a skeletal troponin c mutant under the control of a human cardiac actin promoter served as infused controls. None of the control tissues stained positively for the reporter gene product beta-galactosidase.

In an aortic cross-clamp group (n = 8) each animal received 1 ml of vector at a concentration of 1×10^{10} pfu/ml. Only occasional positively staining cardiomyocytes were found in the epicardial region of both ventricles, amounting to less than 1% of ventricular cardiomyocytes. None of the right ventricular trabeculae from this group stained positively for the reporter gene product.

We conclude that adenoviral mediated gene transfer to rabbit myocardium is more efficiently achieved by selective coronary injection than by the aortic cross-clamp technique. However, high dose coronary infusion is commonly associated with areas of micro-infarction.

1367 In vivo gene transfer into mouse myocardium and arteries: a comparison of recombinant adenovirus and adeno-associated virus vectors

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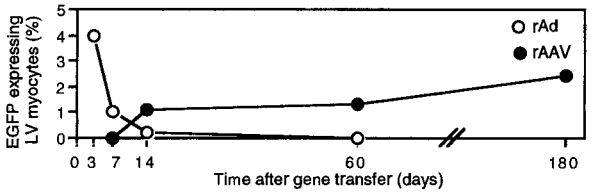
The aim of the present study was to compare recombinant adenovirus (rAd) and adeno-associated virus (rAAV) for myocardial and arterial gene transfer.

Methods: rAd (titer: 5 × 10E9 PFU/mL) and rAAV (titer: 2 × 10E7 TU/mL) expressing a green fluorescent protein (EGFP) marker gene from a CMV promoter were used in the present study. Vectors with no EGFP gene were used as controls (C). Myocardial gene transfer was carried out by virus injection (2 μl) into the anterior LV wall in open-chest CD1 mice (n = 22). Hearts were explanted at various time points after gene transfer and EGFP expressing myocytes were counted on heart slices (n = 5 per heart) by fluorescence microscopy. Arterial gene transfer was carried out by infusion of either virus into mouse carotids (n = 3 each). EGFP expressing endothelial cells were counted on arterial sections (n = 30 per vessel).

Results: Myocardial gene transfer: EGFP expressing myocytes (in % of LV myocytes on heart slices) peaked at 3 days with rAd (median value: 4%; range: 3–14%) and at 180 days with rAAV (2.5%; 1–4%; C = neg.). Gene transfer was focal with up to approximately 30% transduced cells with rAd and 20% with rAAV at the injection site. The time course of gene expression (median values) was as follows:



Arterial gene transfer: EGFP expressing endothelial cells in mouse carotids were 13% (8–30%) after gene transfer with rAd vs. 2% (0–3%) with rAAV.

Conclusions: Under the study conditions (virus titers), rAAV was nearly as efficient as rAd at transducing mouse myocardium but less efficient than rAd at transducing arteries. Gene expression is rapid but short-lived with rAd, slow but stable with rAAV. These data show that rAAV is a good candidate vector for gene therapy of chronic cardiac diseases, where longterm gene expression is required.

1368 Reduction of G-protein β-subunits in atrial cardiomyocytes leads to abnormal sinus node automaticity in mice

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Background: Acetylcholine, acting through M_2-muscarinic receptors coupled to a G-protein system, slows heart rate by opening the atrial muscarinic I_{KACh} channel. This channel is directly activated by $\beta\gamma$-subunits released from G-proteins. In sinus node cells, activation of this channel decreases spontaneous depolarization (pacemaker activity) and slows conduction velocity in the atrioventricular node.

Objective: To determine, whether the reduction of G-protein β-subunits in the membrane of atrial myocytes in transgenic mice (TG) affects sinus node pacemaking function and atrioventricular conduction at baseline (BL) and after pharmacologic stimulation with the M_2-muscarinic receptor agonist carbachol (CCH).

Methods: Surface electrocardiograms (ECG) and intracardiac electrophysiology (EP) studies were performed in TG with a 50–60% reduction of β-subunits in atrial cardiomyocytes, and wild-type (WT) controls. The RR, PR, QRS and QT intervals were measured on surface ECG. Sinus node recovery times (SNRT, CSNRT), AV refractory periods (AVERP), paced AV and VA Wenckebach cycle lengths (AV/VA-W), paced AV 2:1 cycle lengths, and ventricular effective refractory periods (VERP) were assessed by EP study.

		SNRT	CSNRT	AvERP	AV-W	vA-W
WT	BL	360 ± 49	155 ± 49	75 ± 5	89 ± 7	103 ± 10
	CCH	348 ± 53	125 ± 49	80 ± 6	90 ± 8	107 ± 14
TG	BL	213 ± 51*	60 ± 33*	84 ± 11	96 ± 8	120 ± 10
	CCH	181 ± 72*	51 ± 39*	74 ± 15	84 ± 8	100 ± 17

(* = p < 0.01, TG vs WT; values in ms)

Results (see table): SNRT and corrected SNRT (CSNRT) were significantly decreased in TG compared to WT mice at baseline, as well as after parasympathetic stimulation. There were no significant differences in ECG or other EP parameters between groups.

Conclusions: Sinus node automaticity (spontaneous depolarization) is increased as a result of G-protein β-subunit reduction in atrial cardiomyocytes. Reduction of G-protein $\beta\gamma$-subunits constitutes the molecular mechanism responsible for I_{KACh} channel malfunction and abnormal parasympathetic heart rate regulation.

1369 A targeted disruption of connexin40 leads to abnormal heart rate regulation in mice

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Background: Electrical coupling of pacemaker cells at gap junctions, formed by connexins, appears to play an important role in sinus node function. Connexin40 (Cx40) is widely distributed in the sinus node region. Electrical cell-to-cell uncoupling by Cx40 disruption may result in action potential generation delay and loss of shielding the primary pacemaker from the atrial hyperpolarizing influence.

Objective: The purpose of this study was to determine, whether a homozygous deletion of Cx40 ($Cx40^{-/-}$) in mice affects action potential generation and sinus node pacemaker synchronization.

Methods: We developed a method to compute heart rate variability (HRV) analysis in mice. Implantable telemetry devices were used to record conscious heart rate (HR) in 6 transgenic ($Cx40^{-/-}$) and 7 control mice ($Cx40^{+/+}$). Autonomous influences on HR were quantified by standard frequency domain techniques of HRV analysis. Low (LF) and high (HF) frequency bands were defined as 0.4–1.5 and 1.5–4 Hz respectively. LF and HF were also measured in normalized units (LFn, HFn), and LF/HF ratio, reflecting sympathetic/parasympathetic balance, was calculated.

Results: Mean and median RR intervals were significantly increased in $Cx40^{-/-}$ mice. LF and HF bands were increased in $Cx40^{-/-}$ compared to control mice. The LF/HF ratio was also increased in Cx40-deficient mice.

	$Cx\ 40^{+/+}$	$Cx\ 40^{-/-}$	P
RR mean (ms)	88 ± 4	110 ± 19	0.01
RR median (ms)	88 ± 5	110 ± 20	0.01
LF (ms^2)	2.7 ± 2.3	23.9 ± 24.8	0.04
HF (ms^2)	7.2 ± 5.5	19.2 ± 12.8	0.04
LFn	0.25 ± 0.1	0.52 ± 0.19	0.01
HFn	0.75 ± 0.1	0.48 ± 0.19	0.01
Ratio (LFn/HFn)	0.38 ± 0.3	1.34 ± 0.82	0.01

Conclusions: Cell-to-cell communication within the murine sinus node is mediated through gap junction channels formed by connexin40. Electric impulse propagation is impaired in Cx40-deficient mice reflected by decreased basal heart rate and pacemaker desynchronization (increased heart rate variability).

1370 Increased velocity of shortening and relengthening in adult rat cardiomyocytes after S100A1 adenoviral gene transfer

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A compromised contractility in human end stage heart failure is correlated with a decrease in Ca^{2+} release from the sarcoplasmatic reticulum (SR) during systoly. Since S100A1 has been shown to enhance the caffeine induced Ca^{2+} release from SR we hypothesized that S100A1 overexpression might improve contractility and thus would be an attractive candidate for gene therapy of heart failure.

Isolated adult rat cardiomyocytes were transfected with an adenoviral construct containing S100A1 cDNA under the control of a CMV promotor. Green fluorescent protein (GFP) served as reporter protein. Efficacy of transfection was controlled by GFP detection, S100A1 overexpression was documented by Northern and Western blotting. Non-transfected (NT) and empty virus transfected (EV) served as controls. Myocytes were stimulated with 5 ms pulses at 1 Hz. Shortening and relengthening of myocytes were measured by a video edge detection system. There was no significant difference between NT and EV cells concerning contractility thus excluding effects by the empty virus. S100A1 overexpression lead to an increased velocity of shortening (−dL/dt; +19%; p = 0.02) and of relenghtening (+dL/dt; +19%; p = 0.03) as well as an increase of cell shortening (CS; +22%; p = 0.01). These data demonstrate for the first time that adenoviral S100A1 overexpression improves contractility of cultured adult rat cardiomyocytes.

1392 Can coronary flow velocity patterns predict the improvement of left ventricular function after successful reperfusion for acute myocardial infarction?

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The aim of this study was to assess coronary flow velocity (CFV) patterns after successful reperfusion for acute myocardial infarction (AMI) as a predictor of left ventricular function improvement.

Methods: Using a Doppler guidewire, we measured CFV and coronary flow reserve (CFR; ATP i.c.) in 50 AMI patients (pts) immediately after successful primary balloon angioplasty or stenting. The measurements were repeated at 1 month and at 3–6 months follow up. Left ventricular ejection fraction (LVEF) and regional wall motion (RWM; 1 = normal, 4 = aneurysmal) were evaluated by left ventriculography at 1 month and at late follow up.

Results: In 38 pts without restenosis (LAD = 20, LCX = 5, RCA = 13), 16 pts showed low systolic peak velocity (SPV; <10 cm/see) and high diastolic systolic velocity ratio (DSVR; ≥3) (G1) and 22 pts showed normal pattern (G2). Among G1, increase of SPV and normalization of DSVR were observed in 6 pts (G1B). Other 10 pts in G1 showed no significant change of CFV patten (G1A).

	G1A (n = 10)	G1B (n = 6)	G2 (n = 22)	p value
CFR				
Immediate	1.2 ± 0.2	1.4 ± 0.3	1.5 ± 0.3	N.S
1 month	1.8 ± 0.3	2.2 ± 0.3	2.2 ± 0.5	N.S
3–6 months	1.8 ± 0.3	2.4 ± 0.2	2.5 ± 0.4	<0.001
ΔLVEF	−3.4 ± 6.8	4.8 ± 5.1	6.2 ± 4.4	<0.01
ΔRWM	0.8 ± 0.7	−1.0 ± 0.8	−0.3 ± 0.6	<0.01

In conclusion, CFV pattern characterized with low SPV and high DSVR at 1 month may be due to irreversible severe microvascular dysfunction. CFV patterns at 1 month could be available as a predictor of left ventricular function improvement after successful reperfusion for AMI.

1393 Monitoring of coronary blood flow velocity using intracoronary doppler in patients with acute myocardial infarction before, during, and after coronary angioplasty

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Using intracoronary Doppler, we have studied the variations in coronary blood flow observed before, during, and after reperfusion of the infarct coronary artery through angioplasty in 40 patients of 60.2 ± 15.4 years of age admitted to hospital because of a primary myocardial infarction either inferior (n = 22) or anterior (n = 18).

Methods: Average peak velocity (APV) was continuously measured, using a 0.014 doppler guidewire, to quantify collateral flow, and flow velocities during reperfusion and after PTCA.

Results: Before removing obstructions, the collateral flow peak velocity distal to the occlusion is 14.8 ± 8.1 cm/s. Collateral flow, which is bi-directional, is predominantly retrograde (n = 32), negative (n = 1) or positive (n = 5). There is a slight difference between the five Rentrop 0 patients and Rentrop 1, 2 or 3 patients (Rentrop 0: 14.9 ± 6.4 cm/s; Rentrop 1: 12.3 ± 9.9 cm/s; Rentrop 2: 15.2 ± 8.2 cm/s; Rentrop 3: 17.5 ± 6.3 cm/s). The patients with TIMI 3 reperfusion flow display the highest distal APV Doppler velocities ($APV_{TIMI\ 3}$ 20.2 cm/s versus $APV_{TIMI\ 1\ and\ 2}$ 10.9 cm/s; p = 0.05). After angioplasty, distal APV is 18.7 ± 10.4 cm/s (p = 0.001). Diastolic flow is predominant. Seventeen patients showed a retrograde systolic flow, 12 had a small systolic flow and 17 displayed a steep slope of diastolic deceleration.

Conclusion: Thus, intracoronary Doppler reveals that coronary flow in the patients with TIMI 3 flow is highly varied morphologically speaking as well as quantitatively speaking. This disparity might help us to isolate a subset of risk patients, candidates for a complementary therapy.

1394 Flow variation during direct acute myocardial infarction angioplasty with coronary stent implantation

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In order to assess flow variations during direct acute myocardial infarction angioplasty (DAMIA), we retrospectively studied 180 pts (57 +– 17 y.) consecutively treated on native arteries, excluding rescue PTCA and cardiogenic shock. Thrombus (T) was scored; TIMI flow grade and TIMI frame count (TFC, sec.) were assessed at different steps. Baseline TIMI flow was: 0 62%, I 13%, II 16%, III 9%. A T length > 1 cm. was noted in 22%. DAMIA was successful in 162 pts (90%). Stent(s) was used in 76% of the pts. We noted one procedural death. Reference diameter was 3.1 +– 0.5 mm and MLD went from 0.2 +– 0.4 mm up to 2.9 +– 0.6 mm.

TFC decreased from 3.1 +– 1.4 sec. to 1.1 +– 1.1 sec at the end of the procedure (p < 0.001). After stenting, flow was increased in 10%, and decrased in 22%. In 40 pts with post-stenting flow decrease, final flow was III in 33 pts (82%), using i.c. verapamil in 14 pts and IIb/IIIa antagonist in 5 pts. In the global cohort, final flow was I in 6%, II in 9% and III in 85%. Initial T length > 1 cm was associated with a transient slow-flow after stenting (57% vs 17%, p < 0.005) and with a final non-TIMI III flow (50% vs 17%, p < 0.01).

Thus, coronary stenting during DAMIA may be associated with a slow-flow. This flow decrease is usually transient. A large T is a predictive factor of non-TIMI III flow result and adjunctive techniques may be assessed in this subgroup.

1395 The slope of the instantaneous hyperemic diastolic coronary flow velocity-pressure relation can predict myocardial salvage in acute myocardial infarction patients underwent primary angioplasty

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Background: The status of the coronary microcirculation in the infarcted area has been proposed to determine the effects of reperfusion therapy on myocardial salvage in patients with acute myocardial infarction (AMI). Thus, we hypothesized the slope of the instantaneous hyperemic diastolic flow velocity-pressure relation (IHDVPS), reflects the coronary microcirculation status independently from the hemodynamic parameters, can predict LV function in reperfused AMI patients.

Methods: A total of 25 AMI patients (LAD 20, RCA 5) underwent primary stenting was studied, coronary flow velocity and pressure were monitored in the infarcted artery simultaneously. Coronary flow reserve (CFR) was measured by administration of intracoronary ATP and IHDVPS during hyperemia was calculated from coronary flow velocity-pressure loop. Left ventriculogram (LVG) was obtained on admission and follow up (mean 5.7 months) and regional wall motion (RWM: SD/chord) and ejection fraction (EF:%) were assessed. The correlation between IHDVPS and the recovery of left ventricular function (recovery of RWM and EF)were evaluated.

Results: There was no difference in EF between on admission and at follow-up. However, RWM were significantly improved (p = 0.0003). Correlation between flow parameters and recobery of left ventricular function was as in Table.

Correlations

	r	p value
CFR vs recovery of EF	0.28	0.33
CFR vs recovery of RWM	0.10	0.70
IHDVPS vs recovery of EF	0.82	0.0005
IHDVPS vs recovery of RWM	0.84	<0.0001

CFR, Coronary flow reserve; IHDVPS, Instantaneous hyperemic diastolic coronary flow velocity-pressure slope; EF, Ejection fraction; RWM, Regional wall motion

In conclusion: There was good correlatin between IHDVPS and the recovery of left ventricular function. These results indicate that IHDVPS after successful primary stenting is the useful index to predict the improvement of left ventricular function in reperfused AMI patients. Low IHDVPS would possibly reflect severe injury of microvascular bed after primary PTCA.

1396 Time course of recovery of impaired coronary flow reserve in remote vascular areas in acute anterior myocardial infarction

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Coronary flow reserve (CFR) is reduced in the infarct related artery (IRA) directly after primary PTCA in acute myocardial infarction (MI). The CFR may also be impaired in non-obstructed remote vascular beds, (non-infarct related artery, n-IRA). The time course of recovery of CFR in the n-IRA is unknown. We prospectively evaluated the alterations in CFR and average peak flow velocity (APV) in both the IRA and the n-IRA in patients with a first anterior MI.

Methods: Primary PTCA was performed within 6 hours in 41 patients with an anterior MI. CFR and APV were measured directly after successful PTCA at baseline and after adenosine induced hyperaemia in the IRA and the n-IRA, by means of a Doppler guide wire. This was repeated and at 1 week (n = 23) and 6 months follow up(n = 17).

Results: After primary PTCA, the CFR was reduced in both the IRA and the n-IRA and improved in both vessels at 1 week and 6 months. The difference between the CFR in both vessels remained significant during follow up. At 1 week, the increase of CFR in the IRA and n-IRA was due to an enhanced hyperaemic APV (from 34 ± 15 to 42 ± 15, p = 0.18 and from 40 ± 13 to 50 ± 16 cm/s, p = 0.11 respectively) whereas subsequent the increase of CFR at 6 months was due to a decrease in baseline APV (see table).

CFR and baseline APv

	PTCA (A)	1 week (A)	6 months (A)	PTCA (B)	1 week (B)	6 months (B)
IRA	1.7 ± 0.4	2.0 ± 0.4[1]	2.7 ± 0.9[1]	20.0 ± 9.6	21.1 ± 6.7	14.6 ± 7.7[1]
n-IRA	2.4 ± 0.5	2.9 ± 0.5[1]	3.5 ± 0.5[2]	17.0 ± 6.3	17.8 ± 6.6	13.9 ± 6.3

(A): CFR (hyperaemic/baseline APV); (B): baseline APV (cm/s); All figures as mean (± SD): [1]p < 0.05 vs PTCA; [2]p < 0.0001 vs PTCA.

Conclusions: The time course of recovery of baseline and hyperaemic average peak flow velocity determining coronary flow reserve is similar in both the infarct and non-infarct related artery, suggesting disturbed autoregulation in remote normal perfusion territories following acute anterior myocardial infarction.

1397 Coronary and myocardial perfusion mismatch in patients with acute coronary syndromes

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After coronary interventions, coronary flow improves but is usually normalized only after stenting. However, myocardial perfusion may be impaired despite an optimal interventional result. In order to detect a possible mechanism of the disturbed myocardial perfusion after intervention, we investigate whether plaque characteristics may be related to the effect the improvement of coronary flow velocity reserve (CFVR) after stenting.

A total of 54 patients (pts) who had significant coronary luminal narrowing were examined with intracoronary Doppler: stable angina pectoris (SAP) in 31 pts, unstable angina pectoris (UAP) in 11 pts, and in 12 pts with 1 to 3 months after myocardial infarction (MI). Intracoronary flow measurements were performed before, after PTCA and after stent implantation using a 0.014 inch FloWire® (Cardiometrics). CFVR was calculated by the ratio of the hyperemic average peak velocity to the baseline average peak velocity after intracoronary injection of adenosine (18 μg for the left coronary arteries, 12 μg for the right coronary artery).

CFVR	before PTCA	after PTCA	after stent
SAP	1.53 ± 0.90	2.38 ± 0.82*	3.21 ± 0.79*
UAP	1.86 ± 0.79	1.97 ± 0.85#	2.34 ± 1.03*
MI	1.31 ± 0.36	2.17 ± 0.52*	2.44 ± 0.37*

*p < 0.01 versus before PTCA; #p = 0.08

Impairment of CFVR in patients with UAP and MI may still be present immediately after successful stenting despite optimal coronary stenting. As this impairment of CFVR was found in UAP and MI but not in SAP patients, it indicates a preexisting or intervention-induced coronary-myocardial perfusion mismatch.

ADJUNCTIVE PLATELET INHIBITION WITH STENTING

1398 Accelerated inhibition of platelet activity by clopidogrel loading dose in patients following coronary stent implantation

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The incidences of subacute thrombosis following stent implantation into human coronary arteries within the first days after the procedure has decreased substantially. Clopidogrel, a newly introduced ADP-antagonist, was studied as an alternative to ticlopidine. Patients undergoing successful stent implantation were randomized to receive either ticlopidine (500 mg/d) plus aspirin 300 mg/d for 4 weeks (TA; n = 13), clopidogrel 75 mg/d plus aspirin 300 mg/d (CA, n = 13) or a clopidogrel loading dose of 300 mg on day 1 followed by 75 mg/d for the following 27 days plus aspirin 300 mg/d (CALD, n = 14). Platelet aggregation and adhesion molecule expression (CD62p) was determined immediately after stent implantation and after 1, 2, 3, 6 and 13 days. No subacute stent thrombosis was observed in any of the patients. ADP (20 μM)-induced platelet aggregation decreased in the TA group from 80.3 ± 4.9% after stenting to 69.3 ± 7.8% on day 1 and to 36.8 ± 10.8% on day 13. Platelet inhibition was comparable in the CA group with aggregation response to 69.0 ± 8.8% on day 0, 65.1 ± 8.8% on day 1 and 35.9 ± 9.9% on day 13 (p = 0.2 vs TA). In contrast, platelet aggregation was inhibited much earlier in the CALD group with 74.3 ± 13.5 on day 0 before drug administation, decreasing already on day 1 to 48.4 ± 6.7% (p ≤ 0.01 vs TA or CA) and to 30.9 ± 9.9% on day 13. The ADP-induced expression of p-selectin (CD62p) on the platelet surface was influenced to a comparable degree. While initial values for CD62p were not different for the 3 groups, significant differences were seen on day 1 with 63.8 ± 7.5% for TA, 58.5 ± 4.7% for CA and 40.4 ± 5.4% for CALD (p ≤ 0.01).

Thus, administration of clopidogrel instead of ticlopidine following stent implantation results in a comparable degree of platelet inhibition. Administration of a clopidogrel the loading dose (300 mg) on the day of stent implantation markedly accelerates platelet inhibition being statistically significantly different already 1 day following the first drug administration.

1399 A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents

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The introduction of an effective antiplatelet therapy with aspirin (A) plus ticlopidine (T) after the placement of coronary-artery stents has dramatically decreased the risk of subacute thrombosis (SAT) as well as hemorrhagic complications. However, the use of T is limited by hematologic and gastrointestinal adverse effects. Clopidogrel (C), a new thienopyridine derivate, has an excellent overall safety profile. Its efficacy after stenting remains to be established.

Methods: After successful coronary stenting during elective or emergency PTCA, 1000 patients (P) will randomly be assigned to a four week course of either 500 mg T or 75 mg C in addition to their regular medication with 100 mg A. The primary endpoint is a combination of major cardiac (death, myocardial infarction, angiographically documented SAT, revascularisation of the target vessel or hospitalization for unstable angina) and noncardiac (peripheral or hemorrhagic, or discontinuation of study medication due to side effects) events in the first 30 days.

Results: Follow up has been completed for 159 P with C and 178 P with T. Major cardiac events occurred in 13 P (8.2%) and 11 P (6.2%, p = ns) respectively, noncardiac events in 7 P (4.4%) and 16 P (9.1%, p < 0.05).

Conclusion: After the successful placement of coronary-artery stents, antiplatelet therapy with A and C is as effective as A and T. Noncardiac events are significantly reduced by C. Final results will be available at presentation.

1400 Two- or four-week ticlopidine therapy after coronary stent placement?

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Three large randomized studies (ISAR, STARS, FANTASTIC) demonstrated the superiority of combined antiplatelet therapy after stenting. Although they used a 4-week or longer ticlopidine regimen, increasing numbers of patients are only treated for 2 weeks to minimize potential side effects of ticlopidine. To test this rationale, we retrospectively compared the major adverse cardiac event rates (MACE: death, myocardial infarction, repeat target lesion revascularization) in the early (first 2 weeks) with the late period (week 3 and 4) of 2259 patients with and 574 without ticlopidine. Patients were stratified into 2 risk groups according to the incidence of recently published risk factors for MACE (age, diabetes, acute myocardial infarction, unstable angina, impaired LV function, residual dissection, stented segment length, stent overlap). The population quartile with the highest risk constituted the high risk group (HIGH; n = 708), the low risk group comprised the other 3 quartiles (LOW; n = 2128). In the first 2 weeks, MACE rates were significantly lower with ticlopidine in HIGH (7.3% with ticlopidine vs 12.2% without ticlopidine; $p = 0.04$) and LOW (0.9 vs 2.1%; $p < 0.04$). In the late period, MACE rates were higher without ticlopidine. However, this was only of borderline significance in HIGH (1.2 vs 3.2%; $p = 0.06$) and not significant in LOW (0.2 vs 0.5%; $p = 0.44$).

Conclusions: These data provide no support for a general reduction of the ticlopidine regimen from 4 to 2 weeks after stent placement. In a high risk population, this may lead to significantly higher MACE rates in the 3rd and 4th week. In a low risk population however, the minimal benefit of a 4-week therapy has to weighted against potential (ie, hematologic) side effects of ticlopidine. Prospective studies are needed to specifically address this topic prior to any general recommendations.

1401 Does preprocedural ticlopidine treatment modify the short-term outcome after coronary angioplasty?

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In order to improve the antiplatelet treatment during coronary angioplasty, we decided to use in selected pts, since april 1997, a preprocedural treatment with ticlopidine (PPTT). The aim of this single center study is to retrospectively study the effect of PPTT on acute outcome. From april 97 to january 99, we treated 4183 pts with PTCA, among whom 677 pts with acute MI PTCA were excluded from the study. Thus, we compared: group A – 2075 pts treated with ticlopidine after the procedure, group B – 643 pts with PPTT. Baseline data of these two cohorts were not statistically different (including stent use) except a higher rate of type C lesion in group B (37% versus 32%, $p < 0.05$) and a higher rate of multilesion angioplasty in group B (1.46 ± 0.6) versus group A (1.28 ± 0.5) ($p < 0.01$). In both groups, pts have a similar rate of minor thrombotic events during the angioplasty procedure (composite endpoint associating distal embolization, no- flow, new onset of thrombus and rescue use of abciximab) 7% vs 7.1%. However, we noted during the in-hospital stay a lower rate of acute and subacute stent thrombosis in group B (0.5% versus 1.9%, $p < 0.05$) despite a similar rate of MACE (including death, emergency CABG, Q and nonQ MI, need for re-angioplasty during hospital stay) in group B (2.9%) versus group A (4.2%), p = NS. Furthermore, PPTT was not associated with a higher rate of local complications (3.6% versus 3.2%, p = NS).

Thus, PPTT benefit is limited to stent thrombosis reduction but is not effective on thrombotic events during angioplasty or MACE rate during inhospital outcome. Further randomized study is necessary to clarify PPTT effect in comparable cohorts.

1402 Abciximab in coronary stenting: routine use cannot be justified

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The EPISTENT trial reported improved outcomes of coronary stenting procedures after pre-treatment with abciximab in patients at all levels of risk. The cost of using abciximab in all cases where stents are deployed would be enormous. We report results of a protocol encouraging restriction of abciximab therapy to patients at particularly high risk, and calculate consequent cost savings.

Methods and results. During a 34 month period we studied outcomes of all patients who underwent a coronary stenting procedure and who also fulfilled criteria for inclusion in the EPISTENT trial (808 cases). Major adverse clinical events (MACE) for this group are given below;

	Stable angina (367)		Unstable/postMI (234)		Acute MI (207)	
	No abcix (349)	abcix (18)	No abcix (207)	abcix (27)	No abcix (164)	abcix (43)
Ac Occ	–	–	1	–	2	–
Non–QMI	5	1	4	4	–	–
QMI	–	–	–	–	N/A	N/A
CABG	3	1	1	–	2	1
Death	–	–	–	1	7	3
Rpt PCI	2	–	–	1	–	–
SAT	–	–	–	–	–	–

(abcix = abciximab; Ac Occ = acute occlusion; Rpt PCI = urgent repeat percutaneous coronary intervention; SAT = subacute thrombosis)

Overall MACE rate was 4.8%, compared with 10.8% and 5.3% for the placebo and stent-plus-treatment groups respectively in the EPISTENT trial.

Conclusion. For patients undergoing coronary stenting, it is unnecessary to administer abciximab to all those fulfilling EPISTENT criteria in order to achieve similarly low MACE rates. The additional cost of treating all those eligible for the EPISTENT protocol would have been $1,152,000 in order to try to prevent only 27 outcome events ($ 42,667 per event).

1403 The impact of abciximab therapy as bail out procedure in 1903 patients undergoing PTCA

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The clinical efficacy of GP IIb/III antagonists is documented and approved for preinterventional prophylactic application. Aim of this study was to assess the efficacy of postinterventional Abciximab usage as bail out procedure to manage threatened or acute vessel closure without stent implantation.

Methods: Overall acute vessel closure was observed in 105 (5.5%) of the 1903 patients. In this population abciximab was administered in bail out situations in a dosage of 9 mg given as a bolus which was followed by an intravenous infusion of 4.5 mg over 12 hours. Repeat PTCA was performed shortly after the administration of the abciximab bolus.

Results: In 99 of the 105 patients TIMI Flow III could be restored by this procedure only. In 6 patients an additional stent implatation was necessary. One day post PTCA, early follow up angiography was performed and all 105 vessels were patent. In hospital events occurred in 2 patients. Both had to undergo emergency CABG due to subacute vessel closure. One patient died during surgery. Follow-up after one year included clinical status and control angiography of the target vessel. During long term follow up MACE occurred in 18 patients (2 MI's, 12 CABG und 5 RePTCA's).

Conclusion: The results of this prospective trial demonstrate the high efficacy of Abciximab in bail out situations occurring during or early after PTCA. This effect is due to the dethrombotic property of Abciximab in the presence of fresh thrombus. The use of Abciximab as a bail out rather than a prophylactic therapy appears clinically beneficial and economic sound.

NEWER APPROACHES TO CONGENITAL HEART DISEASE

1423 Quantification of stenosis in patients with coarctation by magnetic resonance imaging using haemodynamic and morphologic changes: comparison of phase shift velocity mapping with multiplanar reformation

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Aim: The quantitative, non-invasive assessment of the degree of a stenosis in patients with coarctation can be performed morphologically using the vessel diameters or hemodynamically using the changes in peak velocity. The geometry of restenosis in patients after repair of coarctation is often very complex. Therefore the usually performed 2-dimensional assessment might be not sufficient. In this study we compared the calculation of the cross-sectional areas from a 3-dimensional data set using MPR of a 2-D MR-angiography and MR flow measurements.

Materials and Methods: We examined 25 patients within the age of 5 to 35 years (mean age 19 ± 9 years). The MR examinations were performed with a 1.5 T Gyroscan ACS-NT (Philips, Best, Netherlands) using a standard body coil. Flow measurements were performed using phase shift velocity mapping to calculate peak velocity at the site of a stenosis. The maximum pressure gradient at the stenosis was estimated using the Bernoulli-equation and compared with cardiac catheter and/ or Doppler-echocardiography data. In the first step simple threshold segmentation of data from an two-dimensional in-flow MR-angiography to three-dimensional (3D) was used to reconstruct the aortic lumen. Within this 3D space, a flight path was defined, following the vessel course. The cross sectional area of the vessel lumen was calculated using reformatted image planes perpendicular to the vessel course. Thus, the percentual stenosis of the aorta was derived.

Results: The estimated pressure gradients at the site of a stenosis using PCA correlated very well with pressure gradients estimated by Doppler echocardiography, with a slight tendency to underestimate even as compared with invasively measured pressure gradients, which was extremely high in two patients with high grade stenosis (pressure gradient > 80 mmHg) and a lot of collaterals. With MPR a quantification of the stenosis was possible in all patients and showed advantages as compared to simple quantification from 2 dimensional images, especially to evaluate pseudocoarctation and complex geometry of the stenosis.

Conclusions: The quantification of low- or midgrade stenosis/ restenosis in patients with coarctation with the estimation of pressure gradients at the site of a stenosis by PCA is sufficient for the clinical routine. In patients with high-grade stenosis or complex geometry of the aortic arch and a lot of collateral vessels flow measurements are not reliable. MPR of an MR-angiography supplies additional information in this cases to improve the diagnostic value of the non-invasive MR examination.

1424 Right ventricular geometry in postoperative tetralogy of Fallot as determined by echocardiographic acoustic quantification: correlation with two-dimensional echocardiography

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Background: The right ventricular (RV) geometric changes (from hypertrophy to dilatation) becomes evident in many patients after repair of the Tetralogy of Fallot (TOF) due to a variable degree of pulmonary insufficiency (PI). Echocardiography remains the main modality for monitoring such changes and their hemodynamic consequences.

Objective: To investigate the utility of Acoustic Quantification (AQ) to quantify RV geometric changes (dilatation) in repaired TOF and to compare this new technique with 2D-echocardiography.

Methods: Echocardiographic examination was performed on 24 patients, who underwent total repair of TOF, and 11 controls. Two subcostal orthogonal planes [the subcostal frontal (F) and sagittal (L)] were used to measure the RV geometric parameters, during the (AQ) application and 2D imaging. All measurements were made at end diastole from 10 cardiac cycles and averaged. During the AQ application, the RV area was obtained in both views (F&L). During 2D imaging, the RV areas (F&L) and long axis (A) [from the level of the pulmonic valve to the endocardial surface of the inferior wall) were obtained. The RV volume (V) was then calculated in both techniques from the equation V = FxL/A and corrected for the BSA (M2).

Results: There were good correlations between the RV areas (F&L) and volume during AQ and 2D imaging (r = 0.85, 0.87 and 0.85 respectively). The RV was dilated significantly in TOF when compared with controls by either AQ or 2D (P = 0.02 and 0.01 respectively). The areas and volumes obtained by AQ were significantly less than that obtained by 2D imaging.

Conclusions: The RV becomes significantly dilated in TOF patients after total repair due to a variable degree of PI. AQ is an excellent technique to measure these geometric changes instantly on line and serially. AQ correlates well with 2D, but tends to underestimate the measured areas and volumes.

1425 Thrombembolic complications after Fontan procedure: diagnosis, risk factors and comparison of different therapeutic approaches

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Patients (pts) after Fontan procedure represent a growing subgroup among complex congenital heart disease with special postoperative problems. Even though thrombembolic complications (TEC) cause a high mortality, anticoagulant therapy is not yet recommended uniformly. Aim of this study was to analyse the frequency and clinical relevance of TEC after Fontan using different therapeutic/prophylactic approaches and the value of diagnostic procedures.

Patients: 87 consecutive pts were included in the study (46 male, 8 ± 9 years [y], range 3–45 y). Early postoperative mortality was 16% (14 pts) and not due to TEC. 71 of the 73 residual pts were examined 0.6–12 y (4.2 ± 3.0 y) after Fontan.

Results: 10/71 pts (14%) developed TEC, 5 became symptomatic (2 cerebral strokes, 2 thrombi in the caval vein, 1 pulmonary embolism), the other 5 remained asymptomatic (3 thrombi in the occluded pulmonary artery (PA) trunk, 2 thrombi in caval vein/right atrium). 63% of all TEC occurred within the first year after Fontan. Using prophylactic medication, there was a tendency towards lower cumulative TEC rate: 16.7% in pts without medication (n = 51), 8.3% in pts with antiplatelet therapy (n = 12) and 4.2% in pts with anticoagulant therapy (n = 24, n.s. using log-rank-test).

Invasive controls (45 pts) and transesophageal echocardiography (TEE, 24 pts) revealed the following otherwise not detectable findings: stenoses of the PA (4), the coronary sinus (1) or the atrial tunnel (2) and abnormal veno-venous (4) or veno-left atrial connections (4). Potential risk factors for TEC were persistent connections to an occluded PA trunk in 25 pts or to a rudimentary subpulmonary ventricle in 14 pts and – mostly small-atrial right to left shunts in 17 pts.

Conclusions: TEC are a frequent clinical problem in the first year after Fontan which can be reduced using anticoagulant therapy. Some risk factors and relevant postoperative sequels can only be detected with invasive follow-up examinations or TEE. Routine early postoperative anticoagulant therapy may be a therapeutic consequence.

1426 Survival and complication-free survival in Marfan's syndrome: implications of current guidelines

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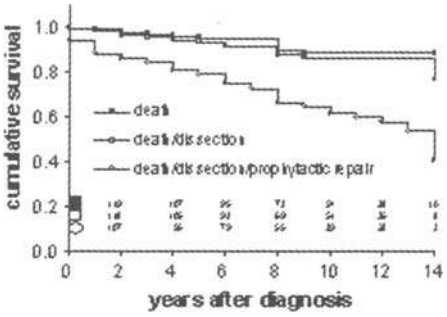
Objective: To evaluate survival in 130 Marfan patients, attending our institution in the past 14 years, and to assess the possible influence of recently revised guidelines for prophylactic aortic root repair in these patients.

Methods: Kaplan-Meier analysis was performed with the endpoints: death, aortic root dissection and prophylactic repair after diagnosis. In the patients developing aortic root dissection, current guidelines for aortic root repair were retrospectively applied to investigate the number of dissections which could theoretically have been prevented. Current guidelines were considered to be: (1) aortic root diameter > 55 mm,(2) positive family history of aortic dissections and aortic root diameter > 50 mm, and (3) aortic root growth > 2 mm/year. Furthermore, survival following emergency surgery (15 patients) and prophylactive surgery (30 patients) of the aortic root were compared.

Results: 5 Patients presented with aortic root dissection before diagnosis was established and were excluded from survival analysis. Of the remaining 125 patients, 13 developed dissection, 30 underwent prophylactive repair and 82 had an uncomplicated course. Results from Kaplan-Meier analysis with defined endpoints are shown in the figure. In the patients developing dissection, 11 out of 13 (85%) could theoretically have been prevented by application of the current guidelines. 5-Year survival following emergency and prophylactic repair of the aortic root was 51% and 97%, respectively.



Conclusions: Survival in the Marfan syndrome in the past 14 years seems satisfactory. By application of current guidelines, survival is probably even improved. This is, however, at the cost of even more surgical intervention, which seems already extensive at 36% in 10 years (figure).

1427 Cardiorespiratory exercise function after arterial switch operation for transposition of the great arteries

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In patients (pts) with Senning repair for transposition of the great arteries [TGA (Senning)] systemic (right) ventricular dysfunction has been documented. This has stimulated the development of arterial switch operation [TGA (switch)]. Only limited information is available about exercise function in pts with TGA (switch) since they only reach now the age at which formal exercise testing is feasible. The purpose of the present study was to compare cardiorespiratory exercise function in pts with TGA (switch) to pts with TGA (Senning) and normal controls (nl). 13 pts with TGA (switch) underwent exercise testing (age at testing: 8.4 ± 3.1 yrs). The pts were compared to a group of 29 pts with TGA (Senning) (age at testing: 10.3 ± 2.5 yrs) and to a group op 13 nl of comparable age (8.8 ± 4.3). Exercise testing was perfomed on a treadmill and gas exchange was measured on a breath-by-breath basis with a mass spectrometer. Cardiorespiratory exercise function was assessed by determination of the steepness of the slope of VO_2 vs exercise intensity (SVO_2) and determination of the ventilatory anaerobic threshold (VAT, V-slope method).

Results:

Patients	N	VAT (ml O_2/min/kg$^{-2/3}$)	VAT (%NL)	SVO_2
TGA (Senning)	29	74.9 ± 12.7*	70.9 ± 12.0*	1.50 ± 0.64*
TGA (switch)	13	94.7 ± 9.8	90.0 ± 9.4	1.96 ± 0.49*
NL	13	105.5 ± 17.3		2.45 ± 0.40

*$p < 0.05$ compared with normals

In conclusion, from a functional point of view, cardiorespiratory exercise function in TGA (switch) is at or only slightly below the lower limit of normal, as compared to pts with TGA (Senning) where the lowest values for cardiorespiratory exercise function were observed.

1428 Acute effect of pulmonary artery banding on right ventricular pressure-volume relationship: relevance to the arterial switch operation

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Background: Preparation of the low pressure, thin-wall morphological left ventricle in transposition of great arteries is achieved by imposing acute pressure overload with pulmonary artery banding (first stage of the two-stage arterial switch operation). Changes in the pressure-volume relations of low-pressure ventricles to such a load have not been documented. We report the functional response of the right ventricles of young sheep to acute pressure overload, using the combined micromanometer-conductance technique.

Methods: 6 Dorset Down sheep (Wt.18.08 ± 1.02 kg, age 3 months) were studied. Surgical access was achieved via a left thoracotomy and the pericardium was opened. Right ventricular function measurements before and half an hour after pulmonary artery banding were obtained using a combined micromanometer-conductance catheter inserted into the right ventricle just below the pulmonary valve. Band tightness was adjusted so as not to allow the left ventricular systolic pressure to fall below 55 mmHg. Further tightening of the band resulted in severe bradycardia and rapid decrease in arterial pressure, which regressed when the band was released. End-systolic (ESPVR) pressure-volume relationships were obtained employing inferior vena cava occlusion. The ESPVR was fitted to a linear function to obtain the slope (Ees) and the volume intercept at 16 mmHg (V16).

Results: Pulmonary artery banding increased the mean ratio between the right ventricular and left ventricular systolic pressure from 0.35 ± 0.02 to 0.63 ± 0.04, $p < 0.05$ (Mean ± SEM). Acute pressure overload to the right ventricle produced no significant changes in heart rate, end-systolic volume and the ejection fraction of the right ventricle. However, there was a significant increase in the end diastolic volume (11.25 ± 1.07 to 13.54 ± 1.44, $p < 0.05$), stroke volume (4.25 ± 0.45 to 6.19 ± 0.78, $p < 0.05$), cardiac output (533.32 ± 72.82 to 771.14 ± 112.11, $p < 0.05$) and Ees (4.19 ± 0.95 to 10.24 ± 4.48,$p < 0.05$). Post banding V16 was significantly reduced (7.34 ± 0.66 to 5.11 ± 0.64, $p < 0.05$).

Conclusion: This first documentation of the pressure-volume relations of the thin-wall, low-pressure right ventricle of young sheep to acute pressure loading showed evidence of an intact Frank-Starling mechanism and an apparent improvement in the contractile state of the right ventricle half an hour after pulmonary artery banding. The reason for this "improved contractility" is unclear and requires further evaluation. Possible mechanisms include neuro-humoral activation and ventricular-interdependence via the interventricular septum.

EMERGING CONCEPTS IN NEUROHORMONAL MODULATION

1437 Blunted cGMP production in adult ventricular cardiomyocytes in heart failure

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Blunted cGMP production in adult ventricular cardiomyocytes in heart failure

Background: The existence of specific cardiac receptors for natriuretic peptides (NPR) has been reported. The specific ligands of the NPR-A and NPR-B subtypes are atrial natriuretic peptide (ANP) or C-type natriuretic peptide (CNP), respectively. Both NPR-A and -B possess an intrinsic guanylate cyclase moiety. The function and regulation of cardiac NPR in heart failure is unknown.

Methods: Heart failure was induced in Wistar rats by an aortocaval shunt, which was created by 1.8 mm needle. Sham- operated animals were used as controls. After 28 days ventricular cardiomyocytes were prepared by collagenase digestion. To decrease the number of non-cardiomyocytes, cells were pre-plated and only the cells which adhered to the cell culture wells were studied. cGMP production was stimulated by ANP and CNP and cGMP was determined by RIA.

Results: cGMP in adult ventricular cardiomyocytes from controls increased, after stimulation with ANP and CNP (10^{-9} to 10^{-6} M peptide) in a dose-dependent fashion. The CNP induced cGMP production increased to the same extent in cells isolated from heart failure rats, compared to controls. In contrast, cGMP production in response to ANP (10^{-9} to 10^{-6} M) was blunted in heart failure rats (at 10^{-9} M ANP from 25 ± 6 fmol/300000 cells to 8.6 ± 2 fmol/300000 cells, $p < 0.05$; 10^{-8} M: 18 ± 5 to 7 ± 1, $p < 0.05$; 10^{-7} M: 25 ± 5 to 14 ± 2 $p < 0.05$; 10^{-6} M: 42 ± 9 to 17 ± 3 $p < 0.01$ control vs heart failure).

In conclusion: Based on the specifity of ANP and CNP to their specific natriuretic peptide receptors these data indicate that functional NPR-A and NPR-B receptors are present on ventricular cardiac myocytes. The blunted cGMP response of cardiomyocytes of rats with heart failure to ANP suggests a selective desensitization of the NPR-A receptor subtype in heart failure.

1438 N-terminal proBNP as a marker of left ventricular dysfunction: the influence of heart failure treatment

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N-Terminal proBNP(NT) may provide a more sensitive index of the presence of LVD than BNP in CHF. It has been suggested that the value of the assay may be reduced in treated populations. The aim of this study was to compare the relationship between plasma NT and LV function in treated and untreated patients within a population undergoing echo-cardiography.

Methods: We studied 243 patients (129 Male, mean age 70 yrs, range 20–94). Echocardiographic LV function was assessed using a 9-segment wall motion index (WMI). NT levels were established by immunoluminometric assay with in-house antibody to the human N-terminal proBNP and blind to WMI. The relationship between WMI and a variety of clinical and laboratory variables was examined, comparing patients treated (ACE inhibitor, diuretic or both) or untreated for heart failure.

Results: 132 (54%) patients were treated with ACEI or diuretic (48 both, 69 diuretic alone, 15 ACEI alone). Those treated were older (74 ± 10 yrs) than those untreated (66 ± 17)($p < 0.0005$). There was a strong correlation between NT (NR < 200 pmol/L) and WMI in treated ($r = -0.661, p < 0.005$) and untreated ($r = -0.587, p < 0.005$) patients. NT levels (pmol/L; Median, IQ Range) were similar in untreated (368, 225–536) compared to treated patients (355, 225–509), those receiving ACEI alone (382, 190–664), diuretic alone (398, 229–498) or both (332, 225–513)($p = 0.981$, Kruskal-Wallis). WMI did not differ among groups ($p = 0.10$). On multiple regression analysis, independent predictors of WMI in treated patients were NT ($p < 0.005$), Age ($p < 0.005$), ACEI use ($p = 0.017$), diuretic use ($p = 0.039$). In untreated patients only NT ($p < 0.005$) and mitral regurgitation ($p = 0.01$) independently predicted WMI.

Conclusions: Plasma NT remains elevated in patients treated with ACEI and/or diuretics. NT is a strong predictor of reduced WMI in treated and untreated patients. Further studies are required to explore the effect of initiation of treatment on plasma NT levels.

1439 Elevated plasma cardiotrophin-1 in patients with left ventricular systolic dysfunction

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Cardiotrophin-1 (CT-1), a member of the interleukin-6 related cytokines that act via the gp130 signalling pathway, may be involved in the process of ventricular remodelling and has been shown to stimulate the assembly of sarcomeric units in series in cardiomyocytes. We hypothesized that CT-1 is increased in left ventricular systolic dysfunction (LSVD).

Method: A competitive immunoluminometric assay using a methyl acridinium ester to label the peptide and an in-house polyclonal antibody to amino acids 105–120 of the CT-1 sequence was developed. We measured CT-1 in 100 patients who were referred for an echocardiogram. All patients with creatinine > 130 mmol/l or a significant valvular lesion were excluded. Sixty two patients (28 male, median age 64 yrs [20–85]) had a WMI of 2 = Group 1. Fifteen patients (11 male, median age 71 yrs [56–85]) had a WMI between 1.9–1.3 = Group 2. Twenty three patients (15 male, median age 67 yrs [43–87]) had a WMI of or = 1.2 = Group 3. Results are expressed as medians (ranges) fmol/ml.

Results: CT-1 levels were 53.9 [18.2–120.8], 48.8 [21.7–99.6] and 75.5 [31.4–130.6] in groups 1, 2, and 3. [Normal range for CT-1 is <40]. Mean log CT-1 differed amongst groups 1–3 ($p = 0.01$) and between groups 1&3($p < 0.005$) and groups 2&3($p = 0.01$) only.

Conclusion: This is the first demonstration of significant elevation of plasma CT-1 in patients with LVSD. The exact role of CT-1 in LVSD and ventricular remodelling remains to be determined.

1440 Powerful vasodilator effect of adrenomedullin in human resistance arteries is preserved in chronic heart failure

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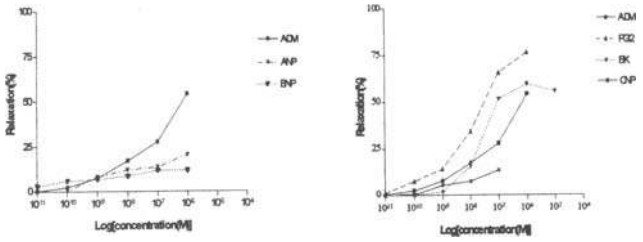
Background: Adrenomedullin (ADM) may be an important endogenous vasodilator though its potency compared to other vasoactive substances is unknown in human vessels. ADM is of particular interest in chronic heart failure (CHF) where plasma blood concentrations are elevated. We have compared the potency of ADM with circulating and locally acting vasodilators in systemic resistance arteries from patients with CHF and controls without CHF.

Methods: Arteries were obtained from gluteal biopsies from 13 patients with CHF and 10 patients with coronary heart disease but preserved left ventricular systolic function and studied using wire myography.

Results: ADM is a more potent vasodilator than the circulating atrial (ANP; $p = 0.03$) and brain natriuretic peptides (BNP; $p = 0.008$).



ADM was similar in potency to the locally acting agents prostacyclin (PGI_2) and bradykinin (BK). There was a trend towards greater potency than C type natriuretic peptide (CNP; $p = 0.06$). ADM was similar in potency when compared to the acetylcholine (ACh) and SNP. Quantitatively and qualitatively similar results were found in the control patients.

Conclusion: ADM is a powerful vasodilator in human resistance arteries and its action is preserved in CHF despite chronically elevated plasma concentrations.

1441 Omapatrilat, a vasopeptidase inhibitor, produces long-term beneficial haemodynamic and neurohormonal effects in heart failure

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Omapatrilat, a novel vasopeptidase inhibitor, is a single molecule that simultaneously inhibits neutral endopeptidase (NEP) and ACE. This study assessed dose-related effects of omapatrilat added to background therapy in patients (pts) with heart failure (HF).

Methods: This randomized, double-blind, multicenter study included 369 pts with HF: NYHA Class II–IV, EF ≤ 40%, PCWP ≥ 15 mm Hg, and cardiac index (CI) ≤ 3.0 L/min/m^2. Serial hemodynamic measurements were made at baseline, on day 1, and after 12 wk of once-daily omapatrilat therapy with 2.5, 5, or 10 mg (first 190 pts, Panel 1) or 2.5, 20, or 40 mg (last 179 pts, Panel 2).

Results: The table shows mean changes from baseline in PCWP, SBP, HR (bpm), CI, and systemic vascular resistance (SVR; dynes·sec/cm^5) measured 4 hr after dosing at wk 12.

	Panel I			Panel 2		
	2.5 mg	5 mg	10 mg	2.5 mg	20 mg	40 mg
PCWP	−6.0	−7.2	−8.4	−4.4	−7.8*	−8.0*
SBP	−12.2	−7.8	−14.7	−5.1	−13.3*	−11.7*
HR	−1.5	−3.1	−2.6	−1.1	−3.7	−6.2
CI	−0.04	+0.02	+0.13	+0.12	+0.20	+0.13
SVR	−84	−34	−253	−118	−190	−232

(*$p < 0.05$ vs 2.5 mg, a dose primarily inhibiting ACE)

In Panel 2 patients, EF increased 2.3% (2.5 mg), 2.5% (20 mg), and 4.9% (40 mg), and the incidence of death, hospitalization for HF, or cointervention for HF was 34% (2.5 mg) and 19% (40 mg). In a substudy, NEP inhibition was evident at wk 12 by dose-related increases (vs trough) of 1% (2.5 mg), 38% (20 mg), and 91% (40 mg) in mean plasma levels of atrial natriuretic peptide 3 hr after dosing.

In conclusion, omapatrilat produces dose-related beneficial hemodynamic effects in HF. Neurohormonal effects consistent with NEP inhibition are observed at higher doses of omapatrilat.

PROGNOSTIC EVALUATION IN HEART FAILURE

1442 Mortality trends in 86,000 patients admitted with heart failure, 1981–1995

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Background: Heart failure is associated with a high morbidity and mortality that result in a significant clinical burden. Prognosis is related to the severity of left ventricular dysfunction and New York Heart Association criteria. Large clinical trials have shown significant benefits from ACE inhibitor therapy. It is however unclear whether these benefits extend to the general population and whether they have contributed to a reduction in case-fatality.

Methods: The Scottish Morbidity Record Database holds comprehensive high quality data linking all 86,336 heart failure patients admitted in Scotland (population 5.1 million) since 1981, and all 71,017 subsequent heart failure deaths. This Scottish-wide-based retrospective cohort study calculated case-fatality to 10 years, with logistic regression and Cox modelling for the effects of age, sex, socio-economic deprivation, prior morbidity and year of treatment.

Results: Overall case-fatality following hospital admission with heart failure was 21%, 46% and 78% at one month, one year and five years respectively. Cox modelling and logistic regression identified statistically significant independent prognostic factors. Thirty day mortality increased with a) each decade of age, and b) with any prior morbidity.

After adjustment for age, sex, deprivation and prior morbidity, short-term (1 month) case-fatality rates fell significantly between 1981 and 1995, by 36% in men and by 20% in women. Adjusted case fatality rates at 1–5 years fell by approximately 30% in men and 10–15% in women.

Conclusions: There was a striking increase in survival amongst patients hospitalised with heart failure in Scotland between 1981–1995. This improvement in prognosis may be due to the wider use of ACE inhibitors in patients with heart failure during the period of study.

1443 Long-term prognostic value of FDG SPECT in patients with ischaemic left ventricular dysfunction

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FDG SPECT has been used to predict improvement of function post-revascularization (REV) in patients with ischemic LV dysfunction. The current study evaluated its long-term prognostic value.

Methods: 135 patients with advanced coronary artery disease and depressed LV function (LVEF 37 ± 11%) were studied with FDG SPECT and early thallium-201 SPECT (to assess perfusion). Data were analyzed using polar maps (13-segment model). Resting function was assessed by 2D-echo. Dysfunctional segments showing normal perfusion or mismatch pattern were considered viable. Patients were classified viable when ≥ 3 dysfunctional segments were viable (this cutoff criterium was derived by previous ROC curve analysis). Fifty-eight patients underwent successful REV, while 77 patients were treated medically (MED). Follow-up was performed by chart review or telephone contact. Only hard events were considered (cardiac death or non-fatal myocardial infarction).

Results: The mean duration of follow-up was 28 ± 11 months. A total of 28 events occurred in 28 patients. The highest event-rate was observed in viable patients (n = 30) who were treated MED: 60% ($P < 0.05$ vs other groups). Viable patients (n = 26) undergoing REV had the lowest event-rate (4%). An intermediate event-rate was observed in nonviable patients treated MED or undergoing REV (9% and 16% respectively).

Conclusions: The results indicate that FDG SPECT (similar to FDG PET) identifies patients with a high risk for future events; patients with substantial viability who are treated conservatively had a significantly higher event-rate as compared to the other groups.

1444 Ventilatory response to exercise but not peak oxygen consumption predicts death in chronic heart failure patients with preserved exercise tolerance

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In chronic heart failure (CHF) the assessment of exercise capacity remains a gold standard in risk stratification. Peak oxygen consumption (peak VO_2) and ventilatory response to exercise (measured as the regression slope relating minute ventilation to carbon dioxide [VE/VCO_2-slope]) are both independent indices used for prognostic purposes in pts with symptomatic CHF. Whether these two exercise testing derived measures would provide a relevant prognostic information in less symptomatic CHF pts with only mild exercise intolerance has never been investigated. This study sought to assess the short (6-month) and long-term (2-year) prognostic power of peak VO_2 and VE/VCO_2-slope in this group. Among consecutive 324 CHF pts who underwent exercise testing in our laboratory between January 1993 and December 1997 we identified 132 pts (41%) with preserved exercise capacity, as evidenced by peak $VO_2 \geq 18$ ml/kg/min (mean age: 56 y, LVEF: 30%; peak VO_2: 23.5 ml/kg/min, NYHA: 1.9). Using 2SD above the mean $VE\text{-}VCO_2$ slope of age-matched controls as cut-off we defined an abnormally high ventilatory response to exercise as a $VE\text{-}VCO_2$ slope of >34.

Results: During the mean follow-up of 40 months, 24 pts (18%) died. In Cox-univariate analysis peak VO_2 was neither a significant predictor of short-term (p = 0.9) nor long-term survival (p = 0.8). On the contrary, VE/VCO_2-slope predicted short-term (p = 0.0009) and long-term mortality (p = 0.002) in pts with preserved exercise capacity. Forty-three (33%) pts who demonstrated a high ventilatory response to exercise had a worse outcome compared to pts with normal ventilatory response (table).

	High VE/VCO_2 (n = 43)	Normal VE/VCO_2 (n = 89)	p
6-month survival	88% (CI: 79–98%)	98% (CI: 95–100%)	0.025
2-year survival	72% (CI: 56–87%)	93% (CI: 87–99%)	0.002

p – log-rank test; CI – 95% confidence interval;

Conclusions: In CHF pts with preserved exercise tolerance, peak VO_2 provides no clinical information in risk stratification. In these pts, augmented ventilatory response to exercise allows to identify those at risk of a poorer outcome.

1445 Prognostic value of neurohormonal changes over time in chronic heart failure

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Neurohormones provide important prognostic information in chronic heart failure, but less is known about the rate of change of theses hormones over time and whether any changes of these hormones correlate with prognosis.

We studied 110 ambulatory heart failure patients still alive without cardiac transplantation at one year (54 ± 11 years, mean ejection fraction (EF) 28 ± 9%, NYHA functional class I to IV). Blood pressure, cardiothoracic ratio, echocardiographic left ventricular end diastolic diameter (EDD) and EF, plasma norepinephrine (NE), plasma atrial natriuretic peptide (ANP) and plasma endothelin-1 (ET1) were obtained from all patients at baseline (V0) and at one year (V1).

After a further follow-up of 474 days, 13 cardiovascular deaths occurred and 3 patients underwent an urgent cardiac transplantation (combined end point). In multivariate stepwise Cox analysis including the following parameters at one year (V1) and their changes from baseline (V1-V0): NYHA class, blood pressure, cardiothoracic ratio, echocardiographic EDD and EF, and neurohormonal parameters, only V1ANP (p = 0.0003), V1EDD (p = 0.007), V1ET1 (p = 0.004) and ANP changes (p = 0.007) were related to prognosis.

In patients with chronic heart failure, change of plasma ANP levels over time appeared to provide additional important prognostic information. Therefore it would be useful to repeat neurohormonal measurements in the management of chronic heart failure patients.

1446 Increased QT dispersion as a predictor of sudden death in postinfarction patients with severe congestive heart failure

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QT dispersion (d) from the 12-lead ECG has been introduced as a non-invasive index of d of ventricular repolarization and increased QTd has been associated with an adverse prognosis in various patient populations. Prognostic value of this parameter in postinfarction patients (pts) is discussed. We examined significance of QTd on intrahospital mortality prognosis in postinfarction pts (infarct age > 1 year) with severe (III–IV NYHA grade) congestive heart failure (CHF).

Methods: We retrospectively evaluated resting 12 lead ECGs from 86 survivors and 39 pts who died in hospital (19 sudden death, 20 death of CHF progression). Exclusion criteria were atrial fibrillation, bundle branch block, low amplitude of T-wave, age > 65 years, ejection fraction (EF) > 30%. All pts clinical investigation has included 12-lead standard ECG at paper speed 50 mm/s and amplifier gain of 10 mm/mv, chest radiography, two-dimensional echocardiography. These groups of pts were not significantly different for age, gender, NYHA grades, cardio-thoracic ratio, EF, left ventricular enddiastolic dimension. Measurements of QT and RR intervals were performed manually in a blinded fashion in respect of outcome data. Heart rate corrected QT (QTc) were calculated by Bazett's formula. Repolarization d was determined by the difference between maximum and minimum QT intervals in each ECG (QT-d, QTc-d). All data were expressed as M ± m.

Results:

	Survivors (n = 86)	Progressive CHF deaths (n = 20)	Sudden deaths (n = 19)
QT max (ms)	376 ± 7.4	367 ± 12.4	393 ± 10.4
QTc max (ms)	467 ± 7.7	480 ± 13.2	508 ± 8.5*
QT-d max (ms)	45 ± 3.2	50 ± 5.0	87 ± 5.2**
QTc-d max (ms)	57 ± 3.8	65 ± 5.3	105 ± 4.3**

* = $p < 0.01$; ** = $p < 0.001$ vs. survivors

QT-d and QTc-d did not depend on infarct localization (anterior or inferior). The prognosis was significantly worse in pts with QTc-d > 85 ms, with sensitivity 91.6% and specificity 94%. The four week treatment 64 pts with captopril (50 mg t.i.d.) resulted in decrease of QT-d and QTc-d (from 46 ± 4.1 to 36 ± 2.7 ms, $p < 0.05$, and from 60 ± 6.1 to 49 ± 3.2 ms, $p > 0.05$, respectively), but individual analysis showed that in 1/3 of pts repolarization d was slightly increased.

In conclusion, increased repolarization d is strongly associated with the occurrence of sudden cardiac death in postinfarction pts with CHF and may be useful for risk stratification of these pts.

1447 CA 12-5: a prognostic marker in heart failure?

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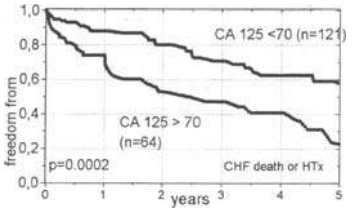
Background: We recently showed that blood levels of CA 12-5 correlate with clinical and hemodynamic parameters of heart failure (CHF) pts. This study should clarify the prognostic power of the oncofetal protein.

Methode: Prospective determination of serum levels of CA 12-5 (ELISA) in 185 CHF pts in the years 1993–1998 (40% NYHA II, 42% NYHA III, 18% NYHA IV, 49% iDCM, mean age 49 ± 9 years, mean EF 24 ± 8%). We compared survival (Kaplan-Meier) in two groups separated by a cut-off level of 70 U/ml = twofold normal (mean observation time 2.4 ± 1.9 years).

Results: CHF pts presenting with a CA 12-5 > 70 U/ml experienced significantly more pump failure death or heart transplants ($p = 0.0002$, CHI-Quadrat 13.9). Sudden death was not associated with elevated CA 12-5 serum levels.



Conclusions: Elevated CA 12-5 serum levels (possibly due to oncofetal gene activation) give prognostic informations in CHF pts.

ARTERIAL THROMBOSIS: UNDERLYING MECHANISMS

1457 Expression of platelet activation markers and monocyte Mac1 is increased in patients with chest pain but angiographically unobstructed coronary arteries

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Background: Activated circulating platelets and interactions of platelets with leukocytes play a central role in acute thrombotic events, but are also suspected to be involved in the development of microvascular disturbance as underlying coronary small vessel disease.

Methods: We investigated the extent of platelet (plt) activation and platelet-leukocyte aggregation (PLA) as well as expression of activation dependent adhesion receptor Mac1 on monocytes in 43 patients (20 female/23 male; age 56.0 ± 9.8) with chest pain and pathological stress test but angiographically unobstructed coronary arteries (microCAD) and 21 patients (5 female/16 male; age 61.5 ± 8.4) with angiographically documented coronary artery disease (macroCAD). Whole blood analysis of platelet degranulation markers P-selectin (CD62) and GP-53 (CD63), extent of platelet-bound fibrinogen (anti fibrinogen), of PLA, and expression of Mac1 (CD11b) was performed by 4-parameter flow cytometry. Results are expressed as an index of percent positive cells times mean fluorescence for surface markers and percentage leukocytes bound in aggregates for PLA.

Results:

	MicroCAD	MacroCAD	p
CD 62 (plt)	38.7 ± 17.2	27.9 ± 8.5	0.02
CD 63 (plt)	61.6 ± 30.8	41.7 ± 12.5	< 0.01
anti fibrinogen (plt)	1037 ± 267	947 ± 212	0.12
PLA (%)	2.8 ± 0.6	2.6 ± 0.9	0.10
Mac1 (monocytes)	2066 ± 981	1527 ± 822	0.04

Conclusion: The significantly higher expression of activation dependent platelet adhesion molecules (CD62/CD63) and activation dependent Mac1 on monocytes in patients with chest pain and pathological stress test despite absence of significant coronary stenoses may reflect underlying disturbances in coronary microcirculation (small vessel disease).

1458 Platelet glycoprotein IIb/IIIa inhibition with or without additional vitronectin receptor antagonism reduces thrombus accumulation and subsequent neointimal formation in a porcine angioplasty model

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Abciximab, an antibody to both IIb/IIIa and the vitronectin receptor (VNR) reduces thrombotic complications associated with PTCA and may reduce restenosis. We investigated the effect of lamifiban (a selective IIb/IIIa inhibitor) and G3580 (which inhibits both IIb/IIIa and VNR) on thrombus accumulation and neointima formation following PTCA.

Methods: Yorkshire White swine were given an iv bolus of lamifiban (0.2 mg/kg) G3580 (0.875–1.5 mg/kg) or saline, followed by a continuous infusion (lamifiban 0.12–0.21 mg/kg/hr, G3580 0.875–1.125 mg/kg/hr or saline). 15 min following the bolus, coronary angiography and oversized PTCA (1.3:1) to RCA and LAD were performed. The infusions adjusted aiming for 80% inhibition of platelet aggregation to 20 μM ADP and were continued for 6 hours (thrombus experiments) or 14 days (28 day neointima experiments). Thrombus formation and neointima were assessed using computerised morphometry at 6 hours and 28 days respectively

Results: 6 animals were used for the thrombus experiments (2 control, 2 lamifiban and 2 G3580). Mean (SEM) platelet aggregation (% baseline) during the infusions; Control 135 (11.5), lamifiban 1.6 (1.0) G3580 0.6 (0.4). 12 arteries were examined; 4 in each group. Mean % lumen obstruction by thrombus; Control 18.7 (4.7), lamifiban 6.4 (2.0) $p < 0.05$, G3580 7.9 (1.9) $p < 0.05$

22 animals were used for the neointima experiments (8 control, 7 lamifiban, 7 G3580). Mean (SEM) platelet aggregation (% baseline) during the infusions; Control 113.9 (2.6), lamifiban 15.9 (1.8) G3580 15.2 (1.7). 37 arteries were analysed (12 control, 13 lamifiban, 12 G3580). The mean (SEM) intimal area/medial area/injury scores were; Control 0.095 (0.027), lamifiban 0.038 (0.003) $p < 0.001$, G3580 0.048 (0.005) $p < 0.05$.

Conclusions: GP IIb/IIIa inhibition reduces thrombus accumulation following PTCA and this reduction is associated with a similar reduction in neointima. Additional effect against VNR does not appear to give additional benefit in either thrombus reduction or neointimal formation.

1459 Monocyte L-selectin down-regulation triggered by platelet-monocyte adhesion: a novel target to improve outcome following coronary intervention?

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Background: Monocyte activation induces pro-coagulant and pro-adhesive inflammatory responses and may play an important role in the thrombotic complications associated with coronary intervention. Platelet-Monocyte Adhesion (PMA) may trigger this. The aim of our study was to determine the level of local PMA during coronary intervention and to characterise its effects on monocyte activation status.

Method: PMA and monocyte activation status was prospectively examined in 30 patients undergoing left coronary system intervention (19 males, mean age 62). Coronary sinus and peripheral samples were obtained at baseline, post-first-inflation, immediately after intervention, and 24 hours later. For PMA, a novel technique was used. Blood samples were labelled with fluorochrome-conjugated monoclonal antibodies directed against CD14 (a monocyte specific marker) and GP1b (a platelet-specific marker). CD14-GP1b positive particles with the correct side scatter (granularity) profile were considered to be platelet-monocyte aggregates and were measured by flow cytometry. Monocyte activation status was assessed by determining the extent of L-selectin down-regulation.

Results: PMA increased significantly in coronary sinus samples immediately after the first balloon inflation (56.4 ± 7.6 vs 36.5 ± 3.3 at baseline, P = 0.014), but this was transient and levels returned to baseline immediately after angioplasty (33.2 ± 3.0 vs 36.5 ± 3.3 at baseline, P = NS). No increase was seen in peripheral samples (36.5 ± 3.3 (baseline) vs 36.2 ± 2.8 (after first inflation) vs 31.7 ± 3.0 (post procedure)). Monocyte activation (assessed by quantifying the degree of L-selectin mean channel fluorescence down-regulation)increased from a baseline level of 30.2 ± 2.5 to 29.3 ± 3 (P = NS) immediately after angioplasty to 20.9 ± 2.5 (P = 0.016 vs baseline) 24 hours later.

Conclusion: Our data suggest that PMA is transiently increased at the balloon injury site during angioplasty. This heterotypic platelet-monocyte interaction results in prolonged monocyte activation and may play an important role in the development of complications following coronary intervention.

1460 Thrombin generation and tissue factor activity of human coronary atherosclerotic plaques

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Tissue factor (TF) is the primary initiator of blood coagulation and its activity is higher in coronary plaques extracted from patients with unstable angina or myocardial infarction than in patients with stable angina. It is not known whether higher contents of TF are associated with higher procoagulant activity in vivo.

Methods: We measured intracoronary thrombin generation (prothrombin fragment 1 + 2; F1 + 2, nM/L) in 40 patients (22 stable angina, 18 unstable angina) undergoing directional coronary atherectomy (DCA). Intracoronary blood samples were collected proximally (Ao) and distally (Co) to the lesion, prior (pre) and after (post) DCA, a model for plaque disruption. TF activity of the extracted plaques was measured by means of factor Xa generation assay (mU/mg plaque weight).

Results: (median, interquartile range)

	Stable (N = 22)	Unstable (N = 18)	P
TF mU/mg	0.15 (0.08–0.25)	0.25 (0.18–0.42)	0.011
F1 + 2 preAo	0.95 (0.78–1.28)	1.16 (0.86–1.49)	NS
F1 + 2 preCo	1.0 (0.7–.17)	1.5 (1.15–2.07)	0.004
ΔF1 + 2 preCo-preAo	−0.06 (−0.22–0.15)	0.13 (−0.04–0.37)	0.002

There was a correlation between TF activity of the extracted plaques and thrombin generation measured after DCA (rho = 0.38; p = 0.018).

Conclusion: Tissue factor activity is increased in unstable coronary plaques and is associated with an increased local thrombin generation in vivo. During DCA-induced plaque disruption the intracoronary prothrombotic response is correlated with TF activity.

1461 Effects of recurrent thrombus formation on tissue factor expression in the arterial wall

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Tissue factor (TF), a membrane glycoprotein that activates the extrinsic coagulation pathway, is normally expressed at low levels in the media of blood vessels. We have previously demonstrated that recurrent thrombus formation upregulates TF in the media of stenotic rabbit carotid arteries with endothelial injury. The aim of the present study was to investigate whether this upregulation of TF is related to thrombus formation, vessel damage, or both. Cyclic flow variations (CFVs), due to recurrent thrombus formation, were induced in stenotic rabbit carotid arteries with endothelial injury. CFVs were observed for either 30, 120, 240, or 480 min in different groups of animals (n = 6 in each group). An additional group of animals (n = 6) was treated with hirudin (1 mg/kg) before inducing the damage to inhibit thrombus formation and observed for 480 min. At the end of the experiment, the carotid arteries were isolated, rinsed with saline, embedded in methyl methacrylate and quick-frozen in liquid nitrogen. Arterial sections (4 μm) were mounted on microscope slides and immunohistochemical staining for TF was performed using AP-1, a monoclonal antibody against rabbit TF, as primary antibody, and rabbit anti-mouse IgG conjugated with peroxidase, as secondary antibody. A semiquantitative score (from 0 to 3) was given to sections as follows: 0 = no positivity in the media; 1 = slight positivity in the media, but less than that observed in the adventitia; 2 = positivity in the media comparable to that of the adventitia; and, 3 = positivity in the media more pronounced than that of the adventitia. Scores were assigned by two different investigators who were blind as per group assignement. At least 15 arterial sections were evaluated per animal. Contralateral, undamaged carotid arteries without CFVs served as controls. An increase in TF expression was observed over time from 0 ± 0 in control vessels, to 0.8 ± 0.3, 1.3 ± 0.4, 1.8 ± 0.6*, and 2.2 ± 0.6*, at 30, 120, 240, and 480 min, respectively (* = $p < 0.05$). In contrast, in hirudin-pretreated animals, a very low level of TF expression was detected at 480 min after the damage (O.5 ± 0.3, p = ns). We conclude that: 1) A progressive increase in TF expression was observed in the media as CFVs progressed; 2) This increase in TF expression seems to be related only to recurrent thrombus formation, as TF was not upregulated in hirudin-pretreated animals, in which arterial damage was not accompanied by CFVs. These data demonstrate that thrombus-induced TF upregulation may contribute to sustain intravascular thrombus formation after the initial thrombogenic stimulus.

1462 Risk of myocardial infarction in association with the platelet collagen receptor GPIa C807T dimorphism

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Aim: The formation of platelet rich thrombi following rupture of atherosclerotic plaque is the primary adhesive event leading to the formation of occlusive thrombus and subsequently to acute myocardial infarction (MI). The platelet collagen receptor, GPIa/IIa, is an important mediator of platelet adhesion. Variation in GPIa/IIa receptor density correlates with functional differences in platelet adhesiveness to fibrillar collagens and is associated with a silent dimorphism at nucleotide C807T of the GPIa cDNA. The aim of this study was to investigate the relationship of the GPIa C807T dimorphism to the risk of MI.

Methods: 1053 subjects were studied (546 patients with acute MI recruited consecutively from the hospital coronary care units and 507 population-based controls). The TaqMan allelic discrimination system was used to determine the GPIa C807T genotypes. All subjects were white Caucasians aged under 75 years

Results: In the overall cohort, the frequency of the 807T allele (which was associated with increased receptor density) was 0.4 (95% C.I. 0.37–0.43) in the case group compared to 0.43 (95% CI 0.40–0.46) in the control group. This gave an odds ratio for MI of 0.88 (95% CI 0.74–1.05, p = 0.17). There was no difference in the genotype distributions between cases (TT 17%, CT 46%, and CC 37%) and controls (TT 19%, CT 48%, and CC 33%, p = 0.22 for TT; p = 0.24 for CT). There was no increase in prevalence of the 807TT or 807CT genotype after stratification for age or sex. Similarly, restriction of the analysis to low risk subgroups comprised of women only, normotensive subjects or subjects with a cholesterol or BMI below the group medians failed to show an increased risk of MI

Conclusion: This case-control study did not demonstrate an association between the GPIaC807T dimorphism and risk of MI. This would suggest that the variation in the GPIa/IIa receptor density and the differences in adhesiveness of platelets to fibrillar collagens associated with the C807T dimorphism do not contribute to an increased coronary arterial thrombotic risk.

CORONARY INTERVENTION FOR UNSTABLE ANGINA

1463 Role of enoxaparin in patients undergoing percutaneous revascularization in the setting of unstable angina. A TIMI 11B substudy

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Percutaneous revascularization (PTCI) in patients (Pts) with unstable angina (UA) is associated with ischemic complications. Recently, enoxaparin (ENOX) has been approved and adopted in many centers as the treatment for Pts with UA. The TIMI 11B trial randomized 3910 Pts with UA/NonQwMI to test the hypothesis that ENOX is superior to unfractionated heparin (UFH). A subset of 784 Pts (20%), after being pre-treated with either UFH or ENOX, underwent PTCI, and represent the subject of this substudy (403 randomized to UFH and 381 to ENOX); 2600 patients received only medical therapy (No PTCI or CABG). The aim of this substudy was to compare the efficacy and safety of a strategy of ENOX prior to and after PTCI versus UFH prior to PTCI. All Pts were treated with open label UFH during the PTCI. Clinical baseline characteristics were similar in the two treatment groups. Approximately 80% of Pts in each group had ECG changes and 45% had elevated serum cardiac markers. The admitting diagnosis was similar in the two groups (56% UA, 40% NonQwMI, 4% QwMI).

Outcome at 43 days

	UFH	ENOX	OR	CI
PTCI Pts	N = 403	N = 381		
Successful	359 (89%)	351 (92%)	1.43	(0.88–2.4)
Death (D)	11 (2.7%)	8 (2.1%)	0.76	(0.30–1.9)
MI	21 (5.2%)	15 (3.9%)	0.75	(0.38–1.47)
Urgent Revasc (UR)	14 (3.5%)	7 (1.9%)	0.52	(0.21–1.30)
Combined (D,MI,UR)	38 (9.4%)	27 (7.1%)	0.73	(0.44–1.23)
Major Bleeding	19 (4.7%)	18 (4.7%)	1	(0.52–1.94)
Medical Rx Only	N = 1286	N = 1314		
D, MI	86(6.7%)	77 (5.9%)	0.87	(0.63–1.19)
All Pts	N = 1957	N = 1953		
D,MI,UR	385 (20%)	337 (17%)	0.85	(0.72–1.00)

Conclusions: The benefit of ENOX was similar in patients who underwent PTCI and those who received only medical therapy. Pre-treatment with ENOX prior to PTCI is safe, appears to increase the success of the procedure, and tends to decrease the rate of ischemic complications. These results suggest a beneficial role for ENOX regardless of whether UA/NonQwMI Pts are managed with an early invasive or early conservative strategy.

1464 Optimal timing of percutaneous intervention in unstable angina

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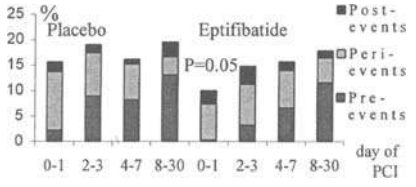
Background. Early PCI prevents recurrent and refractory ischemia and pre-procedural infarction in unstable angina and myocardial infarction without persistent ST-segment elevation (UAP). Both pre-and peri- (<48 hours after PCI) procedural death and myocardial infarction ("Pre" and "peri-events") rates change over time, the sum of both at different moments in time is unknown. In the PURSUIT database the effect of timing of PCI on pre-and peri-procedural (peri) events was documented for eptifibatide and placebo.

Methods. 9.461 patients with UAP were randomized to eptifibatide or placebo, given during 72 hours. Further treatment was left entirely to the investigators.

Results. 30 day pre, peri and post-procedural events in percentages, see graph: Deferring PCI in placebo patients lead to a decline in peri-events (10.8 to 3.6%, P = 0.006), while pre-events increased (2.2 to 13%, P = 0.001). Eptifibatide reduced high peri-events on day one (10.8 to 7.1% P < 0.05), with low pre-events. Over time, peri-events with eptifibatide remained nearly constant, but pre-events cumulated.



Events till day 30, without events after bypass surgery:

Amounts:	Placebo#P = 0.001				Eptifibatide			
Day PCI	0–1	2–3	4–7	8–30	0–1	2–3	4–7	8–30
Patients:	308	311	287	288	308	311	287	288
Pre-	7	28	27	40#	1	10	19	33#
Peri-	34	26	22	11#	22	25	21	14
Post	6	5	3	9	8	11	5	4

Conclusions. More peri- than pre-procedural events were reduced with eptifibatide, therefore PCI on day one demonstrated highest treatment benefit, as peri-procedural risk was reduced markedly and pre-events were still low.

1465 Long-term results of early coronary angioplasty in unstable angina compared with delayed coronary angioplasty

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In unstable angina, the time when angioplasty must be carried out is still discussed. In some cases, a conservative approach to achieve stabilization by medical treatment seems preferable to early invasive strategy. The aim of this study is to assess the immediate and long-term results after early and delayed coronary angioplasty in patients with unstable angina.

Methods: Between January and December 1996, 499 patients were admitted for unstable angina. 170 consecutive patients were eligible for coronary angioplasty of the culprit lesion. They were separated in two groups depending on the duration of conventional medical treatment before the invasive procedure: less than 48 hrs (91 patients, group A) and more than 48 hrs (79 patients, group B).

Results: Group B included more women (35% vs 15%; $p < 0.002$) and the patients were older (67.6 ± 9.5 yrs vs 62.5 ± 11.2 yrs; $p < 0.005$). Other clinical data, angiographic and procedural characteristics were similar in the two groups. Stenting was performed in 82% of the patients in group A and 86% in group B (NS). The immediate success rate was identical (93% in group A vs 95% in group B; NS). In-hospital stay was shorter in group A (2.9 ± 1.1 days vs 8.5 ± 3.6 days; $p < 0.00001$). The clinical outcome at 10.9 ± 6 months in group A and 10.2 ± 6.5 months in group B (NS) was available for all patients. Long-term clinical success rate (asymptomatic patients or with stable angina) was not different between the two groups (91% in group A vs 86% in group B; NS). Recurrent unstable angina during follow-up occurs more frequently in group B ($p = 0.02$).

Conclusion: These results suggest that early coronary angioplasty in unstable angina is a safe and effective strategy with a shorter hospital stay. The excellent long-term outcome after early coronary angioplasty has to be confirmed in a randomized study.

1466 Comparison of early invasive versus early medical management of acute coronary syndromes: a meta-analysis

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Background: One critical controversy in cardiology today is the use of early invasive versus medical management of acute coronary syndromes (ACS). While aggressive management may provide long-term clinical benefits over pharmacologic therapy in some patients, it is unclear whether the risks outweigh the benefits. This meta-analysis was conducted to asses the appropriateness of early invasive versus early medical management of ACS.

Methods: A meta-analysis was conducted of all randomized, placebo-controlled, double-blind clinical trials published from January 1988 to June 1998 of aspirin and/or heparin, glycoprotein IIb/IIIa blockers, and invasive procedures (thrombolysis, coronary angioplasty, coronary bypass surgery) administered within 24 hours to patients presenting with unstable angina or non-Q-wave infarction.

Results: Early invasive management resulted in significantly greater reduction in mortality (−8.5, 95% CI −2.25, −14.75 versus −3.5, 95% CI 2.61, −4.39). Early medical intervention resulted in significantly reduced need for subsequent revascularization (−6.8, 95% CI −2.61, −10.99 versus −0.51, 95% CI −6.02, 5.00) and the combined endpoint of reduced mortality and infarction (−14.62, 95% CI −8.36, −20.87 versus −11.08, 95% CI −22.35, 0.20).

Conclusion: Early invasive procedures for ACS should be reserved for patients at high-risk of mortality and subsequent cardiovascular events. In patients without evidence of high risk, early medical management appears to be sufficient in reducing the need for subsequent revascularization, and reducing the combined endpoint of mortality and infarction when compared to early invasive management.

1467 Early invasive versus early non-invasive strategy in the setting of long-term versus a short-term treatment with s.c. low-molecular-weight heparin in unstable coronary artery disease: a randomised trial with one year follow-up

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There is little evidence from randomised studies to support a policy of early invasive procedures in UCAD without incapacitating symptoms or severe ischemia. Both invasive procedures and antithrombotic treatment have been considerably improved. Thus, there is an urgent need for randomised studies of an early invasive versus an early noninvasive strategy in the settings of different modern antithrombotic treatment alternatives in unstable CAD.

Design: 2456 patients with chest pain and signs of ischemia (ST-depression, T-wave inversion or elevation of cardiac markers) were randomised to a direct invasive strategy (n = 1220) with coronary angiograms and, if appropriate, early revascularisation within the first 7 days or to a noninvasive approach (n = 1236) with invasive procedures only at incapacitating symptoms or severe ischemia at exercise testing. All received aspirin and s.c. lmw heparin (dalteparin) 120 IU/kg b.d for 5 – 7 days and thereafter randomisation to 3 months of s.c. dalteparin or placebo twice daily. Endpoints were death or MI, new revascularisation, symptoms and readmission at 6 and 12 months.

Results There were only minor differences in base-line characteristics. In the invasive group 78% had a revascularisation procedure which in 91% was performed within the first 10 days. In the non-invasive group 38% had a coronary procedure and only 24% of these were performed within the first 10 days. At 6 months the mortality was 2.4% and death + MI 10.6%. The 6 and 12 months end-points in the randomised groups and in subgroups based on short- or long term dalteparin, gender, ECG changes and biochemical cardiac markers obtained in all patients at admission will be presented.

Conclusion: The present study is the first large scale trial randomising patients with UCAD to an early invasive versus an early conservative approach on a background of two alternatives of modern antithrombotic treatment, i.e. short-versus long-term s.c.lmw heparin. The one year results of these alternative strategies will have a large impact on short and long-term management and tailoring of treatment for patients with unstable coronary syndromes.

1468 Invasive versus conservative Treatment of Refractory Unstable Coronary Syndromes (TRUCS study) in geographically isolated areas without cardiac surgery: in-hospital, 30-day events and preliminary follow-up

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The Treament of Refractory Unstable Coronary Syndromes (TRUCS) study is a randomized clinical trial to compare invasive vs medical management of unstable angina (UA) in patients with refractory symptoms in isolated areas without surgical backup.

Methods: Patients with refractory UA (recurrent angina ± ECG changes) were randomised according to the date of admission to Group A (invasive approach-odd dates) and Group B (conservative approach-even dates). Group A patients underwent urgent coronary angiography (CA) followed by revascularization if appropriate (PTCA in-house, CABG in a cardiac surgery center after emergency air ambulance transfer). Group B patients remained on medication and were dealt with invasively only if symptomatic for 5 days. Stabilization, duration of hospitalization, new non-fatal MI, mortality, combined outcome and readmission for UA and revascularization were compared on an intention to treat basis in hospital, at 30-days and 12 month median (8 ± 5 month, mean ± SD) follow-up.

Results: From Mar 1997–Oct 1998, 148/719 (21%) consecutive patients with UA had refractory symptoms (Group A: 76, Group B: 72, similar baseline characteristics). 40 (53%) Group A patients underwent PTCA, 19 (25%) were transferred for CABG and 17 (22%) continued medical treatment. 38 (53%) patients in Group B were managed invasively (CA) due to refractory UA [PTCA: 23 (60%), CABG: 4 (10%), left on medical treatment: 11 (30%)]. Outcomes (Group A vs Group B): a) In hospital: stabilization (96% vs 43%, $p < 0.001$), new non fatal MI (1.3% vs 4.1%, p = NS), mortality (1.3% vs 8.1%, p = NS) and combined outcome (mortality and new non fatal MI: 3.9% vs 12.1%, $p < 0.1$) and hospitalization (11.8 ± 6.3 vs 12.7 ± 8.0 days, p = NS). b) 30-days: new non-fatal MI (2.6% vs 4.1%, p = NS), mortality (2.6% vs 10.8%, $p < 0.1$) and combined outcome (5.3% vs 14.8%, $p < 0.1$). c) 12 month follow-up (median): non-fatal MI (5.2% vs 4.1%, p = NS), mortality (3.9% vs 10.8%, p = NS), combined outcome (9.2% vs 14.8%, p = NS) and readmission's for a) UA: (6.6% vs 9.7%, p = NS), b) PTCA: (11% vs 3%, p = NS) and c) CABG: (4% vs 13%, p = NS).

Conclusion: Invasive treatment of patients with refractory angina in remote areas without surgical backup results in significant stabilization and a reduction of major events in hospital, at 30 days and at 12 months (median) follow-up with fewer re-admissions for UA and CABG, at the cost of increased subsequent PTCA. Initial data suggest that immediate CA and on the spot PTCA or air transfer for urgent CABG should be the treatment of choice for patients with refractory UA under these circumstances.

REGIONAL FUNCTION BY DOPPLER TIME IMAGING

1469 Assessment of non-uniformity of transmural myocardial velocities by colour-coded Doppler tissue imaging: characterization of normal, ischaemic and stunned myocardium

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Transmural contractile performance is nonuniform across the different layers of myocardial walls. We evaluated the accuracy of color M-mode Doppler tissue imaging (DTI) to assess the transmural distribution of myocardial velocities and to quantify the severity of dysfunction induced by ischemia and reperfusion in the inner and outer myocardial layers.

Total brief occlusion of LAD was followed by reperfusion in 13 open-chest dogs. M-Mode DTI was performed from an epicardial short-axis view. We calculated mean systolic velocities (S, cm/sec) within endocardium (endo) and epicardium (epi) of the anterior wall (AW) and the subsequent velocity gradient between endo and epi (Gr). Myocardial blood flow (MBF, ml/min/g) was measured by the radioactive microsphere technique.

S were highly correlated with systolic shortening assessed by sonomicrometry provided by 2 pairs of microcrystals positionned in endo and epi of the AW ($p < 0.0001$). Sendo, Sepi and Gr significantly decreased during LAD occlusion. After 30 minutes of reperfusion, Sendo showed a greater improvement when compared to Sepi and Gr resumed although to a limited extent, indicative of stunning.

	Baseline	Occlusion	Reperfusion	p
S endo	4.9 ± 0.7	0.4 ± 0.1	2.6 ± 0.4	<0.0001
S epi	1.7 ± 0.4	0.2 ± 0.2	0.5 ± 0.2	<0.0001
Gr	3.2 ± 0.5	0.3 ± 0.1	2.1 ± 0.3	<0.0001
MBF	0.88 ± 0.05	0.12 ± 0.04	3.81 ± 0.93	<0.0001

DTI is an accurate method to assess the nonuniformity of transmural velocities. It is promising to quantify ischemia-induced myocardial alterations and to differentiate ischemic from stunned myocardium.

1470 Pulsed Doppler tissue imaging for assessment of myocardial viability

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Objective: To evaluate the value of pulsed Doppler Tissue Imaging (DTI) for quantitative assessment of myocardial viability.

Method: In 30 patients (58 ± 9 years) with prior myocardial infarction positron emission tomography (PET) and dobutamine echocardiography (DE) with additional pulsed DTI were performed to evaluate myocardial viability. Peak systolic myocardial velocities (PSMV) were measured for each segment at baseline and low-dose dobutamine stress (5–10 μg/kg/min.) by pulsed DTI. 364 segments with adequate pulsed DTI tracing were divided according to 2-D DE and according to PET findings into normal, viable and non-viable segments. Pulsed DTI results were correlated with 2-D DE and PET.

Results: Based on 2-D DE there were significant differences between normal, viable and non-viable segments in pulsed DTI findings.

	Normal (N = 241)	Viable (N = 55)	Non-viable (N = 68)	P
Low-dose PSMV (cm/s)	8.16 ± 2.53	6.86 ± 3.11	6.48 ± 2.51	<0.001
PSMV difference (cm/s)	2.72 ± 1.90	1.86 ± 2.15	0.99 ± 1.16	<0.001
% increase in PSMV	54 ± 39	38 ± 39	18 ± 20	<0.001

Based on PET findings % increase in PSMV was 54 ± 40, 24 ± 21 and 18 ± 23 (p ANOVA < 0.001) for normal, viable and non-viable segments, respectively.

Conclusion: Measurement of PSMV by pulsed DTI with low-dose DE is feasible and effective for the identification of regional myocardial function and is likely to complement the standard interpretation of low-dose stress echocardiography in myocardial viability from qualitative to quantitative analysis.

1471 Myocardial strain by Doppler echocardiography: a new method to measure regional myocardial function

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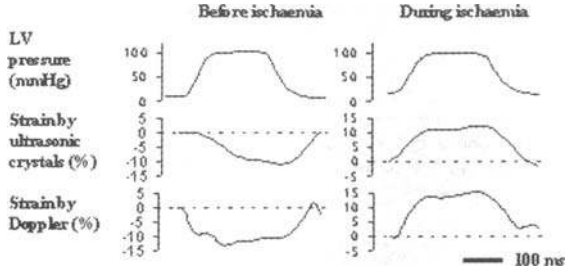
Myocardial strain derived from tissue Doppler velocities has been proposed as a new method to quantify regional LV function. We investigated whether this method reflects changes in myocardial function induced by myocardial ischaemia.

Methods: In 8 anesthetized dogs myocardial ultrasonic crystals were placed longitudinally in the LAD and the Cx regions and micromanometer in the LV. Measurements were done before and during LAD occlusion. Strain rate was calculated in real-time on apical images as differences in tissue velocity per unit length (1/sec). Strain was obtained by integrating strain rate over time. The strain estimates express percentage variations in longitudinal shortening.

Results: LV pressure-strain loops constructed from Doppler strain rate approximated loops constructed from sonomicrometry. Before ischaemia both loops moved counterclockwise and during ischaemia there was a clockwise rotation of the loops. Before ischaemia percentage systolic strain was -16 ± 1 ($\pm$ SEM) by sonomicrometry and -12 ± 1 (%) (ns) by the Doppler method, and during ischaemia 13 ± 2 and 11 ± 2 (%) (ns), respectively. Peak Doppler derived strain correlated with peak strain measured by sonomicrometry ($y = 0.80x - 1.75$, $r = 0.91$, $p < 0.01$). the figure shows a representative experiment and displays myocardial strain by Doppler along with myocardial segment lengths.



In conclusion, Doppler derived strain reflects myocardial ischaemia and may represent a new powerful tool for quantifying left ventricular function.

1472 Strain rate imaging can facilitate evaluation of left ventricular regional wall motion in patients with myocardial infarction: preliminary results

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Background: Color Doppler Tissue Imaging (CDTI) can evaluate regional systolic function of the left ventricle (LV) in ischemic heart disease but it is limited in discriminating passive from active movements of the ventricular walls. Strain Rate Imaging (SRI) is a new method of analysis of myocardial velocities designed to measure regional velocity gradients. Applied to apical views, SRI allows evaluation of in-plane longitudinal myocardial strain rate that can be used as an indirect and inverse estimate of local wall thickening, virtually unaffected by motion of adjacent segments and heart translation. In this study we applied SRI to the study of LV regional systolic function in comparison with conventional CDTI.

Methods: Five normal subjects (mean age 40 ± 8 years, 3 males) and 7 patients (mean age 58 ± 9 years, 5 males) with myocardial infarction and wall motion abnormalities who underwent a clinically indicated nuclear examination were studied. For each patient, the 3 standard apical views were acquired by using a Vingmed System 5 echo scanner in a high frame rate cineloop format and transferred to a computer. According to ASE 16-segments model, a total of 192 segments were available for analysis by SRI and CDTI. The pattern of LV wall motion over time by each technique was displayed as color coded images using a curved anatomic M-mode line passing through the LV walls from base to apex in each apical view. Regional systolic function was visually evaluated on the colored M-mode SRI and DTI images.

Results: In 169 normally perfused segments, SRI showed a normal pattern of motion in 96% (162/169) and CDTI in 94% (159/169). In 23 abnormally perfused segments, SRI showed an abnormal pattern of motion in 91% (21/23) and CDTI in only 69% (16/23) reflecting passive motion of tethered myocardial segments, including 5 infarct segments.

Conclusions: SRI improves evaluation of LV segmental wall motion compared with CDTI because it can identify segments that are moving passively but not thickening normally and therefore can assist evaluation of regional systolic function in ischemic heart disease.

1473 A tissue-Doppler based analysis of the longitudinal left ventricular shortening in patients with different forms of ECG bundle-branch blocks

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The importance of the longitudinal shortening with the systolic movement of the atrioventricular ring (AV plane) towards the apex and the largest movement in the lateral wall is well established as a nominator of cardiac function. Apart from M-mode measurements, the amplitudes of movements can today also be calculated from tissue Doppler based velocity measurements. This means that both velocities, the timing and the movement of the tissue can be measured. The present study was performed to establish reference values during different forms of ventricular electrical activation disturbances.

Methods: 10 normals, 10 patients with left bundle branch block (LBBB), 8 with right bundle branch block (RBBB) and 6 with left anterior hemiblock (LAH), all without known earlier myocardial infarction, were studied. The myocardial velocities during two consecutive beats were acquired on a GE-Vingmed System 5, and transferred to a computer for offline analysis including velocity profiles, integrated velocity and curved M-mode (C-Mode) analysis.

Results: The patients with LBBB had a significantly reduced average amplitude of AV plane movement (7.2 ± 2.2 mm), as compared to RBBB (10.4 ± 2.6 mm), LAH (10.9 ± 2.6 mm), and normals (11.3 ± 2.1 mm). Patients with LAH and normals had the highest amplitude in the lateral wall; RBBB and LBBB in the septal wall. In normals the highest systolic velocity was measured in the posterior wall, in LAH and RBBB in the lateral wall, and in LBBB in the anterior wall. The time delay between maximal velocities in the four locations was longer in LBBB (>110 ms) than in the other.

Conclusion: Electrical activation disturbances induce significant changes in both timing and amplitude of the AV-plane movement. The effect is most pronounced in patients with LBBB.

1474 The systolic descent of the mitral annulus in a large unselected population

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We have identified in a preliminary study left ventricular (LV) long axis shortening (LAS) and stroke volume as the main determinants of the systolic descent of the mitral annulus (DMA). We report the influence of underlying myocardial disease on DMA in a large (500 pts) unselected population, examined by a single operator, subdivided in: normal subjects (Norm, 114), ischemic heart disease (IHD, 146), hypertension with LV hypertrophy (Hyp, 70), dilated cardiomyopathy (DCM, 33), mitral prosthesis (MP, 32), aortic or mitral regurgitation (35), mixed (70). We measured DMA, indexed by BSA, at the 4- (DMA4m) and 2-chamber (DMA2m) mid- and 4-chamber lateral anulus (DMA4l). The independent determinants common to the three DMA indices in both the total population and normal subgroup were: LAS (positive coeff., $p < 0.001$), age (negative coeff., $p < 0.001$), indexed LV diastolic long axis (pos. coeff., $p < 0.001$), LV outflow tract integral (pos. coeff., $p < 0.01$), and presence of atrial fibrillation (neg. coeff., $p < 0.05$). All DAM indices correlated moderately with LV EF ($r = 0.37$ to 0.54, $p < 0.001$) but only in IHD and DCM. Compared to Norm, all DMA indices were similarly reduced, as LV EF, in the IHD, DCM and MP groups (see table). All DMA indices were reduced in MP with normal wall kinesis (MPn, 25), compared to age-matched Norm, and in IHD with (IHDa, 73) compared to without (IHDn, 73) wall diskynesis.

	LV EF	DMA4m	DMA4l	DMA2m	
Norm	66 ± 6	0.66 ± 1.7	0.74 ± 0.18	0.64 ± 0.18	
IHD	58 ± 13**	0.53 ± 0.15**	0.63 ± 0.18**	0.47 ± 0.15**	vs Norm
DCM	34 ± 12**	0.40 ± 0.13**	0.49 ± 0.15**	0.34 ± 0.17**	vs Norm
MP	58 ± 11*	0.50 ± 0.15*	0.61 ± 0.18*	0.52 ± 0.15*	vs Norm
MPn	62 ± 8*	0.55 ± 0.14*	0.64 ± 0.17*	0.57 ± 0.11*	vs Norm
IHDn	65 ± 8	0.57 ± 0.15	0.67 ± 0.17	0.53 ± 0.14	
IHDa	51 ± 12**	0.48 ± 0.15**	0.59 ± 0.18*	0.41 ± 0.14**	vs IHDn

In conclusion, the DMA is multifactorially determined by LAS, age, LV preload (diastolic long axis), and stroke volume. It is an index of LV systolic function distinct from EF, and easier to obtain. The DMA is independently reduced by atrial fibrillation, segmental wall abnormalities and presence of mitral valvular prosthesis, secondary to impairment of LV longitudinal fiber function.

MAGNETIC RESONANCE IMAGING AND ELECTRON-BEAM COMPUTED TOMOGRAPHY IN CORONARY ARTERY DISEASE

1475 Contrast-enhanced three-dimensional breath-hold magnetic resonance coronary angiography for detection of coronary artery stenosis

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Recently, magnetic resonance (MR) coronary angiography made feasible the visualization of coronary arteries by means of the application of T1-shortening contrast-agents and ultrashort gradient-echo sequences. Aim of this study was to evaluate a new, ultrafast Gadolinium-enhanced 3D breath-hold MR technique for detection of coronary artery stenoses in oblique projection angiograms.

Methods: MR investigation was performed in 35 patients with suspected or known coronary artery disease on a 1.5T scanner (VISION, Siemens AG). After visualization of the course of the main coronary arteries using contiguous cross-axial spin-echo images, MR coronary angiography was performed within one single breath-hold using an ultrafast contrast-enhanced 3D gradient-echo sequence (TR/TE 4.2/1.6, spatial resolution 1.25 × 1.25 × 1.5 mm^3). In sucessive studies, the imaging volume which consisted of 32 contiguous parallel sections was positioned along the course of right (RCA) and left circumflex (LCX) and along left main (LM) and left anterior descending (LAD) coronary arteries, respectively. During each measurement, 20 ml Gadolinium-DPTA (0.5 mol/l, MAGNEVIST, Schering AG) were applied intravenously according to the individually determined contrast transit time. Image data were evaluated by two independent observers. The results were compared with conventional contrast angiography in a blinded manner.

Results: 179 of 245 coronary segments (LM, proximal and mid segments of LAD, LCX and RCA) could be visualized (73.1%). In these, 35 of 43 significantly stenotic (>/= 50%) and 123 of 136 non-stenotic coronary segments could be exactly classified. Thus, the overall sensitivity and specifity for stenosis detection resulted in 81.4% and 90.4%, respectively.

In conclusion, using ultrafast Gadolinium-enhanced 3D breath-hold imaging, oblique projection MR coronary angiograms can be successfully performed in the majority of cases. However, sensitivity for detecting coronary stenoses is not yet sufficient and further techniqual improvements are mandatory to introduce this technique as a reliable diagnostic tool in clinical practice.

1476 Non-invasive coronary imaging: a comparison between magnetic resonance imaging and electron beam computed tomography

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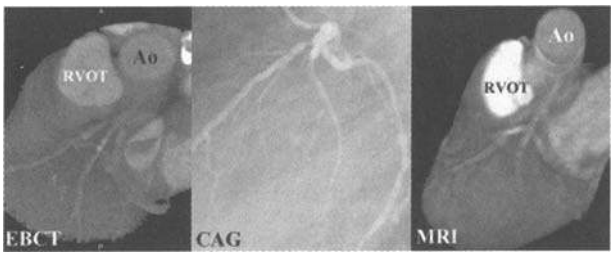
Background: Non-invasive coronary imaging with magnetic resonance imaging (MRI) and electron beam computed tomography (EBCT) are promising new techniques for the detection of coronary artery stenoses. A direct comparison in the detection of significant coronary artery stenosis between both techniques has not yet been performed.

Methods: 27 Patients were examined on the same day with a respiratory gated 3D-gradient echo MRI technique and an intravenous contrast enhanced EBCT technique. Conventional coronary angiography (CAG) was performed within 2 weeks of the non-invasive coronary angiograms. Proximal and mid segments of the RCA, LAD and CX were evaluated by a radiologist and cardiologist unaware of the results of the CAG.



Comparison between EBCT, CAG and MRI

Results: MRI visualized 139 (74%) of the coronary artery segments, EBCT visualized more, 155 (82%), segments with a diagnostic image quality. The parameters of diagnostic accuracy of both techniques for the detection of stenoses of >50% are listed in the table.

	Sensitivity	Specificity	PV+	PV−
MRI	54%	91%	58%	82%
EBCT	77%	95%	74%	96%

Respiratory motion artifacts occurred to the same extent in all three vessels during MR imaging, while in EBCT artifacts originated from non-breathholding, arrhythmias or movement of the RCA during the heart cycle.

Conclusion: MRI and EBCT enable non-invasive coronary angiography. With presently clinical available techniques EBCT is closer to clinical implementation.

1477 Magnetic resonance flow measurements after stent implantation allow the assessment of in-stent restenosis

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We have recently shown a close correlation between noninvasive coronary artery flow measurements with magnetic resonance and invasive flow measurements with Doppler flow wire using a new navigator corrected technique with high temporal resolution. This technique was used to assess flow velocities proximal and distal to coronary stents. In stented segments the coronary arteries cannot be non invasively visualised with magnetic resonance imaging.

Methods: In 64 patients the peak coronary blood flow velocity was determined non invasively within 24 hours and 3 months after stent implantation using a 1.5 Tesla MR tomograph (Philips Gyroscan NT). After localization of the coronary arteries and the stented segments flow measurements were performed proximal and distal of the stent using a flow sensitive gradient echo technique. Spatial resolution was 1 × 0.9 × 4 mm, temporal resolution 45 ms. Adaptive navigator motion correction was used to minimize breathing artifacts. Maximal flow velocity was measured and corrected for cardiac motion perpendicular to the imaging plane.

Results: In 43 patients it was possible to obtain an antegrade pulsatile flow signal distal to the stent. In 4 additional patients no proximal signal could be obtained, as the stent artifact overlapped the origin of the vessel. Non invasive determination of the maximal flow velocity yielded 19 ± 3 cm/s for the RCA, 23 ± 6 cm/s for the LAD and 21 ± 9 cm/s in the RCX proximal of the stent (distal: 18 ± 8 cm/s, 21 ± 7 cm/s, 18 ± 9 cm/s). After 3 months a significant decrease of maximal flow velocity was observed distal to the stent ($p < 0.05$) which correlated with in-stent luminal diameter reduction.

Conclusions: Magnetic resonance techniques allow the determination of coronary blood flow velocities after intracoronary stent implantation. An in-stent restenosis can be detected by a reduction of maximal diastolic flow velocity distal to the stent.

1478 Prospective diagnosis of coronary artery disease with magnetic resonance perfusion imaging

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Magnetic resonance (MR) perfusion measurements allow the determination of myocardial perfusion reserve (MPR). We evaluated prospectively the diagnostic accuracy of MPR by MR for the detection of significant coronary artery stenosis ≥ 75% (CAD) after the definition of a cut off value.

In 40 patients with coronary artery disease referred for angiography one short axis image per heart beat was acquired at the base of the papillary muscle with a turbo gradient echo technique (spatial resolution 1.7 × 1.9 × 8 mm, acquisition time 360 ms) using a 1.5 Tesla MR tomograph (Philips ACS NT). A central venous gadolinium DPTA bolus (0.025 mmol/kg body weight) was injected before and after dipyridamole injection (0.56 mg/kg body weight). The signal intensity (SI) curves of the left ventricle and 6 radial segments of the myocardium were obtained and linear fitting of the upslope was performed and corrected for the upslope of the left ventricular SI curve. MPR was calculated as the relative change of the steepness after dipyridamole in comparison to rest and was compared to angiographic results. If the increase of steepness was below 1.5 MPR was regarded as pathologic. This cut off value was previously defined in a different group of 15 patients with angiographically single CAD and 5 patients without CAD.

MPR showed a highly significant difference between ischemic and non ischemic segments (1.08 ± 0.23 and 2.33 ± 0.41, $p < 0.001$). The sensitivity, specificity and diagnostic accuracy for the detection of CAD were 93%, 89% and 91%, respectively. The linear fit of the upslope showed minimal intra- and interobserver variability ($r = 0.99$ and 0.96).

The determination of myocardial perfusion reserve from magnetic resonance first pass measurements is feasible and reproducible. This technique yields a high diagnostic accuracy for the detection of coronary artery disease in a prospective patient population.

1479 Magnetic resonance real time imaging of left ventricular function: comparison with conventional magnetic resonance techniques and echocardiography

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The development of new ultrafast gradient systems and improvements in software-applications make the aquisition of a complete image in 65 msec possible. Thus, functional cardiac images can be obtained in real time without breath holding or ECG-triggering.

In 21 patients left ventricular ejection fraction (EF), enddiastolic (EDV), endsystolic (ESV) volume and left ventricular muscle mass (LVM) were determined by magnetic resonance (MR) (ACS NT, 1.5T, Philips) from continuous short axis views covering the entire left ventricle with a standard turbo-gradient-echo (TFE), echo-planar-imaging (EPI) and a new real-time technique (RT). EF was additionally obtained by digital echocardiography (Echo) from longitudinal 4- and 2-chamber views using a modified Simpson's formula.

The results of RT technique correlated well with those of ECG-triggered TFE- and EPI-techniques. Differences between RT and TFE were 1.3 ml for EDV, 5.0 ml for ESV and 23.8 g for LVM. Differences between EPI and TFE were 3.9 ml for EDV, 0.9 ml for ESV and 2.6 g for LVM. The correlation and mean error for EF acquired with different techniques are listed in the table:

	Correlation	Mean error
Echo vs. TFE	0.84	25%
RT vs. TFE	0.93	12%
Echo vs. RT	0.86	7%

Using the new real time technique, scan time can be reduced considerably. A close correlation with echocardiography and conventional MR-techniques can be demonstrated. The mean error of 25% for Echo vs TFE can be explained by different approaches (complete cardiac volume with MR vs. geometric assumptions with Echo). MR real time imaging allows to acquire a 3d data set covering the entire heart in minimal measuring time without ECG-triggering. Thus it is feasible to examine patients with atrial fibrillation or frequent extrasystoles.

1480 Predictors of hard cardiac events in patients screened with electron-beam computed tomography

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The prognostic significance of coronary artery calcification (CAC) discovered on a screening Electron Beam-CT (EBCT) scan is the focus of much debate. Investigators have criticized the frequent pattern of patients self-referral for EBCT screening which carries inherent pre and post-test biases, damaging the epidemiological validity of the information collected. We investigated the occurrence of hard cardiac events (HE's = myocardial infarction and cardiac death) in asymptomatic patients referred by primary care physicians (PCP's) for a screening EBCT because of the presence of risk factors for coronary artery disease (CAD), to identify the best predictors of events.

Methods: Prospective follow-up (average of 32 ± 7 months) of 632 patients referred by PCP's for a screening EBCT. Traditional risk factors for CAD and severity of CAC, measured as a calcium score (CS), were employed in a multivariate logistic regression analysis to identify predictors of HE's. Absolute as well as age and gender adjusted percentiles of CS were used.

Results: The mean age of the 632 patients was 52 ± 9 years (range 35–70) and 340 patients (54%) had CAC on the screening EBCT scan. 27 patients suffered a HE and – of these – 26 patients (96%) had CAC. Strong predictors of HE's were smoking (OR = 2.99; CI 1.2–7.3) and CS > 75th percentile (OR = 2.5; CI 1.0–6.2). In contrast, a CS percentile in the lowest quartile (<25th%) portended a very low risk for HE (OR = 0.08; CI 0.01–0.66) independent of the presence of other risk factors for CAD. All other variables were not predictive of HE's.

Conclusions: CAC discovered on a screening EBCT in referred high-risk asymptomatic patients, offers important prognostic information for the occurrence of HE's even after a short follow-up time. Both smoking and high CS percentiles portend a high risk of HE; low CS percentiles identify patients at very low risk of events.

COMPUTER DEMONSTRATIONS

D1493 An integrated multi-centre angiography database and reporting system

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Current database systems for cathlabs often focus on the collection of data for audit purposes and rarely generate reports with enough detail and flexibility to replace the dictated or hand-written report. Furthermore, they are either stand-alone or tightly integrated with commercial solutions.

We developed a database system primarily to assist in the thorough and complete reporting of cathlab procedures, while still collecting data required for local and national auditing (i.e., demographics, risk factors, indications, presenting symptoms and outcome).

An object-orientated model of the coronary anatomy was written in Delphi 4. This model 'understands' the significance of coronary lesions in relation to the underlying anatomy. It scores disease severity by a traditional vessel count and using the Duke Coronary Artery Disease Index. The model allows considerable flexibility in the modification of the coronary anatomy by the user and visualisation of lesions and grafts through a highly graphical user interface. The full ACC/AHA classification of lesion morphology can be indicated, eliminating the need for free text.

The central database is stored at the referring hospital and data-entry performed at the tertiary referral centre. The system is integrated into each hospital's patient information system and the electronic patient record of the referring hospital. Data is transferred by e-mail via NHSnet after encryption with a secure Blowfish algorithm.

A complete report is generated for the case-notes as well as a letter to the general practitioner and any referral letter to the surgeon or interventional cardiologist. These reports and letters are written in natural English and stored as Word 97 documents, allowing the secretary to file them with all other letters and edit them if necessary.

This system eliminates the need to write or dictate cathlab reports. It provides immediate, detailed and flexible reports while gathering data required for audit and research purposes.

D1494 Software for documentation, automated result and report generation, medical and economical statistics, and quality control in the cardiac catheterisation laboratory

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In cooperation with the University of Oldenburg Software was created for Interventional Cardiology. Over the last decade further development of the existing product led to a stable and powerful program which is easy to use. Its main features are:

- Documentation of Left- and Right-Heart-Catheterisation, Coronary Interventions (PTCA, Stent, Atherectomy, Rotablation, etc.), Peripheral Angiography, and Angioplasty
- Automatic generation of results and reports based on standardized expressions without the need for dictation
- Storage and retrieval of up to eight still images per procedure
- Documentation of used materials and serial numbers of products with barcode scanners
- Calculation of all data for the national health system including ICD and ICPM
- Dataexport and statistics for quality control, as well as for medical and economical purposes
- Planning of operating dates for patients and generating letters of appointments for patients automatically
- Partially automated stock-management
- Integration into the documentation system for heart surgery and echocardiography and interfaces with other programs.

The version in operation is based on a client server architecture using ORACLE® 8 as database system. The frontend runs under Windows NT 4.0 and Windows 9x and has been developed with ORACLE®'s Developer 2000. The database contains more than 25,000 records of patients.

Conclusion: Over than 10 years of experience in the development of an information system have resulted in a stable and practical program which makes the task of documentation easier, faster and more reliable and allows doctors and nurses to concentrate on medical treatment. In a further development storage and retrieval of DICOM films are tested.

STENTING: TECHNICAL ASPECTS

P1495 A prospective randomised study of Angio-Seal versus FemoStop for femoral haemostasis after transcathater coronary intervention

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The regional complications related to femoral access site for various cardiovascular interventional procedures cause significant in-hospital morbidity and some times prolonged hospital stay. A number of haemostatic devices are used for closure of the access site and to achieve early ambulation after interventional procedures. We have prospectively compared 150 patients randomly assigned to external compression using the FemoStop or sealing with the Angio-Seal device. The Angio-Seal was immediately deployed in the catheter laboratory. Patients randomised to FemoStop, had their sheath removed when the activated clotting time (ACT) was less than 150 sec. The primary endpoint was the composite of the incidence of bleeding, haematoma, requirement for blood transfusion, and clinical indication for ultrasound examination at 2-hours and 24-hours after the procedure. There was no difference in age, gender, height, weight, and cardiovascular risk factor profile between two groups. 95% of the Angio-Seal and 96% of FemoStop patients were discharged the following day. A higher number of patients in the Angio-Seal group reached a clinical end-point within the first 2 hours (42.6% vs 4%; p = <0.0001). This difference became insignificant at 24-hours (12% vs 9.3%; p = 0.79). FemoStop patients noticed more often moderate to severe groin discomfort compared to Angio-Seal patients (33.3% vs 6.8%; p = 0.0005). 14.6% of Angio-Seal patients crossed over to FemoStop because of persistence bleeding (p = 0.004) and 5.1% required additional manual compression.

	FemoStop (n = 75)	Anglo-Seal (n = 75)	p value
Procedure success	74 (98.6%)	73 (96%)	0.61
Primary end-point at 2 hr	3 (4%)	32 (42.5%)	<0.0001
Primary end-point at 24 hr	8 (10.4%)	9 (11.97)	0.79
Crossover	0	11 (14.63%)	0.004

Although less comfortable, the overall efficacy of the FemoStop appears higher than that of Angio-Seal.

P1496 First report of the European multi-center registry of the Duett vascular sealing device

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Purpose: Conventional management of the arterial access site following diagnostic angiography (DA) and percutaneous vascular interventions (PVI) is associated with patient discomfort, prolonged bedrest and local complications. We report the preliminary experience of the European multi-center registry of a new vascular sealing device, Duett, which is comprised of a balloon delivery catheter (~3F) and a procoagulant consisting of thrombin and collagen in a flowable suspension.

Methods: Immediately following DA and PVI, patients at 23 European centers were treated with the Duett sealing device. Patients were included in the study if the arterial sheath used during their DA or PVI procedure was 5-9F and if the ACT was <400 seconds ± an approved GPIIb/IIIa platelet receptor blocker.

Results: A total of 1202 patients were enrolled in the study. Hemostasis was achieved in 2–5 minutes following deployment of the Duett sealing device. Patients were ambulated at 1–6 hours following their invasive procedure depending on sheath size and level of anti-coagulation. Patients treated with a GPIIb/IIIa platelet receptor blocker were not fully ambulated until completion of the drug infusion. A total of 5 patients (0.4%) required vascular surgical repair (pseudoaneurysm 4, large hematoma 1). Limb ischemia after Duett deployment occurred in 2 patients (0.2%) and was successfully treated in both cases by intra-arterial infusion of urokinase. A blood transfusion was given in 3 cases (0.2%). Pseudoaneurysms were detected in 34 patients (2.8%), the majority of these were small (30/34) and successfully treated with ultrasound-guided compression or resolved spontaneously.

Conclusions: This large multi-center European experience with the Duett sealing device demonstrates that it is highly effective in achieving rapid and reliable hemostasis following DA and PVI with a very low incidence of major complications.

P1497 Non-invasive treatment of pseudoaneurysms of the femoral artery by ultrasound-guided aspiration-reinjection repair

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Both large or compartmentalised postcatheterization pseudoaneurysms (PSA) with great, painful haematomas and anticoagulation therapy are the reasons for unsuccessful ultrasound-guided (UG) compression repair.

The aim of our investigation was to apply another method of UG vessel repair: To achieve thrombosis of the PSA and closure of the communicating channel by aspiration of blood from the PSA and reinjection into the PSA (AR).

In 1998 we applied this method in eight patients (PT) with a mean age of 65.0 ± 8.6 years. All PT were treated with Flucloxacillin or Cefotiam intravenously prior to the procedure and antibiotic therapy was continued orally for the next three days. After skin disinfection and adequate local anaesthesia UG puncture of the PSA followed. Blood was aspirated from the PSA and reinjected after 15 to 30 seconds. The continuous ultrasound control revealed the thrombosis of the PSA and the closure of the communicating tract. In the same period in 58 PT (mean age 62.7 ± 8.9 years) conventional UG compression repair was performed in case of PSA ($p < 0.0001$).

The eight PT presented with a large PSA, mostly complex forms with two to five compartments, severe pain in the groin, massive haematoma, two PT were receiving anticoagulants. In three cases spontaneous reopening had developed up to three times after successful UG compression repair. The mean volume of the PSA was 14.6 ± 2.9 cm^3, in conventional UG compression repair 3.7 ± 2.2 cm^3 ($p < 0.02$). Thrombosis of the PSA was achieved with 4.8 ± 2.6 AR-procedures and 6.2 ± 3.1 ml of blood. In two cases (PT on anticoagulant therapy) further mild UG compression for three minutes became necessary to achieve closure of the communicating channel. No PT suffered from infectious or inflammatory complications following this procedure, no change in ankle-arm index was observed (1.20 ± 0.07 before and 1.24 ± 0.12 after AR, p = 0.42).

The AR-technique offers an effective alternative as a non-surgical method in the treatment of complicated postcatherization PSA. AR is easy to perform, as a non-invasive technique it is safe, efficient and cost-effective. This technique might help to avoid local and hemodynamic complications of PSA.

P1498 Does arterial sealing device decrease the rate of local complication: interim analysis of the haemostase trial?

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In order to evaluate the potential benefit of Angioseal* to decrease the rate of local complications after coronary stenting, a randomized study was organized in 11 centers to enroll high local risk pts (= age > 70, hypertension, previous puncture, aggressive antiplatelet therapy, continuous heparin infusion, lytics, 8 F sheath use). Pts were randomized at the end of PTCA between delayed sheath removal + manual pressure (MP) with delayed ambulation or immediate sheath removal + Angioseal (AS) with early ambulation (4 h.).

From 01/98 to 09/98, 450 pts were randomized. All pts had systematic duplexscan examination at 24 h. and 7 d. follow-up. Baseline data were similar in both groups:

	MP	AS	p
Immediate hemostasis (%)	0	90.6	<0.001
Compression time (min.)	54 ± 75	4 ± 24	<0.001
4 h bedrest cessation (%)	3	68.3	<0.001
Major endpoint (%)	18.6	6.2	<0.001

(= composite of surgery, transfusion, false-aneurysm, AV fistula, infection, vein thrombosis, hematoma > 6 cm., bleeding requiring prolonged compression). After this interim analysis, study was stopped and final results in the global cohort of 612 pts will be available.

AS dramatically reduces need for compression, bedrest duration and complications after coronary stenting in high local risk patients.

P1499 Incomplete expansion and apposition of stents on the focal balloon at nominal versus high inflation pressures: an intravascular-ultrasound-controlled study

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The concept of a focal balloon as a stent delivery system aims at optimal stent expansion with low risk of peri-stent dissection. The optimal pressure to implant stents using this system is not known.

Methods: We randomly implanted this stent-system in de-novo lesions at the rated burst-pressure of 10 atm (inflation pressure IFP 10, n = 10 patients-PTS), at 12 atm (IFP 12, n = 10 PTS) and at 15 atm (IFP 15, n = 10). System size was chosen to exceed reference diameter by 0.1 to 0.4 mm and was 3.0 mm (focal balloon segment) in 8 of 10 PTS in each of the three groups. Complete apposition (CA) was defined as no strut found within the lumen as assessed by intravascular ultrasound (IVUS, Endosonics system), and complete expansion was defined as the minimal cross sectional area (CSAmin) within the stent exceeding 80% of the distal reference cross sectional area (CSAref).

Results: In the IFP 10-group, passage of the IVUS-catheter was impossible in 8 of 10 PTS. In the remaining two, incomplete stent apposition was apparent. High pressure dilatation (HPD) at 20 atm using an additional balloon was neccessary in all 10 PTS to achieve CA and expansion to >80% of CSAref. In the IFP 12-group, IVUS passage after stent was successful in 9 of 10 PTS. However, subsequent high pressure dilatation was neccessary in 5 PTS to achieve >80% of CSAref. In the IFP 15-group, IVUS after stent showed CA in all 10 PTS, and CSAmin averaged 91 ± 4% of CSAref ($p < 0.002$ vs. IFP 12). Peri-stent dissection (1 PT per group) after HPD resulted in an additional stent in one PT (IFP 10).

Conclusion: The focal stent-system requires a primary IFP significantly exceeding the rated burst pressure of 10 atm to achieve complete apposition and expansion of the stent. Post dilatation using high-pressure balloons carries the risk of peri-stent dissection due to the very weak radioopacity of this stent, thus loosing the advantage of "focal" stenting.

P1500 Stent implantation with different pressure: evidence of superior results in experimental studies?

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In an experimental porcine coronary model, different stent implantation-pressures were examined. The vessel reaction and the deployment homogenity of the implants were analyzed.

Methods: Palmaz-Schatz Stents were implanted with a 3 mm balloon in with 3D IVUS selected porcine coronary arteries (diameter 3 mm) using either 12 atm or 18atm (group 1: 12 atm, n = 9; group 2: 18 atm, n = 9). The arteries were explanted after 14 days, embedded in methylmetacrylate, serially cut (120–200 μm), stained histologically (mod. Laczko-Levai) and digital morphometry was performed (Image, 4th Dimension). Inhomogenity of the implant was enhanced at the stent edges (+22% versus mean stent lumen) leading to trumpet-like structures. Inhomogenous circumferential tissue hyperplasia is the predominant feature 14 days after stenting. Initial and luminal areas varied remarkably within the stent. Stenosis at the stent edges might be induced by trumpet-like deployment behavior at the edges of slotted tube stents.

	Group 1	Group 2
Total stent lumen	5.2 mm^2	5.6 mm^2
Lumen range	±17%	±16%
Total intimal area	0.4 mm^2	0.6 mm^2
Intimal area range	±60%	±57%

In conclusion: Uniform circumferential homogenous tissue hyperplasia is an unique feature after stent implantation and offers a clear and defined target for prophylactic approaches. High pressure implantation did not result in enhanced intimal hyperplasia.

P1501 Does stent length affect long-term outcome following coronary stent implantation?

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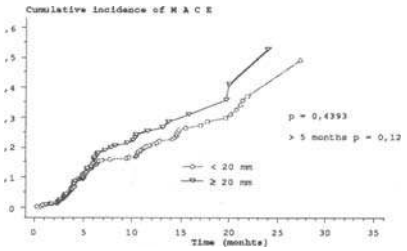
The reported results of stenting for long lesions are unfavorable and the effect of stent length on the rate of major adverse cardiac events (MACE) is not well known.

We analyzed clinical and angiographie data of a consecutive series of 732 pts, with 843 lesions treated with stent implantation. To evaluate the effect of different stent length we used 20 mm as a threshold to separate short (n = 530 pts) and long stenting (n = 202 pts). In comparison with short lesions, coronary stenting on long lesions was safe and associated with a remarkably low reocclusion rate (1.94% vs 1.79%: ns). Clinical follow-up (FU) was performed in 616 patients of 688 eligible patients (89.5%).

At the beginning of FU the outcome is similar in the two groups but after the fifth month, the group longer stent length is associated with a higher rate of MACE. However, after multivariate analysis, type B3-C lesion, Jeopardy score > 6 (importance of proximal lesions), but not stent length, were identified as independent predictors of cumulative events.



Conclusions: In long lesions, unfavorable prognosis of clinical follow-up after five months is explained more by severity of proximal coronary artery disease at baseline, than the implanted stent length.

P1502 Coronary artery side-branch jailing after stent deployment: acute and long-term results

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We aimed to assess side-branch (SB) jailing with various stent designs and relate it to clinical results.

Methods: Stents (n = 185) were deployed over small to moderate (<2.5 mm) SB in 121 patients (pts), with a mean age of 66 ± 14 years.

Results: Jailing occurred in 89 pts (Group A) and non-significant (<50%) SB stenosis occurred in 32 pts (Group B). The percentage of stents used in Groups A and B is given below:

	NIR	GFX	beStent	Cross-flex	Sea-quence	JRII
Group A	74/121	24/121	19/121	8/121	2/121	3/121
SB jail	61%	19%	16%	7%	2%	2.5%
Group B	11/48	19/48	11/48	7/48	4/48	3/48
No SB jail	23%	40%	23%	15%	8%	6%

The incidence of SB jailing according to stent type is 87% (74/85) for NIR, 68% (19/30) for the beStent, 53% (8/15) for the Crossflex, 59% (24/43) for the GFX, 33% (2/6) for the Seaquence and 50% (3/6) for the GRII. Twenty-two pts in Group A (25%) had attempted revascularization of the jailed SB. Of these, 13.6% had major complications (2 MI, 1 CABG), whereas in the group with no attempt to treat the SB (n = 67), only 1 (1.5%) had non-Q MI. Follow-up for 17 ± 6 months is available for 71/89 pts (80%), of which 53 pts (87%) are asymptomatic. Repeated revascularization was required in 8/71 pts (11%) where all events occurred in the group with attempted SB revascularization.

Conclusion: SB jailing occurs more frequently with tubular stents than with coil stents, among those used in this study. Peri-procedural complications are uncommon if jailed SBs are left untreated. Long-term follow-up of these pts shows an excellent event-free survival comparable to non-bifurcation lesions.

P1503 Is the short coronary stent too short and the long too long?

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Introduction: Long stents have been associated with an increased rate of clinical and angiographic restenosis. For this reason, it has been proposed the use of short stents in the treatment of all lesions including long ones. The ESPORT-NIR Registry (ESpaña and PORTugal NIR stent registry) is a multicentre prospective observational study, conducted in 50 centres from Spain and Portugal. To assess the influence of the length of the implanted stent on the angiographic restenosis rate and clinical outcome, we have analysed the results of 1004 patients (1146 lesions) included in the 50 participating centres. Angiographic restenosis rate was evaluated from 300 randomly selected patients.

Methods: We define four groups according to the length of the stent used. Group A (9 mm), Group B (16 mm), Group C (25 mm), Group D (32 mm). From Aug 97 to Oct 98, 1004 pts (1136 lesions) were recruited by 50 centres. Primary end-points were major adverse cardiac events (MACE) at 7 months. Angiographic restenosis rate was evaluated from 213 randomly selected patients (237 lesions).

Results: Clinical, angiographic and procedural data usually correlated with an increased rate of restenosis and worse clinical outcome were similar in all groups. The angiographic restenosis rate and clinical events for each group are summarised below:

	Group A (9 mm)	Group B (16 mm)	Group C (25 mm)	Group D (32 mm)
#Lesions	191	692	133	116
#MACE/#Patients	8/142 (6.3%)	55/622 (8.8%)	11/126 (8.7%)	12/112 (10.7%)
#Restenosis/#QCA	9/37 (24%)	16/147 (11%)	7/27 (26%)	9/26 (35%)
Group[(1)]				

[(1)]Between Group A and B p = 0.033; Between Group B and C p = 0.034; Between Group B and D p = 0.0015. All Groups p = 0.0063.

Conclusion: Short (9 mm) and long (25 and 32 mm) stents were associated with an increased rate of angiographic restenosis in our study. Technical difficulties surrounding the procedure of short stent implantation and longer lesions when using long stents could be the explanation for these findings.

P1504 QCA results of nominal-pressure stent deployment vs high-pressure stent expansion in the same patient

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Background: High-pressure (HP) balloon inflation was shown to achieve larger and more symmetrical stent expansion than nominal-pressure (NP) stent deployment in comparative patient populations. Since HP inflation is also associated with larger balloon diameter using semicompliant balloons, it is not clear whether the salutary effects on stent expansion are secondary to the higher inflation pressure or the larger balloon diameter. **Objectives:** We measured and compared the immediate quantitative coronary angiographic (QCA) parameters of stent expansion initially at NP $\leq$ 12 atmospheres (8–12) and subsequently at HP > 14 atm (14–20) in the same patient. This design avoided the confounding effects of comparing different patients with different atherosclerotic plaque characteristics.

Methods: The study included 30 pts (3 females) with mean age 52 (±4). On-line QCA measurements were recorded using Philips computerized edge detection system. Measurements were performed at large magnification (5 inch) on diastolic frames with the arteries homogeneously filled with contrast, in the same angiographic view (RAO 25, Caudal 20) after the administration of intracoronary NTG 200 μg bolus.

Results: see table.

Post-Stent Data (n = 30)

	NP	HP	p =
Pressure (atm)	10.5 ± 1	17 ± 2	0.001
B/A Ratio*	1.15 ± 1	1.26 ± 0.1	0.002
Stent MLD** (nm)	2.4 ± 0.3	2.9 ± 0.4	0.0001
Acute gain*** (nm)	1.6 ± 0.4	2.2 ± 0.4	0.0001
Largest stent diameter (nm)	3.0 ± 0.3	3.4 ± 0.3	0.0001
Stent expansion index**** (%)	+5 ± 10	+19 ± 14	0.001

*Balloon diameter/reference vessel diameter. **Minimal lumen diameter within the stent. ***Absolute increase in MLD compared to predilatation values. ****Largest stent diameter/reference vessel diameter%.

The mean reference vessel diameter was 2.8 ± 0.6 mm. Acute gain correlated more strongly with the inflation pressure ($r = 0.5$, $p < 0.002$) than with the B/A ratio ($r = 0.37$, $p < 0.02$).

Conclusion: Compared to NP stenting; HP stent expansion was associated with larger stent lumen diameter and greater acute gain. HP appears to be more important than balloon diameter in achieving the increase in stented vessel diameter.

P1505 Effects of pressure and sizing of balloon on immediate lumen gain after coronary stent implantation depend upon stent type and vessel size

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Background: Current strategies of coronary stenting include the use of high balloon pressures (BP) or oversized balloons in order to maximize lumen gain. The aim of the present study was 1) to determine whether operator-dependent procedural factors such as BP and balloon: artery ratio (BA) are predictors of immediate lumen gain, and 2) to evaluate whether effects of BP and BA on lumen gain depend upon differences in stent type and size of the treated vessel.

Methods: Quantitative angiographic analysis was performed in 348 coronary lesions from 265 pts with successful implantation of a single stent per lesion. Chronic total occlusions, bypass grafts, and bailout procedures were excluded. AVE Micro (9%), AVE Gfx (12%), Palmaz-Schatz (14%), Paragon (30%), and Wiktor (35%) stents were implanted. To determine the independent influence of BP and BA on post-intervention minimal lumen diameter (MLD) and relative gain (= {MLD pre − MLD post}/reference diameter [RD]), a multiple regression analysis was performed in a linear fashion and after logarithmic transformation, taking into account MLDpre, RD, lesion location, and stent type.

Results: Multiple linear regression ($p < 0.0001$, $R^2 = 0.39$) revealed BA as a significant predictor of both MLDpost (coeff. = 0.39, $p < 0.001$) and relative gain (coeff. = 0.35, $p < 0.01$), in addition to MLDpre (coeff. = 0.16, $p < 0.01$) and RD (coeff. = 0.53, $p < 0.001$). Significant response to BA was found only for Wiktor (coeff. = 0.47, $p < 0.001$) and Paragon (coeff. = 0.61, $p < 0.001$) stents, and in vessels < 2.5 mm (coeff. = 0.56, $p < 0.01$). BP revealed no relevant influence on MLDpost or relative gain. Using regression analysis after logarithmic transformation of variables ($p < 0.0001$, $R^2 = 0.93$), a mathematical model of immediate angiographic outcome was elaborated: MLDpost = 0.89 * RD * $\sqrt{BA}$.

Conclusions: 1) Stent type and balloon to artery ratio, but not balloon pressure were found to be independent predictors of immediate angiographic result. 2) Response to balloon pressure or sizing was different among stent types and vessel sizes.

P1506 Is high-pressure stent implantation still required with the new less rigid second-generation stents mounted on non-compliant balloons?

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Background: First generation stents were limited by excessive rigidity and non-uniform expansion patterns.

Methods: To analyze whether the new ACS HP MultiLink stent (15 mm length) mounted on a non-compliant high-pressure balloon still requires high pressure implantation quantitative angiography and intravascular ultrasound was performed for 70 native lesions randomly assigned to low pressure stent implantation (10 atm) or high pressure implantation (16–18 atm). Minimal lumen diameter and reference diameter were determined by angiography. Intravascular ultrasound was used to determine stent cross-sectional area (CSA) and minimal lumen diameter at 1 mm increments as well as reference CSA.

Results: Stent apposition was complete in all 70 lesions. A lumen/reference CSA ratio $\geq$ 70% was obtained in 61 vs 75% of stents using low vs. high pressure stent implantation techniques.

	Low pressure (n = 35)	High pressure (n = 35)	P
QCA reference (mm)	3.01 ± 0.50	3.13 ± 0.40	0.104
QCA MLD final (mm)	2.60 ± 0.47	2.81 ± 0.46	0.051
IVUS lumen CSA final (mm^2)	6.03 ± 1.41	7.50 ± 1.22	0.001
IVUS MLD final (mm^2)	2.33 ± 0.35	2.65 ± 0.28	0.002
Lumen CSA/Ref. CSA	0.80 ± 0.21	0.88 ± 0.19	0.255

Conclusion: Implantation of the less rigid MultiLink stent with a non-compliant balloon results in good stent apposition already at low implantation pressure. However, to obtain good stent expansion throughout the whole lesion length high balloon pressures are still required.

P1507 Do second generation stents require high-pressure inflation with non-compliant balloons?

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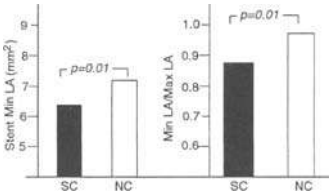
Second generation stents may allow for high pressure (HP) implantation with the semicompliant (SC) balloon on which the stent (ST) is mounted rather than requiring a HP noncompliant (NC) balloon post-stent deployment. We tested the hypothesis that post-dilation with a NC balloon results in better ST expansion at the same inflation pressure for second generation (MultiLink, NIR) as well as first generation (Palmaz-Schatz) ST at sites with post-implantation angiographic stenosis < 10%. We compared by intravascular ultrasound the ST minimal lumen area (Min LA) and the ratio of Min LA to maximum (Max) LA as a measure of ST expansion in 29 lesions in 25 patients using moderate to HP (8–14 atm) after SC inflation followed by NC inflation at the same atm in stented lesions (PS = 9; ML = 18; NIR = 2) (graph).



Despite moderate to HP inflation with the SC balloon, the ST was more fully expanded at the same pressure with the NC balloon. This occurred for the PS, ML and NIR ST. The present practice of HP SC inflation may limit ST expansion with the potential for worse late outcomes.

P1508 Are premounted stents safer than manually crimped bare stents?

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In order to evaluate the influence of the delivery system (premounted stent (PMS) on balloon versus manually crimped bare stent (CBS)) on coronary stenting results, we retrospectively studied 5433 pts who underwent PTCA in our center (4 operators) from 05/95 to 08/98. Eighty-two% of pts who received at least one stent (a total of 6314 stents) were selected. Indication was predominantly acute syndromes: unstable angina 32%, recent MI 26%, acute MI 15%. Type C lesion was noted in 42%. Clinical success rate was 96.7% (emergent CABG 0.1%, MI 1.4%, death 0.8%). Results in PMS group (38%) versus CBS group (62%) were:

	PMS	CBS	p
type C lesion (%)	42	43	NS
Artery diameter < 3 mm (%)	53	60	<0.001
Heavy calcification (%)	31	26	<0.001
stent failure + retrieval (%)	9.5	8.6	NS
Inapropriate deployment (%)	0.8	0.4	NS
Stent loss (%)	2.1	0.6	<0.01
Any kind of stent failure (%)	12.4	9.6	<0.01
Technical success (%)	92	95.8	<0.001
MACE (%)	3.9	1.4	<0.001

(Technical success: successful placement of, at least, one stent on the target lesion).

Thus, in routine practice, the choice of a PMS instead of a CBS is more frequent in calcified artery but this delivery device does not reduce stent failure, stent loss, or MACE.

P1509 A new microforceps device for retrieval of embolized coronary stents

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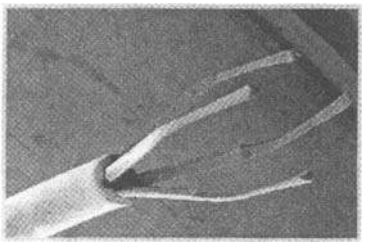
Today, the embolization of premounted or manually crimped coronary stents is a major complication of this widely applied coronary intervention. The incidence in a large registry is reported to be 2.2%. The retrieval of embolized stents is primarily intended but causes technical problems and is time consuming. Especially, the pull-back of the embolized stent into the guiding catheter frequently is troubleshooting.

We present a new retrieval device, which consists of a micro-forceps made of nitinol. The microforceps is closed via a hand-grip by means of a teflon hose which is moved forwards over the distal end. The open forceps has a diameter of 2.0 mm and of 0.82 mm when it is closed. The inner surface of the bits is zigzag shaped to allow better fixation of the stent. The outer diameter of the teflon tube is 1.8 mm with an additional sideport for wire guidance, which



permits access even to small vessel dimensions. The advantage of this device is that it bites the embolized stent at the proximal end and therefore permits a more protected and easier retrieval into the guiding catheter compared to e. g. lasso devices. Furthermore, this device can be provide cost-benefit since it provides reapplication of the retrieved stent because damage is minimized.

P1510 Efficacy and safety of transradial coronary angioplasty: a report of 5354 consecutive cases

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Background: Vascular complications can increase the morbidity and cost of percutaneous coronary intervention procedures (PTCA). Transradial arterial access (TRA) may reduce this risk, especially in patients (pts) receiving anti-coagulant or anti-platelet therapy.

Methods: Between Feb. 1994 and Dec. 1998 TRA was attempted in 5354 of 9070 (59%) PTCA procedures. Only pts with an ischemic Allen test or undergoing PTCA at the time of diagnostic catheterization were systematically excluded. TRA pts were allowed to ambulate 1 hour after completion of the PTCA procedure.

Results: Compared to pts undergoing transfemoral PTCA, TRA Pts were more likely to be male Successful coronary instrumentation was possible in 5244 (97.9%) procedures of which 5224 (99.6%) were successful. Stent implantation was performed in 3350, rotational atherectomy in 96 and excimer laser angioplasty in 38.

Adverse cardiac events occurred in 80 Pts (1.5%) (see table):

Adverse cardiac events

Death	Emergency CABG	Q-wave MI	Non-Q MI	Occlusion > reopened no sequelae
0.3%	0.1%	0.4%	0.5%	0.2%

Vascular complications were as follows: 0.5% hematoma, 0.06% surgical repair, and 4% asymptomatic loss of radial pulse.

Conclusions: We conclude that TRA for PTCA is effective and safe, and is compatible with the use of new devices. It has the potential to reduce complications, hospital stay and cost compared with transfemoral angioplasty.

P1511 Arteriography of the left internal thoracic artery from the right brachial artery using the Yumiko Lita catheter

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Recently, an approach from the right brachial artery for coronary angiography has been increasingly used for patients' benefits. Coronary bypass surgeries using the left internal thoracic artery (LITA) are widely performed and the technique of the arteriography of LITA is therefor critical. However, no satisfactory approach through the right brachial artery has been established for the arteriography of LITA. We accordingly designed our own catheter, named YUMIKO LITA catheter, for this particular purpose. In this study, we investigated the efficacy of the catheter.

Method: The subject included 61 patients with significant stenotic lesion in the left anterior descending artery, or with a past history of the artero-coronary bypass surgery using LITA. To investigate the efficacy of the catheter, we evaluated the total period of fluoroscopy for the catheter engagement, the quality of angiographic image, and the complications.

Results: The average total period of fluoroscopy was 7 minutes 18 seconds.Good images were obtained in 58 of the total 61 patients. No patients were complicated with both cerebro-vascular accidents and damages of the aortic wall.

Conclusion: The use of the YUMIKO LITA catheter makes the arteriography of LITA easy and shorten the time of catheterization procedure. We consider the YUMIKO LITA catheter to be useful in the arteriography of LITA before and after bypass surgery.

ATHERECTOMY

P1512 The X-SIZER catheter system: initial multicenter clinical experience of a novel device for removal of occlusive tissue material from coronary arteries

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The X-SIZER catheter system is a novel device designed to remove obstructive material from coronary arteries and saphenous vein grafts using standard catheterization procedures. The X-SIZER (6 Fr) single use device consists of of a battery driven hand held motor unit, helical cutter and conventional vacuum system and is compatible with conventional 8 Fr guiding catheters and 0.014 angioplasty wires. Preclinical data show successful thrombus removal from PTFE grafts, and from native iliac, femoral and carotid arteries.

The initial multicenter clinical study included 25 pts (LCA 8, RCA 13, SVG 4) at four centers. All pts had unstable angina syndromes, 6 of them evolving MI, 4 stent occlusions. TIMI 0-1 flow was present in 16 pts prior to X-SIZER tx, TIMI 2 in 5 pts. All pts received standard antiplatelet regimen including Ticlopidine & ASS and in selected cases ReoPro. The X-SIZER was successful in 15 pts including two occluded stents (success = TIMI flow increase, stenosis reduction, no MACE), with X-SIZER stand alone success in 2 and routine adjunct procedures in 13 pts. Mean post X-SIZER diameter stenosis was 61%, final stenosis 19%. Lack of success was due to inability to reach/pass lesion (n = 7) and to remove material (n = 3) due to catheter rigidity, profile and technical deficits. In 10 pts tissue particles up to lemon seed size were retrieved and histologically identified (7 pts) as fresh and partially organized thrombus, hyalin and fibroblast containing particles. No coronary vascular, access site or other complication occurred acutely or during FU (3 to 12 mos) to date.

In conclusion, the X-SIZER represents an intriguing simple to use coronary recanalization concept for selected pts, which seems to be safe and effective in removing obstructive atherothrombotic materials from native coronary arteries, SVGs and stents. Further investigation with improved lower profile devices is warranted and under way.

P1513 Long-term efficacy of debulking strategy by rotational atherectomy for complex lesion in small coronary artery

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Restenosis rate following percutaneous coronary balloon angioplasty (PTCA) for complex lesions in small coronary artery still remains high even if stents are implanted. Rotational atherectomy (RA) is effective for plaque debuking in a broad spectrum of lesion types included complex lesions. We examined the efficacy of plaque debulking by RA on reduction restenosis after PTCA for complex lesions in small coronary artery and determined predictors of angiographic restenosis. We analyzed consective 148 complex (AHA/ACC classification type B2 or C) lesions in small vessels (<3.0 mm) which were treated by RA and were eligible for 6 month follow-up angiography. Pre-procedural lesion morphology was as follows; calcified 81%, total occlusion 18%, reference diameter 2.32 ± 0.4 mm, lesion length 18.37 ± 0.93 mm. Adjunctive stent implantation was performed in 55% of lesions. Follow-up angiography was performed 179 ± 53 days after the procedure. Serial quantitative coronary angiography was conducted using Cardiovascular Measurement System. Angiographic restenosis was defined as diameter stenosis (DS) >50% at follow-up. Overall angiographic restenosis rate was 52.3%. Univariate analysis including 56 variables (11 clinical, 25 angiographic, and 20 procedural) showed that post-procedural minimal lumen diameter (no restenosis group (NR) 1.96 ± 0.49 vs. restenosis group (R) 1.79 ± 0.48 mm, p = 0.024), post-procedural DS (NR 23.26 ± 15.01vs. R 29.38 ± 12.50%, p = 0.006), and the presence of post-procedural dissection (NR 18% vs. R 31%, p = 0.067) were predictive of restenosis. Of those variables, post-procedural DS was the independent predictor detected by multiple logistic regression analysis(p = 0.074, Odds ratio = 1.033).

Conclusion: Long-term efficacy of plaque debulking by RA for complex lesions in small coronary artery is not satisfying. Other revascularization strategy should be considered if an optimal result can not be expected in those lesions.

P1514 Long-term clinical outcome of patients undergoing directional coronary atherectomy followed by stent implantation

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Debulking the atherosclerotic plaque by means of directional coronary atherectomy (DCA) prior to stent implantation is a safe procedure which is associated with excellent acute results and a low rate of 6-month angiographic restenosis. The effect of the combined techniques on long-term clinical outcome remains to be determined.

Methods: We prospectively evaluated 197 consecutive patients (171 male, 26 female, mean age 56 yrs) who underwent successful (residual stenosis < 50%) DCA followed by stent implantation of a native vessel for stable (73 pts) or unstable (124 pts) angina. Specific angiographic criteria for enrollment included >75% and <100% stenosis of a proximal non-tortuous coronary artery with a reference diameter of >2.5 mm and a lesion length < 15 mm. All patients were followed-up for a median period of 25.5 months (range 7–61 months). The follow-up evaluation included cardiovascular death, non-fatal myocardial infarction, severe angina requiring re-hospitalization and the need for repeat target lesion revascularization (TLR)

Results: The incidence and average period of onset of the events are:

	Pts.	%	Mean time (months)
Death	3	1.5	5
Myocardial infarction	2	1	0.2
Severe angina requiring re-H	17	8.6	4.8
TLR	19	9.6	5.8

Conclusion: In suitable lesions of native coronary arteries, DCA followed by stent implantation is associated with low incidence of clinical adverse events and with a limited need for repeat target lesion revascularization.

P1515 Rotational atherectomy in small vessels (<2.5 mm): immediate results and six-month follow-up

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Background: Percutaneous revascularization in lesions located in small vessels (<2.5 mm) shows poorer results than procedures performed in larger vessels. Small angiographic lumen diameter is frequently an expression of diffuse arteriosclerotic disease. The aim of this study is to analyze immediate and 6-month results of rotational atherectomy in small vessels.

Methods and results: All rotational atherectomy procedures performed in small vessels (diameter < 2.5 mm) in our institution for two years were assessed retrospectively. 104 procedures in 93 patients (pts) were included, with a mean age of 67 ± 10 years; 43% were women, 27% were diabetic and 73% presented multivessel disease. All of them presented complex lesions (12% B1, 63% B2, 25% C), which were located more frequently in the LDA (80%) and LCX (13%). Procedural success (residual stenosis < 50% and TIMI flow 2–3 with no major complications) was obtained in 97 cases (93%). Minimum lumen diameter changed from 0.69 ± 0.24 mm to 1.76 ± 0.44 mm (67 ± 10% to 25 ± 11%) with a reference diameter corresponding to 2.15 ± 0.2 mm and 2.3 ± 0.4 mm. No deaths during in-hospital stay nor emergency CABG were recorded. 3 pts presented Q-wave AMI and 4 pts non-Q-wave AMI.

6-month angiographic reevaluation was performed in 62.5% of the patients; 29% of the patients reevaluated required re-PTCA because of restenosis; another 11% presented asymptomatic restenosis. No statistically significant differences were demonstrated between rotablator + stent and rotablator + balloon PTCA in restenosis rate (p = 0.3). Clinical follow-up was obtained in 90% of the patients, with a mean follow-up of 18 months. 71.9% of the patients remained free of cardiac events (cardiac death + AMI + re-PTCA) after 12-month follow-up

Conclusions: Rotational atherectomy in patients with small vessels is followed by good immediate results and an acceptable rate of cardiac events at six-month follow-up in spite of unfavorable clinical characteristics.

P1516 Clinical and angiographic follow-up results of the German atherolink registry

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Background: Debulking prior to coronary stenting may result in a lower restenosis rate by theoretical considerations, which are supported by intravascular ultrasound. To test this hypothesis in regard of feasibility and safety a prospective, multihospital registry was established. Directional coronary atherectomy (DCA) was performed prior to stent deployment (S; ACS MultiLink) in patients (pts) with a suitable coronary anatomy for both.

Patients and methods: By protocol, it was aimed to achieve a residual stenosis of <20% after DCA and of <15% after S. The registry included 175 pts (79% males, age 56 ± 19 years; 33% unstable angina, 81% type B2 or C lesions, ejection fraction 64 ± 14%).

Results: DCA was successful by means of the protocol in 58% of pts and S further improved this result to 91%. 3 pts died within 6 months. 6 month angiographic follow-up was completed in 124 pts with the following event rates: unstable angina 6.5%, Q-wave MI 0.8%, non-Q-wave MI 4.8%, CABG 2.4%. 4 pts had acute or subacute stent thrombosis. The binary restenosis rate by means of angiography was 10.5%.

Conclusion: The combined approach of debulking prior to stenting is feasible and safe. The low restenosis rate with regards to the high prevalence of complex lesions justifies a prospective, randomized study to test the hypothesis of reduced restenosis by debulking prior to stenting.

P1517 Is there an appropriate strategy for treatment of non-aorto ostial lesions in large vessels? acute and long-term results

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Background: Ostial lesions have been shown to have higher restenosis compared to non ostial lesions. Non-aorto ostial lesions (ostial LAD diagonal or circumflex) in large vessels (>2.75 mm) pose problems with stent alone, due to plaque shift, resulting in the pinching of the adjacent vessel. Therefore, debulking may be advantageous in this setting. In order to evaluate the acute and long-term results of three different interventional strategies, rotational atherectomy alone (R), stent alone (S), and both we analyzed the results of 212 non-aorto ostial lesions for acute outcome and the need for target lesion revascularization (TLR).

Results: Baseline characteristics revealed high incidence of diabetes in S (34%), and R + S (36%), compared to R (19%) ($p < 0.01$) and higher rest angina and post MI in S.

Characteristics	R alone (n = 114)	S alone (n = 39)	R + S (n = 59)
Reference vessel (mm)	2.82 ± 0.42*	3.31 ± 0.41	3.28 ± 0.42
Final MLD (mm)	2.31 ± 0.21*	3.27 ± 0.21	3.25 ± 0.18
Diameter stenosis post (%)	18 ± 7*	4 ± 3	1 ± 2
Procedural success (%)	98.2	94.8	98.3
Sidebranch narrowing (%)	3.5	12.8	6.8
Major complications (%)	0.9	2.4	0
CK-MB elevations (%)	13.1*	23.1	20.3
TLR (%)	29*	15	12

Conclusions: Three different strategies for non-aorto ostial lesion intervention are associated with high procedural success rate and low complications. S alone is associated with higher incidence of side branch narrowing compared to R or R + S and higher CK-MB release. R alone is associated with higher restenosis. Therefore debulking with rotational atherectomy followed by stent implantation should be the preferred approach in treatment of non-aorto ostial lesions.

P1518 Efficacy of pre-stent plaque debulking for chronic coronary total occlusions

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Background: Stenting improves the patency of successfully recanalized chronic coronary total occlusions (CTO) by percutaneous coronary balloon angioplasty, however restenosis rate still remains high. Massive plaque burden in CTO is considered to interfere with full stent expansion and be a cause of restenosis.

Methods: We examined the pre-stent plaque debulking strategy with rotational atherectomy (RA) for CTO (TIMI flow grade = 0, occlusive duration ≥ 3 months). We performed RA for 34 CTO before stenting. Follow-up results were compared to those of consecutive 127 CTO recanalized with stenting in which RA could be indicated retrospectively. Results: RA was performed with max. burr size was 1.86 ± 0.21 mm. RA procedural success (TIMI flow grade = 3) was obtained in all lesions without perforation, flow disturbance, or any major complications. Adjunctive stenting pressure was 8.0 ± 1.4 atm. No major complications were observed during the hospital stay. Follow-up angiography was performed in 33 lesions 154 ± 53 days after the procedure to date. There were no significant difference in baseline characteristics between the two groups. Quantitative coronary angiography data are shown in the table.

	Stenting after RA	Stenting alone	P value
Reference diameter (mm)	2.61 ± 0.46	2.73 ± 0.46	NS
Post RA MLD (mm)	1.04 ± 0.38		
Post balloon MLD (mm)	2.05 ± 0.41	1.09 ± 0.53	<0.0001
Post procedural MLD (mm)	2.82 ± 0.45	2.42 ± 0.43	<0.0001
Follow-up MLD (mm)	1.90 ± 0.62	1.24 ± 0.86	0.0001
Restenosis rate (%)	18.2	55.1	0.0002

Conclusion: RA is a safe procedure for plaque debulking of CTO in selected cases. Plaque debulking of CTO facilitates Sub-sequent stent dilatation and reduce the restenosis rate.

P1519 Excimer laser for total coronary occlusions: results of the EXACTO trial

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The impact of debulking for recanalization of totally occluded coronary arteries (TOC)is controversial. In the multicenter randomized EXACTO trial a strategy of excimer laser and ancillary balloon angioplasty (ELCA) is compared to standard balloon angioplasty alone for treatment of TOC. In 15 centers in Europe, Asia and US, 314 patients with angina and/or ischemia and TOC were randomized to ELCA (157) or balloon (157) after a coronary guidewire had passed the occlusion and its position within the free distal lumen of the treated artery had been proven by angiography. Additional stenting was not restricted by the study protocol.

Acute results and 30 days events

Acute	ELCA	Balloon	30 days	ELCA	Balloon
Proc success	94%	90%	MI	2.5%	4.5%
TIMI > 2	97%	96%	CABG	1.9%	1.3%
Add. stent	68%	80%*	RePTCA	1.3%	1.9%
Tamponade	1.9%	0	Death	0.6%	1.3%

*$p < 0.05$

Acute results and cumulative events within the first 30 days after treatment are given in the table. Although ELCA was performed "aggressively" (1.7 or 2.0 mm laser catheters in 63% of procedures), there was no increase in major adverse events or necessary surgery as compared to standard balloon angioplasty. In the ELCA group significantly fewer additional stents were used due to a more satisfying primary result with less prominent dissection or threatening reocclusion when compared to balloon alone. In contrast to previous studies, therefore, laser angioplasty with subsequent balloon dilatation in the EXACTO trial compared favorably to standard balloon angioplasty concerning immediate results and early follow-up. Since enrollment was completed at the end of June, 1998, final clinical results as well as 6 months angiographic follow-up data will be available at the time of the presentation.

COATED AND BIODEGRADABLE STENTS

P1520 Evaluation of the biocompatibility of two new diamond-like stent coatings (Dylyn™) in a porcine coronary stent model

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Hydrogenated Diamond-like Carbon films (DLC, a-C:H) and Diamond-like nanocomposite coatings (DLN or Dylyn™), offer a promising solution for many industrial applications. In this study the biocompatibility of two diamond-like stent coatings are evaluated in a porcine coronary stent model.

Methods: Either coated or non-coated stents were randomly implanted in two coronary arteries of 20 pigs so that each group contained 13 stented arteries. Quantitative coronary analysis, before, immediately after stent implantation, and at 6 weeks, was performed using the semi-automated Polytron 1000® system. Morphometry was performed using a computerized morphometric program.

Results: Histopathology revealed a similar injury score in the 3 groups. Inflammation was significantly increased in the DLN-DLC coating group. Thrombus formation was significantly decreased in both coated stent groups. Neointimal hyperplasia was decreased in both coated stent groups, however, the difference with the non-coated stents was not statistically significant. Area stenosis was lower in the DLN coated stent group than in the control group (41 ± 17 vs. 54 ± 15%, p = 0.06).

Conclusion: The results indicate that the Diamond-like Nanocomposite stent coatings (DLN) behave as biocompatible stent coatings, resulting in a decreased thrombogenicity and a decreased neointimal hyperplasia. Covering this coating with another Diamond-like Carbon film (DLC) resulted in an increased inflammatory reaction and no additional advantage compared to the single layer Diamond-like Nanocomposite coating.

P1521 Clinical evaluation of a biocompatible phosphorylcholine-coated coronary stent

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Background: The ByodivYsio™ stent is a new coated with phosphorylcholine, a cell membrane molecule, which was designed to reduce the formation of thrombus and potentially the risk of restenosis.

Methods: We prospectively studied 224 consecutive patients (pts) who underwent elective (67%) or bail-out implantation of 303 BiodivYsio™ stents in 286 lesions. Most lesions (62%) had unfavorable characteristics (type B2 or C) and 50% had thrombus and/or chronic occlusion. Clinical follow-up was obtained in all pts at one month and in the first 132 pts (147 lesions) at six months. Repeat angiography was undertaken in all pts with recurrent ischemia.

Results: Successful stent deployment was achieved in 284 lesions (99.3%). Angiographic success rate (post-intervention stenosis < 30%) was 98.3% (281/286 lesions). There was 1 (0.4%) subacute stent thrombosis (with Q-wave myocardial infarction) and 2 (0.9%) non-stent related in-hospital deaths. No emergency CABG was required. Reference diameter was 2.82 ± 0.32 mm. Minimal luminal diameter increased from 0.38 ± 0.25 to 2.97 ± 0.35 mm and diameter stenosis decreased from 83.8 ± 12.1% to 5.8 ± 9.7%. No cardiac event occurred during the first month after intervention. At 6 months follow-up, repeat target lesion revascularization was required in only 8 lesions (5.4%).

Conclusions: The implantation of phosforylcholine-coated stents appears to be safe and efficacious in the treatment of complex coronary lesions and is associated with an extremely low target vessel revascularization rate. Randomized studies are warranted to compare this coated stent with currently available non-coated stents.

P1522 Immobilized hyaluronic acid: a potential thromboresistant coating for endovascular devices

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Background: Stainless steel stents are highly thrombogenic and may therefore lead to an increased acute or subacute closure rate after coronary stenting. Coating of stents with a biocompatible and non-thrombogenic material may solve the problem. Hyaluronic acid (HA) has been shown to inhibit platelet aggregation when administered systemically. However, the effect on platelet deposition of coating stents with immobilized HA is unknown. We therefore assessed the thrombogenicity of stainless steel tubes and stents coated with immobilized HA and compared these results with uncoated control stainless steel tubes and stents.

Methods: Thrombosis was assessed by continuous Indium^{111}-platelet imaging using a gamma camera over 2 hours after exposing coated and uncoated stainless steel tubes and stents (4.0 mm diameter, n = 16) to non-anticoagulated blood (100 ml/min) in exteriorized baboon arteriovenous (AV) shunts.

Results: Time course of platelet deposition is presented as mean (SD). A 2-way ANOVA test to compare the effect of coating or time found that coating tubes and stents with HA resulted in a significant decrease in platelet deposition ($p < 0.001$ and $p = 0.003$ respectively).

Time course of platelet deposition

	Platelets × 10^{-9}			
	30 min	60 min	90 min	120 min
HA Tubes	0.02 (0.02)	0.001 (0.002)	0.04 (0.07)	0.24 (0.29)
Control Tubes	0.5 (0.29)	3.44 (0.83)	5.49 (0.89)	6.12 (0.97)
HA Stents	0.03 (0.05)	0.09 (0.06)	0.30 (0.19)	0.65 (0.52)
Control Stents	0.13 (0.12)	0.98 (0.77)	1.73 (1.19)	1.90 (1.03)

Conclusions: In this primate AV shunt model, coating stainless steel tubes and stents with immobilized hyaluronic acid significantly reduced platelet deposition. Immobilized HA may therefore provide a thromboresistant coating material for endovascular use.

P1523 Comparison of the heparin-coated and the uncoated version of the JOMED stent with regard to stent thrombosis and restenosis rates

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Heparin coating has been proposed to reduce stent thrombosis and proliferative vascular response. We compared the uncoated (U) and the heparin-coated (C) version of the recently available Jomed stent. In the coated version heparin molecules are covalently bound to an inert polyamine chain layer covering the stent surface (Corline Corp).

A total of 368 stents were implanted in 303 lesions from 278 patients. Stents were successfully delivered in 99%. After stent implantation patients received ASS and ticlopidin (96%). Clinical and angiographical 6-months follow-up was done in 95% and 79% of the lesions, respectively. The treatment groups (U/C) did not differ in terms of: de-novo stenoses 125/124, restenosis 26/32, LAD 65/79, CX 23/30, RCA 55/40, CABG 8/7, AHA B2 or C lesion 56/43, occlusion 25/27, unstable angina 66/65, stable angina 44/42, acute infarction 23/24, and risk factors. Heparin coating (U/C) had no impact on the incidence of stent thrombosis (2/4) or myocardial infarction (3/3), restenosis rate (29.2% versus 30.5%) or reintervention rate (25.0% versus 24.4%).

	Uncoated (U)	Heparin Coated (C)	
MLD [mm] pre PTCA	0.53 ± 0.40	0.54 ± 0.40	n.s.
MLD after stenting	2.48 ± 0.52	2.48 ± 0.44	n.s.
MLD at follow-up	1.77 ± 0.89	1.69 ± 0.87	n.s.
RD [mm] pre PTCA	2.65 ± 0.64	2.58 ± 0.91	n.s.
RD after stenting	2.66 ± 0.53	2.66 ± 0.52	n.s.
RD at follow-up	2.63 ± 0.66	2.75 ± 0.62	n.s.
Late loss index	0.37 ± 0.45	0.41 ± 0.42	n.s.

The design of the Jomed stent provides a high success rate. Heparin coating has no impact on in-hospital complications such as stent thrombosis or the angiographic long-term results.

P1524 Tantalum coating reduces surface corrosion of stents

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After deployment, stents may suffer from corrosion which could provoke inflammatory processes of the coronary wall tissue. In the present study we therefore investigated the corrosion behavior of different actually used stent materials.

Methods: Commercially available stents (316L stainless steel, deployed and non-deployed state) with different treatments and coatings were tested for their corrosion behavior in vitro after exposure to a mildly acid solution (aqueous Machu solution = 5% NaCl, 1% H_2O_2 buffered by acetic acid to pH 6), well simulating physiological conditions due to its oxygen potential similar to the one in circulating blood. After a 30, 60, 180 and 300 minute exposure to this solution the morphology of stent surface corrosion was investigated by scanning electron microscopy (SEM).

Results: Stainless steel stents without additional treatment or coating exhibited a high degree of surface corrosion with severe damage of single stent struts. Coating with 5 mm thick gold layer led to even greater surface damage due to the formation of pores > 200 mm and partly loss of the gold layer. Best results were achieved by high vacuum annealed stents with additional tantalum coating. Surfaces of this type of stents showed very little or no damage at all, even after the longest exposure to the acidic solution.

Table 1

Stent Material (316L)	SEM Results of Corrosion Test
No HV annealing	Major surface defects pore size > 100 μm
+ HV annealing, + Tantalum implantation	Minor surface defects pore size < 5 μm
+ 5 μm Au coating	Major surface defects pore size > 200 μm
+ Tantalum HV annealing + Ta coating	No surface damage no pores visible

SEM = Surface electron microscope, HV = high vacuum, 316L = stainless steel

Conclusion: Most actual stent models exhibit severe surface corrosion in chemical environments similar to blood. However, annealing and additional coatings highly reduce surface damages and therefore might improve performance of stents deployed in vivo.

P1525 Quantitative angiographic results of the phosphorylcholine coated bio-divYsio stent in the SOPHOS study

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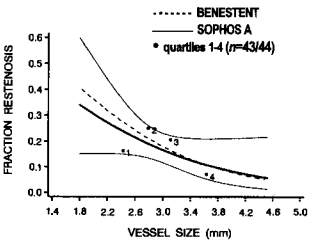
In the SOPHOS Study (Study Of PHosphorylcholine coating On Stents) 426 patients with (un)stable angina and a target vessel of 2.75 mm (QCA)/3.0 mm (visually) – 4.0 mm diameter were selected for implantation of the 15 mm phosphorylcholine coated biodivYsio stent. Angiographic follow-up at 6 months was performed in the 200 first patients (SOPHOS A).

Aim: We investigated the relationship between the vessel size (reference diameter pre-procedure; RD_{pre}) and the restenosis rate (RR; >50% diameter stenosis at 6-month follow-up).

Methods: With 177 6-month angiograms available, 174 matching lesions could be assessed. Mean vessel size was 2.99 mm and the overall restenosis rate was 17%. To investigate the relationship between vessel size and restenosis rate, logistic regression was performed on SOPHOS A data (log $RR/[1 - RR] = 0.75 - 0.97 \cdot RD_{pre}$) and compared to the same analyses of the BENESTENT I/II^{rand} trial data. In addition, quartile means are given for SOPHOS A.

Results:



Conclusion: The overall 17% restenosis rate in SOPHOS is comparable with the outcome of the BENESTENT trials. Both logistic regression analysis and quartile data (1st quartile = 1.80–2.66 mm) indicate a specific beneficial effect of the biodivYsio stent in small vessels, suggesting that the phosphorylcholine coating is especially beneficial under these stringent conditions. However, this promising feature needs confirmation in a prospective study.

P1526 Reduction of platelet adherence by different coatings of coronary stents

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Although antiplatelet therapy has improved the results after coronary stenting, restenosis and vessel occlusion still play an important problem. We tested the role of different stent coatings in reducing platelet adherence.

Methods: We investigated the in vitro platelet adherence on different stents in an uncoated, electropolished stainless steal and a coated version (carbon, carbon and additional heparin, silicon carbide, heparin). 100 μm thick stainless steal plates (uncoated, electropolished, carbon and carbon with additional heparin) were examined too. Stents and stainless steal plates were incubated in heparinized whole blood with radiolabeled ^{14}C-arachidonic acid platelets in the presence of 30 μM ADP. After washing the stents and plates four times, radioactivity, caused by the adhesion of radiolabeled platelets, was measured. Also electron microscopy studies of platelet adherence on different stent coatings were performed.

Results: Platelet adhesion measured on the uncoated, electropolished stent was defined as 100% and was compared with the same stent model with coating. For carbon coating the adherence of radiolabeled platelets was measured with 108.7%, for silicon carbide with 58.6%, for carbon and additional heparin coating 32.9% and for heparin coating 7.7.% (median). Heparin coating was statistically different from all other tested stent coatings ($p = 0.043$). The platelet adhesion measured on the uncoated stainless steal plate was also defined as 100%. For the stainless steal plates we measured an adhesion of 95.6% for the electropolished plate and 88.8% for the carbon plate. Additional heparin coating of the carbon coated stent reduced platelet adhesion to 39.0% compared with the uncoated plate. The results for additional heparin coating were statistically different from all other tested plate coatings ($p = 0.043$).

Conclusion: Heparin coating of coronary stents is very effective in reducing platelet adherence on stent surface.

P1527 Multicentre open evaluation of the phosphorylcholine coated biodivYsio stent in native *de novo* coronary lesions: the SOPHOS study

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The biodivYsio stent is a stainless steel, balloon expandable, 15 mm mesh stent, with a unique phosphorylcholine copolymer coating to limit thrombus formation. The **SOPHOS** Study (**S**tudy **O**f **PH**osphorylcholine coating **O**n **S**tents) is an efficacy and safety evaluation of the biodivYsio stent for treatment of patients with (un)stable angina and de novo coronary lesions.

Aim: The aim of the study is to assess the major adverse cardiac events (MACE) at 6 months, testing a null-hypothesis of 15% MACE (taken from historical control data).

Methods: 426 patients (74% male, mean age 59.5 y) were included from July 97 to July 98 in 24 European, Canadian and South-American centers. All patients were treated with ticlopidine 250 mg/day for 1 month (M) and with aspirin $\geq$ 100 mg/day and had or will have a clinical follow-up at 1, 6 and 9 months. The first 200 patients (SOPHOS A) had also an angiographic follow-up at 6 months, contrary to the last 226 patients (SOPHOS B).

Baseline Results: Preprocedure ischemic status was unstable (41%), stable (53%) or silent (6%). The target vessel were LAD: 52%, LCX: 17% and RCA: 31%. All patients but 1 were effectively stented (3 with another brand, 47 required multiple stenting). 97.4% patients were MACE-free at discharge.

Follow-up Results (*to be updated for 6 and 9 months*): Significantly (*) lower Target Vessel Revascularization (TVR) and % MACE-free occurred in SOPHOS B versus A:

MACE (%)	1 M	6 M			9 M
		A + B	A	B	
Death	0	0.9	0.5	1.3	1.2
MI Q/NON Q	1.2/1.6	1.6/2.3	5.0	3.1	1.6/2.3
CABG	0.2	1.4	2.5	0.4	1.4
CABG	0.2	1.4	2.5	0.4	1.4
TVR	0	5.6	10.5	4.0*6.3	
MACE-free	96.9	88.0	84.0	91.6*87.1	

Conclusion: The impact of 6-month angiography on revascularization rates cleary appears comparing SOPHOS A and B. The overall result indicates that the phosphorylcholine coated bidivYsio stent is at least as safe and effective as "classical" stents.

P1528 Impact of surface electrochemical polishing on stent performance: insights from a porcine coronary model

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The interface between the outer layer of the metallic surface of a stainless steel stent and blood on the one hand and the vascular wall on the other hand, are considered to be important players in the induction of the neointimal hyperplastic response.

Methods: Non-polished (n = 10) and polished MultiLink 16 mm coronary stents (Guidant, Santa Clara, CA, USA) were randomly implanted in 2 of the coronary arteries of 10 pigs. All pigs underwent a control angiogram at 6 weeks and were then sacrificed. Quantitative coronary analysis, before, immediately after stent implantation and at 6 weeks was performed using the semi-automated Polytron 1000® system (Siemens, Erlangen, Germany). Morphometry was performed using a computerized morphometric program.

Results: Selected vessels, stent oversizing and final post stent diameter were similar in both groups. At 6 weeks follow-up, the minimal luminal stent diameter was smaller in the non-polished MultiLink group (2.70 $\pm$ 0.93 vs. 2.80 $\pm$ 0.18 mm, p: NS). Histopathology revealed an increased injury in the non-polished group (1.05 $\pm$ 0.44 vs. 0.74 $\pm$ 0.28, p = 0.052). Inflammation and perivasculitis were significantly more pronounced in the non-polished stent group. Morphometric analysis showed a significantly more pronounced neointimal hyperplasia (2.31 $\pm$ 1.13 vs. 1.25 $\pm$ 0.34, p < 0.005), and a more severe area stenosis in the non-polished MultiLink group compared to the polished stent group (46 $\pm$ 23 vs. 24 $\pm$ 8%, p = 0.004).

In conclusion: This study demonstrates again the importance of surface electrochemical polishing of stainless steel coronary stents to decrease the foreign body response and subsequent neointimal hyperplasia.

P1529 Long-term outcome after the implantation of the autologous venom graft-covered stent

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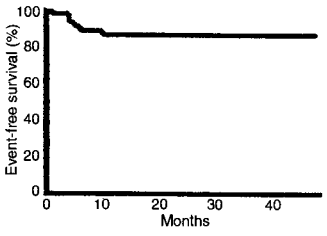
The autologous venous graft-covered stent (AVGCS) was implanted in patients (pts) with coronary artery disease. The immediate and mid-term results were favourable. This study demonstrates the long-term clinical outcome of 51 pts.

Methods: Conventional stents were covered by autologous venous grafts that were removed from the right cephalic vein. The stabilization of the venous grafts on the stents was accomplished by the application of sutures. A stent was either covered completely both externally and internally or only externally by the graft. Non-premounted (Palmaz™, a Palmaz-Schatz™) and premounted stents (Multilink™) were used. Fifty-three AVGCSs were implanted in 51 pts for several indications (elective lesions, ostial lesions, totally occluded vessels, thrombus containing-lesions, by-pass vein grafts, and bail-out cases). Follow-up was obtained in all pts until 3.5 $\pm$ 12.3 years.

Results: The procedure of AVGCS preparation and delivery to the target vessels was feasible and uncomplicated. The duration of AVGCS preparation was not prolonged (<20 min). Acute thrombosis was not observed. One patient suffered from subacute thrombosis. The angiographic restenosis rate was 13.95%. The target lesion revascularization (TVR) at 2 years was 9.43% and remained unchanged until 3.5 $\pm$ 12.3 years. However, one patient required by-pass surgery due to the progression of the disease in another vessel. The event-free survival rate was 86% at 42 months (figure).



Conclusions: Long-term follow-up did not reveal late restenosis after AVGCS implantation. The clinical outcome of these pts is favourable and no late stent-related complications were mentioned.

P1530 Angiographic and histomorphometric outcome of ePTFE-covered stent grafts in pig coronary arteries

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Background: ePTFE-covered stent grafts (SG) are being used in the treatment of perforations and aneurysms in coronary arteries. However, information on histologic and angiographic appearances at 1 month is sparse. We therefore evaluated the histologic, histomorphometric and angiographic effects in pig coronary arteries.

Methods: A SG was implanted in the LCX or RCA, and an ungrafted control stent in the LAD of 8 farm pigs. All pigs were pretreated with aspirin and ticlopidine. QCA was done at implantation and prior to harvest at 28 days. Plastic embedded sections were prepared by saw-and-grinding and measured by computer-assisted histomorphometry.

Results: Baseline QCA showed no differences between the two groups. 1 pig died within 24 h due to acute SG thrombosis. At follow up angiography, 2 other SG were found to be occluded and there was a trend to increased late loss (p = 0.08). Neointimal area was significantly increased without a loss in luminal area.

QCA	Control stents	Stent Grafts	p-value
MLD at 28 days	1.89 $\pm$ 0.5 mm	1.18 $\pm$ 0.86 mm	0.08
Late loss	1.15 $\pm$ 0.65 mm	1.79 $\pm$ 0.63 mm	0.08

The excessive neointima internal and external to the graft consisted of a prominent foreign-body reaction with numerous multinucleated giant cells, organized thrombus and prominent neovascularizaton channels.

Histomorphometry	Lumen area (mm^2)	Vessel area (mm^2)	Intimal area (mm^2)
Control stents	3.07 $\pm$ 1.4	8.95 $\pm$ 1.9	3.37 $\pm$ 1.78
Graft stents	2.49 $\pm$ 1.8	11.37 $\pm$ 1.9	5.39 $\pm$ 1.27
p-value	0.52	0.03	0.03

Conclusions: In coronary arteries of pigs treated with antiplatelet therapy, ePTFE-covered stent grafts were associated with marked thrombus formation, severe inflammatory reaction, and excessive neointima formation at 28 days compared to ungrafted control stents.

P1531 Does a newly developed covered stent with PTFE-membrane prevent restenosis after stent implantation?

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Background: Restenosis after stent implantation is due to neointimaproliferation (NP) through the spaces between stent struts into the vessel lumen. A newly developed stent with a membrane of polytetrafluoroethylene (PTFE) sandwiched between two stents was investigated for capability of prevention of NP.

Methods: In 19 rabbits NP was analyzed by histomorphometry 5 weeks after implantation of 15 PTFE-covered and 14 uncovered stents with identical design in iliac arteries.

Results:

#Areas [mm²]	Center part of stents		End of stents	
	Covered	Uncovered	Covered	Uncovered
#Strut area*	1.58 ± 0.13	0.37 ± 0.05	1.24 ± 0.25	0.47 ± 0.08
#Neointimal area	0.68 ± 0.65	0.7 ± 0.22	1.52 ± 0.54	1.34 ± 0.29
#Lumen area	3.18 ± 0.67	3.35 ± 0.34	2.55 ± 0.37	2.7 ± 0.41
#Vessel area*	5.44 ± 0.43	4.42 ± 0.31	5.31 ± 0.49	4.51 ± 0.44
#Stenosis [%]*	41.4 ± 11.8	24.2 ± 4.9	51.8 ± 8.1	39.9 ± 6.2
Stenosis [%]** max	covered: 76.0 ± 13.7		control: 62.9 ± 12.9	

*, **covered versus uncovered (*$p < 0.001$, **$p < 0.05$). #mean values

Conclusions: Mean neointimal area and free lumen area are not different between covered and uncovered stents. Due to thicker strut area in covered stents, there is an overdilatation of the vessel wall leading to a significantly higher relative lumen stenosis despite comparable free lumen area. Locally, especially at the end of the membrane there was a higher degree of NP in covered stents compared with control stents. Therefore, covered stents have no advantage with respect to NP as the barrier function of the membrane cannot compensate for local proliferation processes at the end of the membrane.

P1532 PTFE-covered stent in percutaneous coronary interventional procedures: results and outcome

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We evaluated the outcome of patients who had PTFE (polytetrafluroethylene) covered coronary stent implantation.

Methods: 55 consecutive patients with 58 lesions where treated with 62 covered stents in: 43 denovo lesions (35 in saphenous vein grafts [SVG]); 8 coronary aneurysms; 4 vessel rupture; 3 restenosis Clinical follow-up was assessed in all patients (8 ± 4 months). Angiographic follow-up (8 ± 4 months) is in progress and at present performed in 26 patients.

Results:

Mean age (years)	67 ± 10	Lesion length (mm)	14 ± 12
Diabetes, n (%)	10 (18)	Ref vessel diam (mm)	3.5 ± 8
Unstable angina, n (%)	20 (36)	MLD pre (mm)	1.1 ± 9
LVEF%	55 ± 16	MLD post (mm)	3.8 ± 9
Previous CABG, n (%)	35 (63)	Residual Stenosis, %	3.6 ± 9
Time to CABG (yrs)	9 ± 4	Procedure Success, %	96
3 vessel disease, n (%)	39 (71)	Acute thromb, n (%)	0
Type C lesion, n (%)	35 (60)	Subacute thromb, n (%)	0
Ostial & prox site n (%)	39 (67)	30-day MACE, n (%)	3 (5)
Balloon/artery ratio	1.1 ± 1	6-month MACE, n (%)	7 (13)
Max Inf Press (atm)	17 ± 3	TLR, n (%)	9 (18)
Stent length (mm	21 ± 6	Restenosis rate, n (%)	8 (31)

MLD = minimal lumen diameter. MACE = major adverse cardiac event. TLR = target lesion revascularization.

Conclusions: Short and long-term clinical outcome with this device show it to be a safe and effective tool especially for the treatment of SVG disease and vessel rupture, while its role to reduce restenosis still needs to be defined.

P1533 The influence of external stent porosity on early neointima formation and medial wall thickening in a pig model of saphenous vein bypass grafting

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External, non-restrictive, macro-porous, stents around pig vein grafts prevent neointima formation and medial thickening. Whether porosity determines this effect, however, has not been determined. The effect of external micro-porous stents (polytetrafluorethylene [PTFE]) of equal diameter on neointimal and medial thickening, microvessel formation and platelet derived growth factor (PDGF) content and receptors was therefore investigated in pig vein grafts.

Methods: Bilateral saphenous vein-carotid artery interposition grafting was performed in Landrace pigs with external placement of 8 mm diameter stents made of: 1) macro-porous Polyester velour and 2) micro-porous PTFE. One month later, grafts were excised and morphometry and histology carried out. PDGF protein content and receptor expression was assessed using immunochemical methods.

Results: In grafts with miro-porous stents there was marked neointima formation and medial thickening, which was dramatically less in grafts with macro-porous stents (table 1). Micro-porous stents significantly increased PDGF content and PDGF receptor expression in all regions of the grafts compared to macro-porous stents. Microvessel formation was also suppressed by micro-porous compared to macro-porous stents.

Table 1. Morphometry of stented vein grafts

Parameter	Dacron stent	PTFE stent	p value
Wall thickness (mm)	0.2 ± 0.04	0.42 ± 0.03	0.0005
Medial thickness (mm)	0.1 ± 0.02	0.17 ± 0.02	0.0007
Intimal thickness (mm)	0.1 ± 0.02	0.25 ± 0.03	0.001

In conclusion, porosity is crucial to the efficacy of external stents in preventing neointima formation in porcine vein grafts. Changes in PDGF protein and receptor expression mediates, at least in part, the difference. In addition, macro-porous stents allow adventitial microvessels to connect with the vasculature outside the stent, thus improving oxygenation of the graft.

P1534 Treatment of degenerated saphenous vein conduits with coronary polytetrafluorethylene stent grafts

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Background: Interventional therapy of degenerated saphenous vein grafts is associated with high rates of procedural complications and of restenosis. Coronary stent grafts [SG] containig a microporous [PTFE]- membrane provide a hermetic sealing of the vessel wall, which may prove beneficial for 1) reducing distal embolization of debris during deployment; 2) eliminating protrusion of residual plaque; 3) providing a barrier to the transmigration of inflammatory cells and diffusion of macromolecules, thus potentially reducing restenosis.

Methods: In a prospective multicenter observational study, 59 patients [pts] aged 66 ± 7 years (10% female) were treated with PTFE-SG, a median of 123 months after bypass surgery. A total of 67 SG were implanted (mean 1.1 ± 0.3 SG; total length 18.5 ± 8.2 mm) with a pressure of 16.3 ± 3.1 atm on balloons sized 3.6 ± 0.5 mm.

Results: (6 mo)

	Death	MI	Occlusion	Re-PTCA
In-hospital	0	2 (3.4%)	0	0
Follow-up	5 (8.5%)*	1 (1.7%)	2 (3.4%)	5 (8.5%)

*: 4 cardiac, 1 non-cardiac; MI = myocardial infarction

Quantitative angiography data are available for 42 pts. Dichotomous restenosis rate was 9.5%. Diameter stenosis pre-, post-procedure and at follow-up were 70% ± 16, 13% ± 12 and 27% ± 25, respectively.

Conclusions: Implantation of coronary PTFE stent-grafts allows for a safe and effective acute therapy of degenerated saphenous vein grafts and is associated with an extremely low restenosis rate. However, delayed vessel occlusion may occur and clinical outcome needs to be evaluated in a randomised, prospective trial.

P1535 Distribution of neointimal proliferation inside polytetrafluorethylene stent grafts in human coronary arteries

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Background: Stent-grafts [SG] containing a polytetrafluorethylene [PTFE-] membrane have recently become available for implantation into human coronary arteries. The microporous PTFE-layer in the body of the SG may inhibit restenosis by eliminating plaque protrusion, attenuating diffusion of cytokines and hindering transmigration of inflammatory cells. There are no data available on the pattern of neointima [NI] formation in these novel devices.

Methods: We performed intravascular ultrasound [IVUS] in 21 patients aged 64 ± 7 years at 3–6 months follow-up after coronary implantation of 1.1 ± 0.3 SG with a total length of 18.1 ± 7.8 mm. SG were deployed into 12 native coronary arteries and 9 saphenous vein grafts at 19 ± 1 atm.

Results: Angiographic minimal lumen diameter before and after intervention and at follow-up was 0.72 ± 0.57, 3.03 ± 0.38 and 2.01 ± 0.89 mm respectively. At follow-up, there was complete SG-apposition in all cases and no indication of PTFE-membrane disruption.

IVUS:	Prox. edge	SG-body	distal edge	P
SG-area [mm^2]	7.40 ± 2.05	7.01 ± 1.80	7.47 ± 2.34	n.s.
NI-area [mm^2]	1.55 ± 1.05	0.74 ± 1.37*	1.59 ± 1.27	<0.01
Max. NI [mm]	0.34 ± 0.24	0.14 ± 0.19*	0.31 ± 0.25	<0.01

Conclusions: Neointimal proliferation in coronary PTFE stent-grafts occurs predominantly at the edges not covered by the PTFE-membrane. There is only minimal proliferation in the body of PTFE stent-grafts, indicating an antiproliferative effect of hermetically sealing the vessel wall.

P1536 PhVEGF coated stent reduces restenosis intimal hyperplasia

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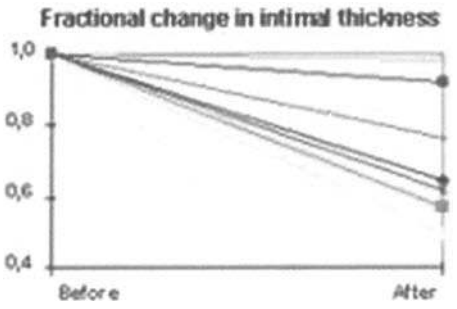
Background: Restenosis after PTCA is characterized by endothelial injury and proliferation of arterial smooth muscle. The restenosis process can be counteracted by reendothelialization that can be stimulated by Vascular Endothelial Growth Factor (VEGF). The aim of our study was to evaluate the effect of phVEGF coated stent on intimal hyperplasia.

Methods and Results: The study was performed on seven rabbits. Endothelial injury was created by balloon angioplasty over-dilation (20%) of the iliac artery, 3 × 30 sec. Cook stent, active or control were, respectively, dipped into a saline solution with phVEGF or with placebo plasmid (control). Thereafter the phVEGF stent was implanted into the left and the control stent into the right iliac artery. To avoid thrombosis all rabbits received dalteparin 200 IE/kg/day from a subcutaneous osmotic pump during the study period of three weeks. Morpho-metric analysis of the tissue sections after three weeks showed that all arteries with phVEGF coated stent had a decreased intimal thickness (figure) with a mean of 29 ± 18%, $p < 0.016$ compared to arterial segments treated with placebo plasmid.



Conclusion: The phVEGF coated stent reduced intimal hyper-plasia. Suggesting a new mode of treatment against restenosis.

P1537 Acute recoil of biodegradable poly-l-lactic acid coronary stents in humans

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Background: Although, metallic stents are thought to be effective to prevent acute reocclusion and to reduce late restenosis following coronary angioplasty, the long-term safety still remains to be studied. A biodegradable stent is thought to solve the problems of metallic stents. This is the first report of recoil of PLLA stents in human with intravascular ultrasound (IVUS).

Methods and Results: The Igaki-Tamai stent is made of PLLA monopolymer with 0.17 mm thickness, and has a zigzag helical coil design with self expanding ability. Fifteen patients electively underwent PLLA Igaki-Tamai stent implantation for coronary artery stenosis. There were 14 males and 1 female in this study, and 25 stents were implanted through 17 procedures in 19 lesions (8 in left anterior descending artery, 4 in right coronary artery and 7 in left circumflex coronary artery). PLLA stents were successfully implanted in all patients. To evaluate recoil of the PLLA stent IVUS studies were performed immediately after, and at 1-day using 40 MHz IVUS system (Discovery SCIMED) with motorized pullback system. The mean stent cross-sectional area (ST-CSA) was analyzed with computerized measurement system (Manual Measure: Goodman Co.,Ltd.) in all stents. There was no significant difference in ST-CSA between immediately after and at 1-day (7.42 ± 1.52 mm^2 vs 7.37 ± 1.44 mm^2, n.s.). Thus far three patients underwent 3 months angiographic and IVUS follow-up, and no restenosis were detected. IVUS showed that the mean ST-CSA was significantly bigger at 3 months than at 1 day (11.68 ± 0.74 mm^2 vs 8.91 ± 0.65 mm^2, $p = 0.026$) with minimal neointimal hyperplasia.

Conclusions: IVUS showed no significant stent recoil between immediately after implantation and at 1 day and self expanding ability at 3 months. Long-term IVUS follow-up will determine the efficacy of PLLA stents.

P1538 Sustained intramural retention and regional redistribution of locally delivered nanoparticulate probucol

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Background: Probucol (Pr) reduces restenosis following angioplasty, provided oral administration is begun 1 month prior to the procedure. The urgency of many angioplasties, however, hampers its therapeutic utility. Local vascular delivery of a nanoparticulate formulation of Pr may obviate the need for drug loading by acutely raising arterial intramural concentration and providing sustained intramural retention. We characterized the retention and redistribution of 35S-Pr encapsulated in liposomal (Lip)and polylactic-coglycolic acid (PLGA) nanoparticles following local delivery.

Methods: Nanoparticles were delivered using a Crescendo microporous infusion catheter (Cordis, Warren, NJ) following balloon angioplasty of rabbit iliac arteries (n = 12–18 arteries/formulation/time point). Animals were euthanized on day 0, 3, or 7 following delivery. Iliac arteries, perivascular fat, and downstream tissues were harvested and the radioactivity (dpm) measured. Autoradiographic and confocal microscopic analyses of tissue sections were performed to evaluate intramural distribution of Pr.

Results: Immediately following delivery, radioactivity in the iliac arteries (log[dpm/mg], mean ± S.E.M.), was greater with PLGA (2.72 ± 0.08) than with liposomal encapsulation (2.10 ± 0.08), $p = 0.001$. Intramural retention of Pr was 23% at 7 days using liposomes and 10% using PLGA, corresponding to a Pr concentration of 0.1 ng/mg tissue for both formulations. At day 3 following iliac delivery, radioactivity in peri-iliac fat, femoral arteries, and hindlimb muscle increased by 88%, 29%, and 154%, respectively. Thereafter, radioactivity fell to 56%, 43%, and 134% of initial dpm respectively, by day 7. Autoradiography demonstrated a homogeneous distribution of radiolabeled Pr in the arterial wall at day 7. Confocal microscopy confirmed retention of nanoparticles through day 7.

Conclusions: 1) Nanoparticulate formulation of probucol resulted in sustained intramural retention; 2) Although delivery efficiency was superior with PLGA encapsulation, intramural concentrations of probucol were similar on day 7 using both formulations; 3) Radial and axial redistribution of probucol was observed, manifest as an early increase in adjacent tissue concentrations followed by delayed washout.

P1539 A comparison of a biodegradable poly-l-lactic acid coronary stent and a metallic stent in porcine coronary artery

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Background: Although biocompatibility of biodegradable stents is controversial, stents made of high molecular weight Poly-l-Lactic Acid(PLLA) are thought to be the most promising among biodegradable polymers. The aim of this study was to assess the biocompatibility of PLLA stents histologically and angiographically in porcine coronary arteries.

Methods: Igaki-Tamai stent is made of PLLA monofilament (molecular mass 183 kD) with a zigzag helical coil design. Fourteen PLLA stents in 6 pigs and 9 Palmaz-Schatz(P-S) half stents in 9 pigs were implanted in 15 normocholesterolemic juvenile domestic farm pigs, weighing 25 to 35 kg. Stents were mounted on the delivery catheter 3.0 mm in diameter, and were implanted percutaneously into coronary arteries. Coronary angiography was performed before and immediately after stenting, at 2 and 6 weeks in 5 PLLA pigs and 9 P-S pigs. Histologic studies were performed in PLLA pigs; 2 pigs at 2 weeks, at 3 pigs at 6 weeks and 1 pig at 16 weeks with hematoxylin-eosin and van Gieson's methods.

Results: No acute or subacute thrombotic occlusion was detected in PLLA and P-S groups. There were no differences in percent stenosis angiographically between the PLLA and P-S groups immediately after (4.2 ± 4.6%; n = 14 vs 8.4 ± 5.5%; n = 9), at 2 weeks (23.8 ± 14.4%; n = 12 vs 13.7 ± 6.3%; n = 9) and at 6 weeks (24.2 ± 19.8%; n = 7 vs 15.9 ± 15.6%; n = 4). Histological findings at 2, 6 and 16 weeks revealed no inflammation with minimal neointimal coverage on the stent struts of PLLA stents and showed that the PLLA stent maintained scaffolding force at 16 weeks in porcine coronary arteries.

Conclusions: The results in the study suggest biocompatibility and sufficient scaffolding force of PLLA biodegradable stents in porcine coronary arteries. Clinical trial will be required to validate the efficacy of PLLA stent in humans.

P1540 Polyhydroxybutyriate (PHB) biodegradable stent – experience in the rabbit

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Stents are established devices in interventional cardiology but their long-term vascular trauma might be reduced when being manufactured of biodegradable material.

Methods: After implantation into the iliac arteries of 19 New Zealand White Rabbits 19 biodegradable PHB stents and 18 tantalum stents were compared. The animals were kept on aspirin 6 mg/kg/day. Animals were sacrificed at various intervals. Specimens were fixed in paraformaldehyde (2%), cut to slices of 5 mm each, the tantalum struts were removed, the PHB struts were left in place, and the specimens were paraffin embedded and stained by H&E and Goldner.

Results:

	4 wks	11 wks	16 wks	26 wks
– Tantalum stents	5	4	2	7
Stent stenosis	<20%	30–40%	<20%	<20%
– PHB stents	5	5	4	5
Stent stenosis	>90%	>90%	<20%	<80%
Stent biodegraded	None	incomplete	nearly completely	

In conclusion, the prototype PHB-stent is nearly completely dissolved after 16 to 26 weeks but the marked transient proliferation makes it inferior to ordinary tantalum stents.

P1541 Acute result of biodegradable poly-l-lactic acid coronary stents in humans: an alternative to metallic stents?

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Background: Although, metallic stents are thought to be effective to prevent acute reocclusion and to reduce late restenosis following coronary angioplasty, the long-term safety still remains to be solved. Poly-l-lactic acid (PLLA) biodegradable stents are expected to solve the problem. This is the first experience with PLLA stents in humans.

Methods and Results: Fifteen patients electively underwent PLLA Igaki-Tamai stent implantation for coronary artery stenosis. The Igaki-Tamai stent is made of PLLA monopolymer with 0.17 mm thickness, and has a zigzag helical coil design with self expanding ability. There were 14 males and 1 female in this study, and 25 stents were implanted through 17 procedures in 19 lesions (8 in left anterior descending artery, 4 in right coronary artery and 7 in left circumflex coronary artery). Coronary angiography was performed before, immediately after, and 1-day after the procedure and assessed by quantitative coronary angiography method. PLLA stents were successfully implanted in all patients with mean inflation pressure of 10.8 ± 1.5 atm. The reference vessel diameter was 2.85 ± 0.34 mm, and the lesion length was 13.4 ± 5.9 mm. The percent stenosis before, immediately after, and 1-day after stent implantation were 64 ± 11%, 12 ± 8%, and 13 ± 11%. The acute recoil ratio of the stent defined as (1-minimal lumen diameter immediately after implantation/maximal balloon diameter) × 100(%) was 22 ± 7%. After stent implantation there was no further recoil at 1-day. No stent thrombosis and no major cardiac events developed within 30 days. Three patients underwent 3 months follow-up angiography, and no restenosis were detected.

Conclusions: Our preliminary experience suggest feasibility, safety, and efficacy of PLLA biodegradable stents in humans. Long-term follow-up with larger numbers of patients will be required to validate the long-term efficacy of PLLA stents.

MANAGEMENT OF UNSTABLE ANGINA

P1542 Abciximab provides cost efficient, safely expedited care for unstable angina

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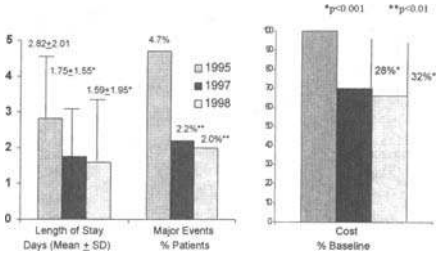
To determine influence of abciximab (AB) on cost and outcomes of treatment following percutaneous coronary intervention (PCI) in patients with unstable angina (UA), we analyzed three cohorts of consecutive patients with UA having PCI by Ohio Heart Health Center operators at The Christ Hospital: 1995 (April–June; n = 94), 1997 (Jan–June; n = 321), 1998 (Jan–June; n = 352).

Results: No demographic differences between cohorts were noted. Procedural use of AB and coronary stents were 16 and 19% (1995); 70 and 60% (1997); 75 and 81% (1998) respectively. AB use during PCI for UA was guideline driven in 1997 and 1998. Hospital length of stay, major events (death, Q-wave infarction, urgent revascularization) and total hospital cost (percent baseline 1995) are shown. Urgent revascularization to 30 days post PCI was significantly reduced in both 1997 and 1998.



In conclusion, practice guideline driven AB for PCI allows safely expedited care for patients with UA. Cost of AB can be counterbalanced by shorter length of stay and low incidence of costly major complications.

P1543 Long-term outcome of a prospective randomized, multicentre, placebo-controlled trial of 3 months treatment with low-molecular-weight heparin (dalteparin) in unstable coronary disease: the FRISCII trial

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Despite the salutary effects of early antithrombotic treatment in UCAD there still is a disappointingly 10 – 15% rate of myocardial infarction (MI) during the subsequent 3 – 6 months. Several trials have demonstrated a reactivation of the underlying disease early after termination of the intense antithrombotic treatment. This is the first presentation of the late follow-up after three months twice daily subcutaneous lmw heparin versus placebo treatment.

Design: 2266 patients, 68% men, median age 68 years, with chest pain and signs of ischemia (ST-depression, T-wave inversion or elevation of cardiac markers) were randomised to 3 months s.c. dalteparin or placebo b.d. All patients had aspirin, 5 days s.c dalteparin. beta-blockade and a primarily non-invasive approach concerning revascularisation. Endpoints are death or myocardial infarction, revascularisation, readmissions, and symptoms at 3 and 6 months. Subgroup analyses are based on baseline characteristics, ECG and biochemical markers in blood samples obtained at admission from all patients

Results: At entry 33% had hypertension, 26% ere smokers, 60% cholesterol > 5.5 mmol/l and 29% history of previous MI and 81% of chest pain at rest. In 50% ECG showed ST-depression and 59% had troponin-T > 0.1 ug/l. After the acute phase 92% entered the three months randomised treatment which was concluded by 81% and prematurely terminated in 7% because of patient request, 7% adverse events and 4% other reasons. The 3 months rate of death or myocardial infarction was 10.5% and revascularisation 20%.

Conclusion: The long-term outcome of these vastly different durations of antithrombotic treatment will have a large impact on the future treatment strategy and tailoring of treatment for these patients and on the design of future trials on similar issues.

P1544 Early angiography in the evaluation of patients presenting with unstable angina

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Background: The role of early angiography in the evaluation of patients with unstable angina or suspected non-Q-wave myocardial infarction remains controversial.

Methods: We reviewed data from the Olmsted County Acute Chest Pain Study, a population-based dataset which includes all patients residing within Olmsted County presenting for emergency department evaluation of acute chest pain from 1985–1992. Patients presenting with symptoms consistent with myocardial ischemia qualifying as unstable angina by conventional definitions were classified as undergoing early (≤7 days of index presentation) angiography or not.

Results: 2282 consecutive patients with unstable angina were identified, of which 892 underwent early angiography. Mean duration of follow-up was 5.9 years. For the entire cohort, early angiography was associated with an adjusted relative risk reduction in all-cause mortality (RR 0.66, 95% CI 0.55–0.78). When patients were risk stratified according to Agency for Health Care Policy and Research guidelines, early angiography in intermediate risk patients (n = 1562) was associated with a reduction in all-cause mortality (RR 0.64, 95% CI 0.52–0.79) as well as the composite endpoint of death, myocardial infarction, congestive heart failure, stroke, or cardiac arrest (RR 0.65, 95% CI 0.52–0.80). Early angiography was weakly associated with mortality reduction in high risk patients (n = 442) (RR 0.75, 95% CI 0.55–1.02), but not in low risk patients (n = 278) (RR 0.34, 95% CI 0.08–1.51).

In conclusion, in this population-based retrospective study, early angiography was associated with a reduction in all-cause mortality during the course of long-term follow-up, which was most evident in the intermediate risk cohort. Further analysis of various subgroups will also be presented.

P1545 Perhexiline normalizes platelet responsiveness to nitric oxide in patients with stable and unstable angina pectoris

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Perhexiline is a prophylactic anti-anginal agent which inhibits the enzyme carnitine palmitoyltransferase-1 (CPT-1), thus inhibiting metabolism of long-chain fatty acids and increasing responsiveness to insulin and glucose utilization. We examined the effect of short-term perhexiline therapy on platelet responsiveness to nitric oxide (NO).

Methods: Inhibition of ADP-induced platelet aggregation by the NO donor sodium nitroprusside (SNP) was examined in patients with stable angina (SAP, n = 30) and unstable angina pectoris (UAP, n = 40) who had refractory angina despite conventional therapy, before and after initiation of adjunctive treatment with perhexiline. SNP responsiveness was compared to normal volunteers (n = 24). Correlations were sought with symptomatic responses and plasma perhexiline concentrations.

Results: After initiation of perhexiline therapy, SNP response was significantly increased (towards normal) from baseline (see Table). In patients with SAP, anginal frequency reduced from 7 ± 1 to 1 ± 0.3 episodes per day, while 73% of those patients with UAP became asymptomatic. These UAP patients demonstrated a larger increase in SNP response than those who remained symptomatic. The increase in SNP response was correlated ($p < 0.01$) with resolution of symptoms in both groups of patients. Perhexiline plasma concentration was not correlated with either SNP responsiveness or resolution of symptoms. A cohort of UAP (n = 11) not receiving perhexiline demonstrated no change in responsiveness to SNP. Platelet response to perhexiline did not vary between diabetic (n = 20) and non-diabetic (n = 50) patients.

Table: Inhibition of aggregation

Group	Baseline	Perhexiline	P-value
Normals	51 ± 4		
SAP	35 ± 5	52 ± 4	<0.001
UAP	28 ± 3	39 ± 4	<0.01

%; mean ± SEM.

Conclusion: Perhexiline markedly improves platelet responsiveness to NO, both in SAP and UAP. While this may contribute to resolution of symptoms, the mechanism of benefit remains to be elucidated.

P1546 Bed-side predictors of the degree of platelets activation in patient with unstable angina

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Platelets play an important role in the pathophysiology of unstable angina (UA). However, which patients (Pt) may benefit from or may need a stronger antiplatelet therapy is not established. The purpose of this study was to determine predictors of the degree of platelets activation (PA) in pt with UA. PA was determined by flow cytometry measuring the expression of P-Selectin (P-S), CD-63 and Anti-Fibrinogen (AF) at admission and 48–72 hs after antithrombotic treatment (aspirin and iv Heparin) in 32 pt admitted with UA. Several clinical (prior history, prior meds, clinical presentation, etc), laboratory (CK, CK-MB, Troponin T, fibrinogen, and PCR) and EKG (ST vs T changes) variables were studied in order to find predictors of PA. None of the variables evaluated predicted the degree of PA at admission but the timing of the last episode of pain to admission, with higher PA in pt with > 6 hs compared with <6 hs (P-S, 1.3 ± 2.3% vs 0.67 ± 1.2%, p:0.3; CD-63, 7.1 ± 10% vs 1.6 ± 2%, p:0.02; AF, 61 ± 26% vs 40 ± 22, p:0.04). Two variables predicted the response to treatment, the Troponin T and the type of EKG changes. Pt with Troponin T(+) and ST changes had a significant lesser response or even higher levels of PA after treatment. The table shows the change in PA markers between admission and treatment.

	Troponin T (+)	Troponin T (–)	EKG (ST)	EKG (T)
P-S (%)	(In) 1.1 ± 2.3	(Dec) 0.4 ± 2.3	(In) 0.4 ± 1.2 *	(Dec) 0.23 ± 1.2
CD-63 (%)	(In) 6.4 ± 11 *	(In) 1.1 ± 4.7	(In) 2.6 ± 4.4 *	(In) 2.1 ± 9.1
AF (%)	(Dec) 5.5 ± 22	(Dec) 15 ± 32 *	(Dec) 7.0 ± 27	(Dec) 20 ± 37 *

Increase (In); Decrease (Dec); *p < 0.05

Conclusions: Bed-side variables like the timing of the last episode of pain, the admission Troponin T and the type of EKG changes were associated with different degree platelets activation at admission and response to antithrombotic treatment. These findings may have important clinical implication in the treatment of patients with unstable angina.

UNSTABLE CORONARY DISEASE: MECHANISMS AND STRATIFICATION

P1547 Infection with cytomegalovirus and risks of coronary heart disease

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The human cytomegalovirus plays a causal role in atherosclerosis etiology,but it is discussed as controversial.We conducted a case control study to investigate whether previous infection with cytomegalovirus is associated with coronary heart disease and markers of systemic inflammation,because systemic inflammation may play a role in atherosclerosis too.

We enrolled 100 cases aged 38–70 years (mean age 59.8 years) with a coronary stenosis greater than 50% in the study and 150 controls(blood donors without angina pectoris)who were matched for sex and age. Cytomegalovirus serology was performed to determine presence of specific IgG-antibodies.In addition C-reactive protein(CRP),leucocytes and neutrophils were determined.The prevalance of specific antibodies to cytomegalovirus was 55% in cases and 52% in controls ($p > 0.05$ for difference among groups). Mean value of CRP was 1.68 mg/l in IgG-positive cases, 1.49 mg/l in IgG-negative cases, 1.30 mg/l in IgG-positive controls.The odds ratio for coronary heart disease was 1.05 (95% confidence interval 1.00–1.08) given a positive serostatus of IgG-antibodies to cytomegalovirus after adjustment for covariates.

In conclusion,although cases had higher mean CRP-values than cytomegalovirus-negative subjects,serological evidence of previous infection with cytomegalovirus is no independent risk factor for coronary heart disease in this population.

P1548 Hepatocyte growth factor as a novel marker for unstable angina in patients with chest pain at rest

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Background: We previously reported that serum hepatocyte growth factor (HGF), a novel endothelial growth factor, were elevated in patients with unstable angina pectoris. We hypothesized that elevated serum HGF levels might have a diagnostic value for unstable angina. To verify our hypothesis, we measured serum HGF in patients with chest pain at rest.

Methods: The subjects were 44 consecutive patients who complained chest pain at rest without any abnormalities of ST-T segments in ECG. Serum HGF levels were measured by the ELISA method before administration of heparin. +2 S.D. value of serum HGF levels in 20 normal subjects was used as a cut off value (normal 0.21 ± 0.03 ng/mL, cut off value >0.28 ng/mL). Patients with acute myocardial infarction, renal failure, and liver disease were excluded.

Results: 27 patients were confirmed having significant stenosis in coronary angiography (Plaque group). 16 patients were finally diagnosed as a variant angina and 1 patient was a chest pain syndrome (non-plaque group). The non-plaque group did not have a significant stenosis in coronary angiography. The plaque group had significantly higher serum HGF levels than the non-plaque group (0.34 ± 0.07 vs 0.23 ± 0.03 ng/mL, $p < 0.01$). A cut off value of >0.28 ng/mL had 85% of sensitivity and 88% of specificity for diagnosis of having stenosis on CAG in patients with chest pain at rest.

Conclusions: High serum HGF levels have favorable sensitivity and specificity for diagnosing an unstable angina. Measurements of serum HGF may influence a diagnosis of unstable angina pectoris.

P1549 The activity of antioxidant enzymes in red blood cells of patients with unstable angina

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It is thought that the activity of enzymes with antioxidant properties is changed by toxic oxygen metabolites released during oxidative stress. The oxidative stress takes place in ischemia and reperfusion and therefore should be observed in patients with myocardial ischemia. The study aim was to evaluate whether the activity of endogenous antioxidants in patients with unstable angina (UA) differs from noticed in healthy subjects. The activity of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) were measured in red blood cells of 125 UA patients (59.1 ± 10.7 years old; 42 female) and 35 healthy people (57.3 ± 8.7 years old; 12 female). Results presented in U/ml are shown in table 1. The obtained results indicate that there is an increase in erythrocyte SOD activity in patients with UA compared with healthy subjects. On the contrary, the activity of CAT and GPx in red blood cells of UA subjects are significantly lower than observed in healthy people.

Table 1

All in U/ml	Healthy subjects	UA patients	p value
SOD	1251 ± 378	1971 ± 908	<0.0001
CAT	34.0 ± 4.8	27.1 ± 10.9	=0.0007
GPx	31.1 ± 2.9	22.0 ± 11.6	<0.0001

The noticed changes in the activity of enzymes playing a crucial role in antioxidant systems support the concept of the oxidative stress appearance in the course of myocardial ischemia.

P1550 The role of intensive metabolic control by insulin infusion on fibrinolytic profile during an acute coronary event

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We investigate the impact of intensive insulin therapy on fibrinolytic parameters during an acute coronary event (unstable angina or myocardial infarction) in patients with type 2 diabetes mellitus.

Methods: The study group consisted of 48 type 2 diabetic patients. 24 randomized to conventional treatment plus intensive insulin therapy (Group A) and 24 to conventional therapy only (Group B). Group A patients received insulin by infusion for at least 48 hours according to a predefined protocol. Multiple dose subcutaneous insulin treatment was started immediately after insulin infusion cessation until the end of hospitalization aiming to maintain normoglycaemia. The two groups were comparable according to sex, age, bmi, whr, duration of diabetes, antidiabetic treatment, type of ischaemic events and the classic risk factors for coronary artery disease. Insulin treated patients were excluded from the study. Plasma levels of Fibrinogen, t-PA, PAI-1 were measured on admission and discharge. Differences between groups were tested by Student's unpaired t-test and Wilcoxon test for two samples for continuous data and Fisher's exact test for nominal data. Differences within groups were tested by students paired t-test. A two tailed p value less than 0.05 was considered statistically significant.

Results: t-PA increased in both Groups during hospitalization (Group A: $p < 0.000037$, Group B: $p < 0.001$ respectively) (see table). On the contrary, fibrinogen and PAI-1 levels increased remarkably in controls (Group B: $p < 0.002$ and $p < 0.003$ respectively) finding that was not observed in intensive insulin therapy group (Group A:p = NS and p = NS respectively).

Fibrinolytic parameters values

	Group A	Group B
Fibrinogen on admission	2.87 ± 0.73 gr/lt	2.98 ± 1.04 gr/lt
Fibrinogen on discharge	2.67 ± 0.72 gr/lt	3.59 ± 1.01 gr/lt
t-PA on admission	15.42 ± 4.4 ng/ml	14.47 ± 6.31 ng/ml
t-PA on discharge	21.2 ± 5.74 ng/ml	19.18 ± 6.88 ng/ml
PAI-1 on admission	30.75 ± 15.81 ng/ml	30.6 ± 17.34 ng/ml
PAI-1 on discharge	27.75 ± 6.43 ng/ml	40.62 ± 23.48 ng/ml

In conclusion: Intensive insulin therapy during an acute coronary event improves fibrinolytic profile in patients with diabetes mellitus.

P1551 Nutcracker oesophagus – a common finding in unexplained chest pain patients

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Non-cardiac chest pain remains an important clinical problem. The most common etiology is esophageal dysfunction; gastroesophageal reflux, esophageal dysmotility and visceral hypersensitivity. Nutcracker esophagus is the principal dysmotility associated with chest pain. The aim of this study was to explore the prevalence of esophageal dysmotility in patients referred for esophageal evaluation because of chest pain.

Methods: 597 consecutive esophageal investigations 1993–98 were studied retrospectively. Esophageal motor function (by esophageal manometry) and acid related disorders (by 24-h pH), were compared to symptoms of referral. Nutcracker esophagus was defined as mean amplitude of >180 mmHg at any level of the esophagus; Hypertensive lower esopageal sphincter was defined as amplitudes >45 mmHg in the sphincter region and Diffuse esophageal spasm as >30% simultaneous contractions. A pH < 4 in >4% of recorded time was considered as a sign of gastro esophageal reflux disease.

Results: 244 patients (41%) were referred for evaluation because of chest pain; 203 had chest pain as only symptom. 60 investigations in chest pain patients (25%) showed esophageal dysmotility; most commonly nutcracker esophagus in 14.3% (compared to 4.5% in the patients without chest pain, $p < 0.0001$, and 2.6% in 234 patients with reflux dyspepsia). 55% of patients with esophageal dysmotility also had an increased acid exposure time >4%.

Conclusions: Esophageal dysmotility is a common finding in patients referred for esophageal evaluation because of chest pain, and was found in 25% in this study. Nutcracker esophagus is 3 times more common in patients with chest pain, compared to patients referred for other symptoms. If only 24-h pH measurements were carried out, 45% of patients with possible esophageal etiology of chest pain may have been missed. Esophageal manometry should be part of the esophageal investigation of chest pain patients, in addition to 24-h pH.

P1552 Clinical relevance of apoptosis mediator-soluble forms in acute myocardial infarction

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Background: Fas and tumor necrosis factor receptor I (TNFRI) are cell-surface proteins and apoptosis-signaling molecules. Furthermore, Fas ligand (FasL), a member of the TNF family, induces apoptosis in Fas (the receptor of FasL) bearing cells. This study investigates the kinetics of soluble forms of these apoptosis mediators (sFasL, sFas and sTNFRI) in relation to the severity of acute myocardial infarction (AMI).

Methods: Serum concentrations of sFasL, sFas and sTNFRI were determined in 31 AMI patients (20 men and 11 women; aged: 59 ± 8 yrs) without present history of infection or malignancy by high sensitive Elisa assays serially during the first week of hospitalization. Patients of group A (n = 16) had uncomplicated AMI (Killip class I), while patients of group B (n = 15) had severe AMI (Killip class ≥ II). Finally, 10 age-matched volunteers were used as healthy controls.

Results: Peaks of sFasL levels were not significantly different between the two groups of AMI patients (102 ± 29.1 vs 109.5 ± 31.2 pg/ml, p = NS) but were significantly higher than the respective levels of healthy controls (79.1 ± 21.3 pg/ml, $p < 0.03$). Peaks of sFas and sTNFRI levels were significantly higher in group B, compared with group A (sFas: 5.7 ± 1.5 vs 3.4 ± 0.7 ng/ml, $p < 0.01$ and sTNFRI: 4.1 ± 1.1 vs 2.9 ± 0.6 ng/ml, $p < 0.01$) and healthy controls (sFas: 2.6 ± 0.9 ng/ml and sTNFRI: 1.9 ± 0.1 ng/ml, $p < 0.001$). In group B, regression analysis showed that the peak of sTNFRI levels was significantly correlated with peak of sFas levels ($r = 0.55$, $p < 0.05$), white blood cell counts ($r = 0.60$, $p < 0.01$), peak of serum CK MB isoenzyme ($r = 0.63$, $p < 0.01$) and ejection fraction ($r = -0.65$, $p < 0.01$). In the same group, the peak of sFas levels was also significantly correlated with white blood cell counts ($r = 0.49$, $p < 0.05$), peak of serum CK-MB ($r = 0.57$, $p < 0.05$) and ejection fraction ($r = -0.60$, $p < 0.01$). Finally, in group B non survivors (n = 4) had significantly higher peaks of sTNFRI and sFas levels (both $p < 0.05$) than those of survivors (n = 11).

Conclusions: Serum activity of apoptosis mediator soluble forms increases substantially in AMI. Furthermore, we observed a significant relation of sFas and sTNFRI levels with the severity of AMI. Thus, these molecules closely correlated with worse prognosis of severe AMI patients, may be used as alternative prognostic indicators of severe AMI.

P1553 Increased cell adhesion molecules levels in patients with chest pain and normal coronary arteriograms

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Background: The pathogenesis of anginal chest pain in patients with angiographically normal coronary arteries (CPNA) remains unclear, however, endothelial microvascular dysfunction appears to play a role. A chronic inflammatory process with leukocyte activation and adhesion to vascular endothelium may lead to vascular dysfunction. The aim of this study was to test whether markers of endothelial activation i.e. intracellular and vascular cell adhesion molecules (ICAM-1 and VCAM-1) are increased in CPNA patients.

Methods: We studied 21 patients (6 men; mean age: 56 ± 9 ys) with exertional anginal chest pain, positive response to exercise stress testing and completely normal coronary angiograms (CPNA), 36 patients (34 men; mean age 62 ± 9 ys) with chronic stable angina and documented coronary artery disease (CAD) and 11 healthy volunteers (8 men; mean age 49 ± 14 ys) (Control). Circulating ICAM-1 and VCAM-1 plasma levels were measured in all subjects, using commercially available ELISA methods.

Results: Plasma ICAM-1 levels were significantly higher in CPNA patients compared to controls and similar to those of patients with CAD. VCAM-1 levels were also higher in CPNA and CAD patients than in controls. Results are summarized in the table:

	CPNA (n = 21)	CAD (n = 36)	Control (n = 11)
ICAM-1 (ng/ml)	362 (22)*	328 (26)#	225 (29)*#
vCAM-1 (ng/ml)	656 (43)	626 (42)	551 (60)

*CPNA vs Control: $p < 0.05$, #CAD vs Control: $p < 0.05$

Conclusions: Our findings indicate that chronic inflammation with endothelial involvement, as suggested by increased cell adhesion molecules levels, is present in patients with chest pain and normal coronary angiograms. The precise role of these findings in the pathophysiology of this condition deserves further investigation.

P1554 Elevated plasma homocysteine is associated with increased myocardial injury in the acute coronary syndromes

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Moderately raised plasma homocysteine levels are an independent risk factor for coronary artery disease and predict mortality in this patient group. The relationship between elevated plasma homocysteine levels and the degree of myocardial injury during acute coronary events is not known.

Methods: Plasma samples were collected on admission and prior to clinical intervention in patients presenting with acute myocardial infarction (MI)(n = 205), and unstable angina pectoris (UAP)(n = 185). Homocysteine assay was performed by high performance liquid chromatography. Troponin T (TnT), a highly specific marker of myocardial injury was measured on admission (admission TnT) and 12 hours after admission (Peak TnT).

Results: There was a significant correlation between homocysteine and peak TnT in MI ($r = 0.2$, $p < 0.003$), and UAP ($r = 0.3$, $P < 0.0001$). There was no correlation between homocysteine and admission TnT in both MI and UAP. Categorizing the patients by quintiles of admission homocysteine revealed a significant rise in peak TnT levels with increasing homocysteine quintiles in MI (ANOVA, $p < 0.02$) and UAP (ANOVA, $p < 0.0001$). A threshold effect was observed in MI with TnT levels (11.33 ± 1.29 ng/ml) in the 4th and 5th quintiles being significantly higher than TnT levels (6.82 ± 0.75 ng/ml) in the 1st, 2nd and 3rd quintiles ($p = 0.002$). Similarly in UAP, peak TnT levels were significantly higher in the 4th and 5th quintiles Vs the lower three quintiles (0.43 ± 0.09, 0.14 ± 0.03 ng/ml respectively, $p < 0.001$).

Peak TnT by Homocysteine Quintiles

Unstable Angina	(1)	(2)	(3)	(4)	(5)
Homocysteine Quintiles (umol/l)	<8.5	8.5–10.3	10.3–12.1	12.1–15.6	>15.6
Peak TnT (ng/ml)	0.14 ±0.06	0.18 ±0.07	0.10 ±0.05	0.30* ±0.13*	0.57* ±0.13*
Myocardial Infarction	(1)	(2)	(3)	(4)	(5)
Homocysteine Quintiles (umol/l)	<8.5	8.5–10.1	10.1–12.6	12.6–16.9	>16.9
Peak TnT (ng/ml)	7.42 ±1.66	5.66 ±0.78	7.32 ±1.26	10.131** ±1.81	12.54** ±1.86

TnT = Troponin T, TnT valus are expressed as mean ± SEM, *$p < 0.001$ Vs lower three quintiles,**$p = 0.009$ Vs lower three quintiles.

Conclusion: Elevated admission plasma homocysteine levels are associated with increased myocardial injury in the acute coronary syndromes.

P1555 Prevalence of the mutation of the gene for factor V is significantly increased in myocardial infarction

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Mutation of Factor V has been identified as the underlying cause of resistance against activated protein C (APC). APC has been shown to be responsible for 50% of congenital defects causing thrombophilia in the venous system. While early publications in 1995 and 1996 did not find an association between APC resistance and myocardial infarction, there is increasing evidence of a possible correlation in more recent publications, probably due to the availability of improved functional tests. Also, patient numbers in published studies were too low to reach significance due to high regional differences of the prevalence of the underlying genetic defect (1–15%). Therefore, we investigated a more homogeneous group of patients with myocardial infarction using a test with higher sensitivity.

The patient population analyzed comprised 237 patients with documented myocardial infarctions, 25.5% women and 74.5% men, age 23–86 (mean 52.5) years, 82.7% single and 17.3% multiple myocardial infarctions. Prevalence of the gene in the normal population in southern Germany is 5.5% (control group). A sensitive functional test was used, with all patients with pathological test results also genotyped.

Prevalence of factor V mutation in those patients with myocardial infarctions was 10.1% (24/237), with 2 homozygote and 22 heterozygote patients, which is a nearly two-fold increase of prevalence of resistance against APC compared with the normal population (10.1% versus 5.5%, $p < 0.05$). Of those 24 patients 33.3% of patients were women and 66.7% men. Age ranged between 35–80 (mean 52.0) years at the time of the first myocardial infarction and 13 patients were 50 years or younger.

Conclusion: A nearly two-fold incidence of resistance against APC in patients with myocardial infarctions may indicate a role in the etiology (dysmobility) of this disease, and perhaps even more in arterial thromboembolism.

P1556 "Low-risk" patients with chest pain have a high prevalence of significant coronary artery disease

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Patients with chest pain who have low risk clinical features and negative cardiac troponins may be suitable for direct discharge from the Emergency Department. Little is known about the prevalence and severity of coronary artery disease (CAD) in such patients, though this has implications for follow-up.

Methods: Subjects included all patients who entered the Cardiac Ischaemia Rule Out study at our institution, who were at <7% risk of acute myocardial infarction (MI) at presentation, had cardiac troponin I levels $<2\ \mu g ml^{-1}$ and remained clinically stable (using predefined criteria) at 0, 3, 6 & 12 h (n = 432). Those undergoing stress tests (STs) during this admission had these scored (high risk positive, positive or negative for reversible ischaemia and positive or negative for prior MI) by 2 independent blinded observers using predefined criteria. Coronary angiograms (CAs) were graded using AHA/ACC criteria: high risk if CABG would be recommended on prognostic grounds, positive for other patterns of CAD and normal or insignificant CAD (ie no stenosis >50%).

Results: Twenty five percent of patients had a history of MI, 11% of PTCA and 8% CABG. Fifty five percent had a history of hypertension, 22% were diabetic and 20% were current smokers. Ten percent had pathological Q waves on their presenting ECG, 13% had ≥1 mm ST segment +/or T wave deviation in ≥2 contiguous leads and 30% had more minor changes. Of the 165 STs performed, 7% were high risk positive for ischaemia, 20% positive and 73% negative. Of the 82 CAs, 10% were high risk positive, 61% positive and 29% normal/insignificant. Overall, 34% (149/432) of 'low risk' patients had objective evidence (a ST showing ischaemia or infarction +/or a positive CA +/or a history of revascularisation +/or pathological Q-waves) of significant CAD.

Conclusion: Many 'low risk' patients with chest pain have significant CAD and/or risk factors. This does not preclude early discharge from the Emergency Department but makes adequate follow up mandatory.

P1557 Early risk stratification of patients with unstable coronary artery disease based on cardiac troponin T, admission ECG and ST-segment monitoring. Proposal of a risk score system

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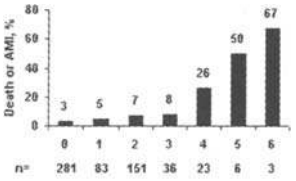
Patients admitted to hospital for unstable angina or non-Q wave infarction have a 15–20% risk of death or re-infarction during the first year after discharge from hospital. The majority of these events occur during the first 30 days. Cardiac troponin T, the admission ECG and continuous ST segment monitoring have been proven useful to risk stratify these patients. We constructed a comprehensive risk score based on each of these markers.

Methods and Results: Among 1209 patients participating in the multicentre TRIM study, 583 patients had at least 2 of the three markers prospectively recorded. Each of the three risk markers contributed 0, 1 or 2 points in a total risk score for each patient (table). The total risk score of 0–6 points was related to the event rate of death or myocadial (re-) infarction within 30 days of follow-up (figure).

Contibution of each marker to risk score

Points	Troponin T	ECG	ST monitoring
0	less than 0.1	0–1 mm ST depr	0 episodes
1	0.1–0.19	2–3 mm ST depr	1–4 episodes
2	0.2+	4+ mm ST depr	5+ episodes



Event rate according to risk score.

Conclusion: Risk stratification of patients with unstable coronary disease is improved by a simple risk score based on 3 major markers of risk.

P1558 Peripheral arterial tonometry – a novel sensitive noninvasive method for the detection of silent myocardial ischaemia in unstable angina

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Unstable angina (UA) is a heterogeneous clinical entity. In some patients, ischemia resolves after hospitalization and initiation of therapy, whereas in others repeated ischemia occurs despite therapy. In these patients there are by fluctuations in coronary blood flow due to constant change in size of the intraluminal thrombus and release of vasoactive substances, resulting in diastolic and then systolic dysfunction, electrocardiographic (ECG) changes and pain. Not all ischemic episodes cause ECG changes or pain. Hence, ECG is relatively insensitive for detection of ischemia. Currently, the troponin tests give us retrospective information whether the recent ischemic episodes were severe enough to cause myocardial damage. Ability to enhance online detection of ischemia noninvasively may help in diagnosis and monitor therapy.

Methods: 17 patients (pts)(15 men) with UA underwent overnight monitoring in ICCU with continuous 12-lead ECG and a peripheral arterial tonometry (PAT). The PAT is basically a pneumatic volume finger plethysmograph which monitors a peripheral arterial pulse wave amplitude (PWA) with however, improved performance in eliminating false signals. A reduction in the PWA signals an underlying peripheral arterial vasoconstriction (PAVC).

Results: 38 episodes of PAVC were detected in 14 pts (1–6 episodes per pt). In 3 pts no PAVC episodes were detected. Episodes lasted 2.5- 77 min. ECG changes (ST– or ST^-) were noted in 21 (55%) of the PWA episodes. In episodes with ECG changes, PAVC preceded (n = 18, 86%) or occurred simultaneously (n = 3, 14%) with ECG changes and PAC continued to be attenuated for several min after ECG changes resolved. There was only 1 episode of ECG changes without PAC. Chest pain was noted in 10 PAC episodes, in 9 of them ECG changes were noted.

In conclusion, PAT is a simple and noninvasive method that can be used for online detection and monitoring of spontaneous silent ischemia.

P1559 Myocardial gated spect using Tc-99m tetrofosmin can detect high risk patients whose symptoms had been resolved before arrival

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Accurate and immediate diagnosis is need for a therapy in patients with unstable angina. Previous reports have demonstrated the diagnostic usefulness of initial myocardial perfusion imaging in the evaluation of patients with chest pain. However, it was not confirmed whether this strategy could be useful among patients whose symptoms had been resolved prior to examination. Subjects consisted of 76 patients (45 males, 31 females; 66 ± 10 years) with history of recent chest pain, who were admitted to coronary care unit (CCU) and demonstrated no evidence of acute myocardial infarction. Electrocardiogram (ECG) and echocardiography (ECHO) were performed on admission, and myocardial gated SPECT using Tc-99m tetrofosmin (gated TF) were subsequently performed. We defined positive ischemia as residual ischemic ST-T change on ECG, focal asynergy of left ventricular wall on ECHO, and focal decrease of myocvardial perfusion on gated TF. Coronary artery disease (CAD) was defined as exceeding 50% narrowing in diameter on coronary angiography (CAG). We estimated the sensitivity, specificity, and accuracy of each diagnostic method based on CAG findings. An event-free ratio was determined by Kaplan-Meier estimation for an average of 199 days.

Results: Sensitivity, specificity, and accuracy of each diagnostic method and the average time duration from the time of most recent chest pain to each diagnostic evaluation were as follows (table).

	ECG	ECHO	Gated TF
Sensitivity	0.57	0.50	0.79
Specificity	0.36	0.80	0.56
Accuracy	0.52	0.54	0.74
Duration (by hour)	15.6	15.6	23.9

Further, Kaplan-Meiere estimation revealed that the significant increase of needs of revascularization (RE) was noted in positive gated TF as compared to that in negative gated TF (total RE: 24/53 vs 3/23 $p < 0.01$, urgent RE: 9/53 vs 0/23 $p = 0.06$). In conclusion, gated TF allowed for reasonably accurate evaluation of high risk group of CAD under emergency circumstances even in the case that the episode of chest pain had been resolved prior to examination.

THE ECG IN UNSTABLE CORONARY DISEASE

P1560 The incremental prognostic value of continuous ST-segment monitoring to baseline clinical descriptors in acute myocardial infarction

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We sought to define the incremental prognostic value of ST recovery parameters from continuous 12-lead ECG monitoring when added to the main adverse prognostic risk factors from the GUSTO-I mortality model.

825 patients were analyzed from substudies of 6 major thrombolytic trials. ST recovery parameters were: time to stable ST-recovery (>50% resolution of ST-segment elevation > 4 hours) and late ST elevation after stable ST recovery. High-risk patients had at least 1 of the following GUSTO-I predictors: age > 70, systolic BP < 110 mmHg, heart rate > 90, anterior MI, or previous MI. High, moderate, and low risk ST-groups were defined by the presence of both slow ST recovery (>2 hr) and late ST elevation, one or the other, or neither, respectively. Clinical endpoints were death, re-infarction, and congestive heart failure.

Results are shown in the table below.

Combined Outcome (%)

	Low ST	Medium ST	High ST	Overall
Low clin.risk*	21/143 (15)	14/99 (14)	7/19 (37)	42/261 (16)
High clin risk**	64/274 (23)	70/219 (32)	33/71 (49)	167/564 (30)
Overall**	85/417 (20)	84/318 (26)	40/90 (44)	209/825 (25)

*$p = 0.038$, **$p < 0.001$

Multivariable analysis revealed age, heart rate and late ST elevation as independent predictors of mortality, with model c-indices of 0.81 for clinical descriptors alone and 0.84 when combined with ST recovery variables.

In combination with baseline clinical descriptors, continuous 12-lead ST-segment monitoring significantly enhances the ability to predict clinical outcome.

P1561 Markers of risk in patients with unstable angina and MI without ST elevation: UK Prospective Registry of Acute Ischaemic Syndromes (PRAIS-UK)

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Background: The acute coronary syndromes (ACS) of unstable angina (UA) or myocardial infarction (MI) without ST elevation on the admitting ECG are important and frequent causes of admission in UK hospitals. Little is known about their outcomes or risk factors.

Methods: A prospective cohort registry of patients with UA or MI without ST elevation on the admitting ECG was carried out in 56 UK hospitals. Twenty consecutive eligible patients were enrolled in each centre.

Results: Data are available on 950 patients (target sample 1000). Mean age (standard deviation) was 66 (12) years, 40% female, 47% prior MI, 23% previous PTCA/CABG, 16% diabetes, 36% hypertensive. Admission diagnosis was 95% UA and 5% MI without ST elevation. On admission 15% had a normal ECG, 66% had other abnormalities (T wave changes, Q waves etc.) and 19% had ST segment depression. Median length of hospital stay was 4.5 days (inter-quartile range 2–7). The in-hospital rate of death or new non-fatal MI was 5.0%, and the rate of death, MI and severe recurrent ischaemia with documented ECG changes was 13.7%. Rate of death or new MI in those with normal ECG, other abnormality, and ST depression was 1.4%, 4.4%, and 9.9% respectively (odds ratio [OR] for other abnormality compared to normal ECG was 3.3 [$p = 0.11$] and, for ST depression compared to normal was 7.9 [$p = 0.006$]). Risk of death or new MI was greater with advancing age. In an analysis of age as a continuous variable, the proportional excess risk was 3% (95% confidence interval 0–6%) for each year ($p = 0.02$). The rate of death or new MI for those <60, 60–70 and >70 years was 2.0%, 5.6% and 6.9% respectively (OR for 60–70 compared to <60 was 2.9 [$p = 0.03$] and, for >70 compared to <60 was 3.7 [$p = 0.005$]).

Conclusion: These data confirm that age and ST depression on the ECG are important markers of risk in patients with unstable angina or MI without ST elevation. A multi variable model evaluating these and other risk factors will be presented using complete in-hospital and 6 month follow-up data.

P1562 One-year mortality predicted non-invasively during the first four hours of acute myocardial infarction

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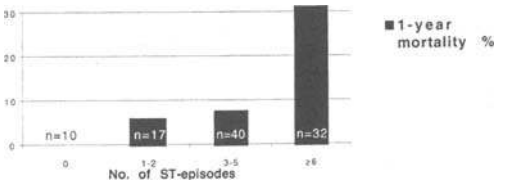
Introduction: ST-recovery has been used to predict patency and outcome in acute myocardial infarction (AMI). Continuous ST-monitoring provides real-time presentation of the dynamics in ECG-changes. ST-variability has been shown to predict outcome in patients with acute coronary syndromes. We have re-analysed ST-vector-monitoring in a unique material of 178 patients with suspected AMI, treated with either t-PA or placebo.

Methods: 178 patients with suspected AMI were monitored for 24 hours after admission using vectorcardiography. Changes in ST-Vectormagnitude (ST-VM) were calculated and presented as a trend-curve. Patients were included within 2.75 hours from onset of symptoms, randomised to 100 mg of rt-Pa or placebo. Heparin, aspirin and betablockade were given unless contraindicated. ST-segment variability was defined as an increase in ST-VM exceeding 25 μV, for at least 2 min. In the final analysis only patients with diagnosis of AMI were included (n = 102). 1 patient was excluded due to lack of 1-year-information, 2 due to lack of sufficient VCG-data.

Results: Patients alive at one year (86%) had significantly less ST-variability, 4.3 vs. 7.1 episodes ($p = 0.007$) and lower maximal ST-VM, 255 vs. 424 μV ($p = 0.002$). In a multivariate analysis, only ST-variability contributed to information about prognosis. The patients receiving t-PA had fewer ST-episodes 3.9 vs. 5.7 ($p = 0.015$) and a trend towards lower 1-year-mortality. 12 vs. 17% (p = ns).



Conclusion: ST-variability observed in the acute phase of AMI significantly is associated with adverse long-term outcome.

P1563 QT interval prolongation and mortality in type 1 diabetic patients: a 5-year cohort prospective study

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The association between QT interval prolongation on resting ECG and excess mortality in diabetic populations has been suggested in non diabetic populations and, recently, in newly diagnosed type 2 diabetic patients. **Aim:** To assess the relationship between QTc and mortality in type 1 diabetic patients.

Methods: We assessed neuropathy and corrected QT in a random sample of 379 out of all 766 type 1 diabetic patients attending 22 outpatients clinic in Piemonte, Italy and 118 healthy subjects matched for sex and age. This sample was representative of the type 1 diabetic population in the area of the study. Data on survival after 5 years were obtained in 316/379 patients (83.3%) and 106/118 control subjects (90.5%). The patients lost at follow up were not significantly different in age, duration of disease, body mass index, blood pressure and prevalence of autonomic neuropathy.

Results: Mortality at 5 years was 6.32% and 0.9% in the control group ($p < 0.001$). Patients who survived had a significantly different age (31.4 ± 11.1 vs 36.7 ± 10.7 years, $p = 0.04$), duration of diabetes (13.6 ± 8.7 vs 18.7 ± 10.9 years $p = 0.01$), systolic (123.9 ± 20.0 vs 138.0 ± 35.6 mmHg, $p = 0.004$) and diastolic blood pressure (80.5 ± 13.6 vs 83.6 ± 11.2 mmHg, $p = 0.03$) and QTc (0.41 ± 0.03 vs 0.45 ± 0.02 sec, $p = 0.000005$) compared to those who died. At univariate analysis patients had a higher risk of dying (OR, 95% CI) if they had a prolonged QTc (20.14, 5.7–70.8) or were affected by autonomic neuropathy (3.55, 1.4–8.9). QTc prolongation was the only variable which showed a highly significant mortality OR at multivariate analysis ($p = 0.000004$).

Conclusion: This is the first cohort-based prospective study indicating that QTc prolongation is predicitve of increased mortality also in type 1 diabetic patients. Even though the mechanism linking QTc prolongation and the excess mortality remains to be elucidated, QTc interval analysis is a simple non-invasive test that could be used to stratify the death risk in diabetic patients, particularly those who are candidates to surgery or kidney and/or pancreas transplantation.

P1564 Does bundle-branch block at hospital admission predict mortality in patients with acute myocardial infarction? A study in the thrombolytic era

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Aim of the study: A poor prognosis has been reported for patients with bundle branch block (BBB) on admission ECG in the setting of acute myocardial infarction (AMI). We investigated incidence and outcome of unselected, consecutive patients (pts) with AMI and BBB in the thrombolytic era.

Methods and results: Between 6/94 and 12/96, 6068 patients with acute AMI were admitted to one of 54 hospitals in southwest Germany and consecutively enrolled in the MITRA-registry (Maximally Individually Optimized Therapy after Acute Myocardial Infarction). Out of these, 593 pts (7%) presented with right- or left-BBB. Recanalisation therapy (including thrombolysis, primary PTCA, or both) was performed in 57.8% of pts without and 41.8% of pts with BBB ($p < 0.0001$). Pts with BBB had cardiogenic shock or heart failure in 10.8% and 14.0% of cases at admission, resp., compared to 4.0% and 8.3% in pts without BBB ($p < 0.0001$). 2-fold higher in-hospital mortality rates were found in pts with BBB and AMI compared to patients with AMI without BBB (31.4% vs. 15.2%, $p < 0.0001$), and analysis of long-term mortality of survivors revealed an even 2.5-fold higher mortality rate of pts with BBB and AMI compared to those without BBB (27.5% vs. 11.7%, $p < 0.0001$). After adjustment for other prognostic factors, BBB remained an independent predictor of in-hospital and long-term mortality (OR 1.7 and 1.6, resp.), with an higher prognostic impact of LBBB.

Conclusions: 1. BBB in pts with AMI is an independent predictor of in-hospital and long-term mortality. 2. Despite poor outcome of these pts, they receive recanalisation therapy less often than pts with AMI without BBB. 3. A careful monitoring of this high-risk subgroup of AMI pts is indicated, and 4. Reperfusion therapies need to be initiated more often to ameliorate the poor prognosis of pts with AMI and BBB.

P1565 QT dispersion in patients after acute myocardial infarction and unstable angina is dependent on the time from ischaemic event

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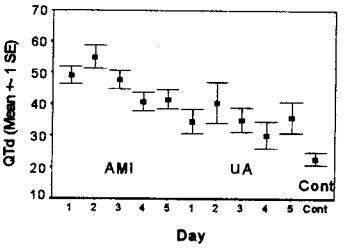
Background: The optimal timing for QT dispersion (QTd) measurement is important in ischaemic patients but there is a lack of information on the time course of QTd after an ischaemic event.

Aim: We hypothesised that QTd after acute myocardial infarction (AMI) and Unstable Angina (UA) are not static and may have an impact on the QTd measurement.

Method: 81 AMI patients (61 M, age 63 ± 12) and 22 UA patients (17 M, age 63 ± 13) were prospectively examined using Marquette MAC VU electrocardiograph equipped with QT Guard software which automatically analysed QTd on digitally stored ECGs. 10 consecutive ECGs were recorded and the mean QTd calculated each day from day 1 to 5 after AMI or UA. 68 controls (33 M, age 38 ± 9.3) each had 10 ECGs recorded and their mean QTd calculated.

Results: Compared with controls using student's t-test, AMI patients had higher QTd from day 1–5 after the index infarct (day 1, 2, 3, 4, 5: $P < 0.0001$) (fig.) UA patients had higher QTd from day 1–3 only and normalised on day 4 and 5 (day 1, 2, 3: $P < 0.05$, day 4, 5: P = NS). AMI patients had higher QTd than UA on day 1 ($P = 0.004$), 3 ($P = 0.012$) and 4 ($P = 0.046$) and a trend on day 2 ($P = 0.058$) but insignificant on day 5 (P = NS).



Conclusions: 1) QTd is increased on day 1–5 after AMI but on day 1–3 only in UA patients. 2) AMI patients had higher QTd on day 1, 3, 4 and a trend on day 2 than UA patients. 3) AMI and UA patients have different pattern and degree of dynamic changes of QTd. 4) The timing of QTd measurement is crucial in ischaemic patients and must take into account the time from ischaemic event as well as the degree of ischaemia

P1566 ST-segment depression patterns in transmural acute myocardial infarction: an analysis of significance using echocardiography

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Concomittant ST segment depression in leads other than infarct-related areas in acute transmural MI can be "reciprocal phenomena" or "ischemia at a distance". In order to investigate the significance of the presence of concomittant ST segment depressions, we restrospectively studied all ECG patterns together with the echocardiographic wall motion findings of patients with acute transmural MI.

Methods: 138 patients with acute transmural MI were randomly chosen and their records reviewed. 62 patients met the inclusion criteria. ECG on admission and 24 hours after admission were evaluated. Echocardiographic and demographic data were reviewed.

Results: Among the patients with inferior wall MI, 45% died and were found to have significantly larger infarct areas based on the peak CK-MB value. Forty-two percent precented with maximal ST segment depression in leads V4-V6(group III); these same patients were also found to have larger infarct sizes ($p = 0.005$), experienced more severe heart failure ($p = 0.04$) and cardiogenic shock ($p = 0.04$), experienced higher incidence of ventricular tachycardia ($p = 0.03$) and had significantly higher in-hospital mortality rates ($p = 0.045$) than among patients who did not have ST segment depressions (group I) or had ST segment depression sums in leads V1 to V3 equal to or more than the sum of ST segment depression in V4 to V6 (group II). Inferior, Posterolateral and Anteroseptal regional wall motion abnormality differences were statistically significant in the groups II patients with inferior wall MI. Among patients with anterior wall MI, 50% died. The patients who had maximal ST segment depression in both lateral and inferior leads (group A3) had statistically significant larger infarct sizes ($p = 0.01$), more severe heart failure upon admission ($p = 0.04$); cardiogenic shock ($p = 0.03$) and higher in-hospital mortality rates ($p = 0.02$). Posterolateral region wall abnormality score was also found to be significantly higher in these patients.

Conclusion: Certain ST segment depression patterns in patients with acute transmural MI in areas other than the infarct-related leads do not simply point to a "reciprocal phenomena", but rather an "ischemia at a distance". This ECG finding during admission of patients with acute transmural myocardial infarction might be an important and inexpensive tool for risk stratification and management in the era of therapeutic revascularization.

ACUTE MYOCARDIAL INFARCTION — MANAGEMENT STRATEGIES

P1567 How management strategy for acute myocardial infarction is influenced by established guidelines in an academic centre: comparison between 2 populations at 5 years interval

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Aim: To examine the evolution of the management strategy of acute myocardial infarction (AMI) according to established guidelines at a 5 year interval in an academic centre.

Methods: A retrospective study comparing 2 pts cohorts referred for AMI in 1991 and 1996.

Results: 156 pts in 1991 (average age 68 ± 13 years) and 144 pts in 1996 (average age 66 ± 13 years) were referred for AMI. Clinical characteristics were similar. Between 1991 and 1996, median time to hospitalisation decreased from 6 ± 2 hours to 5 ± 2 hours, and length of hospital stay from 7 ± 2 days to 6 ± 2 days. In-hospital mortality decreased from 10.2% in 1991 to 8.3% (NS). Reperfusion therapy was undertaken more frequently in 1996, due to increased use of primary angioplasty. Medications prescribed during hospital stay and at discharge varied significantly during the observational period. Use of nitrates and of Ca blockers dececeased, whilst use of beta-blockers, Ace inhibitors and statins increased. Coronary angiography and PTCA were carried out before hospital discharge in 47.4% and 30% of pts respectively in 1991 versus 72.2% and 48.6% in 1996 ($p < 0.0001$).

Treatments undertaken during hospital stay

	1991 (n = 156)	1996 (n = 144)	p value
Reperfusion%	43.6	53.5	0.08
Thrombolysis%	43	41.6	0.86
Primary PTCA%	0.6	11.8	0.0001
Rescue PTCA%	4.5	4.9	0.87
Aspirin%	73	82.6	0.03
Nitrates%	37	5.5	0.0001
Beta-blockers%	45	50	0.0001
Ca blockers%	39.7	3.5	0.0001
ACE inhibitors%	34	40.9	0.21
Statins%	1.2	58	0.0001

Conclusion: Reperfusion therapy is more frequently applied to AMI thanks to more frequent primary PTCA. Medical therapy is more frequently in keeping with established guidelines, but complementary invasive and revascularization procedures after the initial period are increasingly used, despite the lack of established guidelines. This may be related to the short length of hospital stay, and the need for early discharge of patients.

P1568 How many patients with acute myocardial infarction are at risk of being erroneously released from the emergency room?

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Patients with chest pain and no ST segment elevation on admission may be inappropriately discharged from the emergency room without the knowledge that they are having an acute myocardial infarction (AMI). It has been estimated that this occurs in 5% of patients, with an out of hospital mortality rate over 20%.

Methods: In order to increase diagnostic accuracy we have developed an algorithm to systematically evaluate patients with chest pain in the emergency room. From a series of 1003 consecutive patients 635 had neither ST segment elevation or left bundle branch block (LBBB) in their first ECG nor a definitely not angina-type chest pain associated with a normal/non-specific (N/NS) ECG. These patients underwent serial ECG and plasma CKMB measurements and 79 of them had an AMI by typical CKMB curve.

Results: Table depicts the observed incidence of AMI in these patients:

1st ECG	AMI	Plus 1st CKMB	AMI
↓ST/↓T (n = 159)	28%	Normal (n = 120)	18%
N/NS (n = 476)	6%	Normal (n = 395)	4%

Irrespective of ECG, patients with atypical angina had a very low rate of AMI, specially when first CKMB was normal.

Conclusions: Patients with chest pain and no ST elevation or LBBB on admission had an 11% chance of having AMI. Neither N/NS ECG nor normal first CKMB ruled out AMI, even when both were associated. Chest pain type was a good discriminator for non-AMI in these patients, specially when first CKMB was normal. If systematic and careful screening is not done atypical AMI patients will continue to be missed in the emergency room.

P1569 Clinical impact of local implementation of agreed guidelines for the management of patients with acute myocardial infarction

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Development of clinical practice guidelines is one of the most popular methods intended to promote translation of results from clinical trials into routine care. However, very little is known about the actual impact on pt. routine care of clinical guidelines for the management of pts. with AMI. To address this issue, we reviewed a prospectively collected cohort of consecutive pts. discharged with diagnosis of AMI from a 870-bed community based hospital in North-East Italy. Eighty-six consecutive pts. treated in 1996 (before guideline implementation) were compared with 70 consecutive pts. treated in 1997 (after guideline implementation) with respect to patterns of use of guideline directed pharmacotherapies for AMI, diagnostic testing, length of CCU stay, and clinical outcome.

The 2 groups were similar in male gender, age, AMI location and severity. Pts. managed before guideline implementation were less likely to receive thrombolysis (36% vs. 50%, $p = 0.05$), i.v. B-blockers at admission (13% vs. 31%, $p = 0.002$), oral B-blockers at CCU discharge (45% vs. 74%, $p = 0.0003$). When given, pts. managed before guideline implementation received lower dosage of i.v. heparin as manifested by a lower proportion of pts. reaching adequate aPTT levels at 24 hrs. (14% vs. 62%, $p < 0.0001$), of oral B-blockers (−50%, $p < 0.0001$) and higher dosage of aspirin (+100%, $p < 0.0001$). The time to mobilization (+1 day) and the length of CCU stay (+0.5 day) were longer in pts. managed before guideline implementation ($p < 0.0001$). Incidence of major complication were similar between the two groups (19% vs. 13%, respectively, $p = NS$).

Pts. with AMI managed after local implementation of clinical practice guidelines were more likely to receive evidence-based effective pharmacotherapies, had an earlier mobilization and an earlier discharge from CCU. This study strongly supports the role of clinical practice guideline local implementation to optimize management of pts. with AMI.

P1570 Clinical characteristics and in-hospital mortality of patients receiving ACE-inhibitor therapy for acute myocardial infarction

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The aim of this study was to evaluate the effects of ACE-Dinhibitor therapy (ACE-I) for acute myocardial infarction (MI) in the Greek population. We also examined the clinical characteristics of the studied patients (pts) with regard to ACE-inhibitor therapy.

Methods: The GEMIG study is an ongoing, multicenter, prospective study focused on Genetics and Epidemiology of acute MI in the Greek population. A total of 1217 concecutive pts (954 men and 263 women, mean age 62 ± 13 years) with the diagnosis of MI have been enrolled in this study from April 1997 to December 1998. Out of the 1217 pts, 625 (51.4%) received ACE-I (group I pts) while 592 (48.6%) did not (group II pts). The unadjusted in-hospital mortality was 9.1 and 6.3% for women and men, respectively.

Results: The characteristics of patients' subgroups are shown in the table:

	Group I	Group II	P value
Age (years)	64 ± 12	61 ± 13	<0.001
Females/Males (%)	47/52	53/48	0.131
Diabetics/Non diabetics (%)	60/48	40/52	0.001
Smokers/Non smokers (%)	51/52	49/48	0.629
Hypercholesterolemics/Non (%)	53/50	47/50	0.219
Positive heredity/Negative heredity (%)	55/50	45/50	0.083
Hypertensives/Normotensives (%)	61/43	39/57	<0.001

Group I pts had significantly lower in-hospital mortality rate (3.2% vs 10.8%, $p < 0.001$). In univariate analysis, most likely to receive ACE-I were pts with an anterior MI (66 vs 34%, $p < 0.001$), pts admitted in the CCU (56% vs 44%, $p < 0.001$), those with echocardiographic left ventricular ejection fraction < 40% (63 vs 37%, $p = 0.013$), thrombolyzed pts (55 vs 45%, $p = 0.002$) and those who also received b-blockers (55 vs 45%, $p = 0.019$) and nitrates (56 vs 44%, $p < 0.001$). In multivariate analysis, left ventricular dysfunction, previous MI, transient conduction abnormalities and lethal arrhythmias, although strongly related to prognosis, were not significantly related to the administration of ACE-I. When all of these factors were included as covariates in a logistic regression model, ACE-I therapy was still significantly associated with lower in-hospital mortality.

Conclusion: ACE-I therapy was strongly related to improved early outcome after acute MI. Although this is not a specifically designed randomized trial and consequently we could not control for all characteristics of the studied pts that might have influenced the physician's decisions, our results are in favor of the beneficial effects of ACE-I therapy for MI in this low coronary risk population.

P1571 Prehospital thrombolysis may abort myocardial infarction

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Following initiation of a prehospital treatment program at two Nijmegen hospitals, we found the delay between symptom onset and thrombolytic treatment (TT) shortened by 63 minutes. In large trials it has been difficult to prove that early treated patients have a reduced mortality, so we hypothesized that the incidence of abortion of myocardial infarction (MI) can be used to evaluate a prehospital thrombolysis program.

Methods: Abortion of MI was diagnosed when chest pain disappeared, together with a decrease of the cumulative ST-segment elevation and depression to less than 50% within two hours after thrombolysis and with a less than a twofold increase of the normal value of cardiac enzymes (CK and CK-MB). Data from prehospital treated patients in the Nijmegen region were compared with those from Arnhem, where MI patients were all treated in-hospital.

Results: In total 227 prehospital patients were treated and compared to 269 in-hospital treated patients. We found significantly ($p < 0.05$) more abortion of MI using prehospital TT (30/227, 13%), compared to in-hospital TT (12/269, 4%).

Aborted MI after...	Prehospital TT	In-hospital TT	p
Age (range)	62 (36–68)	55 (42–81)	ns
Minutes to treatment (median)	85	165	<0.05
Anterior MI	13 (43%)	9 (75%)	ns
Total ST-segment shift (mean)	1.2 mV	0.9 mV	ns
12 months reinfarction	5 (17%)	3 (25%)	ns
12 months revascularisation	13 (43%)	9 (75%)	ns
• PTCA	9	6	
• CABG	4	3	
12 months mortality	0	0	ns

Conclusion: Prehospital thrombolysis results in a threefold increase of abortion of MI, due to earlier treatment. Assessment of aborted MI might be a better criterion for the efficacy of early thrombolysis than mortality data.

P1572 The prognosis of patients with a first non-Q-wave acute myocardial infarction in the pre and thrombolytic eras

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Previous studies have shown that patients (pts) with non-Q wave AMI have better in-hospital and similar long-term prognosis compared to pts with Q wave infarction. The aim of the study was to compare the management and outcome of pts with a first non-Q wave MI in the pre and thrombolytic eras. Among 5839 consecutive AMI pts hospitalized in 13 CCUs during 1981–83, 610 (10%) had a first non-Q wave infarction. In a national 5 month survey conducted in the same CCUs during 1996, 437/2377 (18%) had a first non-Q wave MI. Characteristics, management and prognosis in the two groups were as follows:

	1981–83 (n = 610)	1996 (n = 437)	p Value
Men	397 (65%)	299 (68%)	NS
Age (mean)	63 ± 11 yrs	62 ± 13 yrs	NS
Diabetes	134 (22%)	108 (25%)	NS
Hypertension	255 (42%)	180 (41%)	NS
Smoking	185 (30%)	157 (36%)	NS
ASA	537 (4%)	400 (91%)	<0.001
β-Blockers	143 (27%)	262 (60%)	<0.001
Thrombolysis	-	116 (26%)	<0.001
Coronary Angiography	12 (2%)	185 (42%)	<0.001
PTCA/CABG	-	118 (27%)	<0.001
Mortality: 30 day	77 (12.6%)	26 (6.0%)	<0.001
1 year	117 (19.2%)	42 (10.4%)	<0.001

Conclusion: The frequency of non Q-wave infarction increased significantly in the thrombolytic era. Baseline characteristics were fairly similar, and early and late mortality declined by nearly 50% between the two periods. It is possible that changes in management were responsible for the significant mortality reduction in the '90's.

ACUTE CORONARY SYNDROMES — PHARMACOTHERAPY

P1573 Prognostic influence of pre-treatment platelet counts on coronary angioplasty with abciximab

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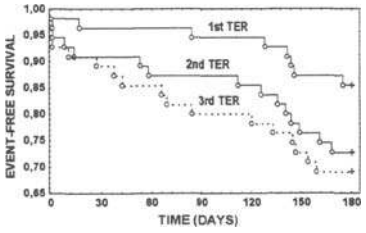
Background: Pre-treatment platelet counts may influence the magnitude of platelet IIb/IIIa receptor blocking achieved with the standard weight-adjusted regimen of Abciximab.

Objective: We sought to examine the prognostic influence of pre-treatment platelet counts on coronary angioplasty (PTCA) with Abciximab.

Methods: We studied 165 consecutive patients who underwent PTCA with Abciximab. Patients were divided in 3 groups according to pre-treatment platelet counts: 1st tercile (114 to 179 × 10^9/L), 2nd tercile (180 to 234 × 10^9/L) and 3rd tercile (235 to 446 × 10^9/L). There were no significant differences among all groups in baseline demographic and clinical characteristics, unplanned use of Abciximab ("rescue") and implantation of stents.

Results: Rate of hemorrhagic complications requiring blood transfusional therapy was 1.8% in each group. Thrombocytopenia (<50 × 10^9/L) occurred in 3.6% in 1st tercile group and 1.8% in the 3rd tercile. In-hospital rate of death or myocardial infarction was 1.8% in the 1st tercile group, 3.6% in the 2nd tercile and 5.4% in the 3rd tercile. Composite 6-month event rate of death, myocardial infarction or target vessel revascularization was 14.5% in the 1st tercile group, 27.3% in the 2nd tercile and 30.9% in the 3rd tercile ($p < 0.02$ between 1st tercile and 2nd plus 3rd terciles).



Conclusion: In the present population of patients undergoing PTCA with Abciximab, lower pre-treatment platelet counts were associated with a more favourable 6-month outcome.

P1574 Left ventricular thrombus after acute anterior myocardial infarction: a prospective study of streptokinase, tissue plasminogen activator and heparin

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Left Ventricular Thrombus (LVT) is a relatively common and potentially serious complication of Acute Anterior Myocardial Infarction (AAMI). The value of heparin in preventing LVT is controversial. This is the first prospective randomised study to examine the effect of LV heparin on LVT after AAMI.

Patients with documented first AAMI (N = 609) had echocardiography prior to discharge for evidence of LVT. 438 patients received Thrombolysis (Tx) and 171 did not (NoTx). Tx was Streptokinase (SK) in 279 and r-tPA in 159. The SK group was randomised to 4 days of I.V Heparin (n = 147) or Placebo (n = 132). NoTx group was also randomised to Heparin (n = 88) or No Heparin (n = 83). However as recommended, all r-tPA group had I.V Heparin. APTT was maintained at 3–4 normal. All patients received 325 mg oral Aspirin daily.

Overall, LVT was detected in 21.4% in Tx Vs 26.4% in NoTx groups (P = N.S). In SK group, LVT incidence was 20.7% with Heparin Vs 20.1% without Heparin (p = N.S). In r-tPA group, LVT incidence was 22.5%. In NoTx group, LVT incidence was 22.5% with Heparin Vs 33.3% without ($p < 0.05$). When the r-tPA group was compared with the SK sub-group on heparin, there was a tendency towards more frequent LVT in the former (22.5% Vs 20.7%, but this was not statistically significant). When the entire group was analysed using multiple regression analysis, disregarding the therapy received, it was evident that those with LVT had larger infarction as shown by higher peak CPK (3662 ± 2237 U/ml) than those without LVT (2954 ± 2050 U/ml).

Conclusion: Thrombolytic therapy reduces the incidence of LVT following AAMI. However, I.V Heparin *after* thrombolysis does not enhance this effect. LVT seems to be related to the size of infarction. Heparin seems important only in patients who did not receive thrombolysis. A different anticoagulant may have to be tried.

P1575 Systematic review of trials evaluating abciximab as a pre-treatment of patients undergoing PTCA

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Abciximab (Ab) has been demonstrated to prevent thrombotic events if used as a pre-treatment before PTCA. We performed a systematic review of three large trials (EPIC, EPILOG, CAPTURE) which evaluated Ab in specific, different subgroups of patients (pts) undergoing PTCA. Methods. Analysis was performed upon 5461 pts enrolled in the three trials and allocated to receive placebo (P, n = 2270) or Ab (n = 3191; 0.25 mg/kg bolus + 10 μg/min 12-hour infusion). Six-month major end-points were considered death, myocardial infarction, repeated PTCA and bypass surgery; six-month major complications were considered intracranial haemorrhages and non-intracranial haemorrhages requiring transfusions. Number-needed-to-treat (NNT) was calculated for composite and single end-points and number-needed-to-harm (NNH) was calculated for complications as: 100 divided by the difference of percentage incidence of composite and single end-points and complications in P and Ab groups. Results. At six months, 70.13% of P pts versus 74.96 of Ab pts were free of end-point events (RR 0.84, IC 95% 0.77–0.91; NNT for composite end-point 21). NNT was 227 for death, 24 for myocardial infarction, 37 for repeated PTCA and 75 for bypass surgery. NNH was 1667 for intracranial haemorrhages and 63 for non-intracranial haemorrhages requiring transfusions. Conclusion. Ab is effective in preventing six-month thrombotic events across the spectrum of pts undergoing PTCA.

P1576 Safety of enoxaparin in the geriatric population

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Background: Administration of intravenous heparin and aspirin has become an integral part of the therapeutic regimen in patients with unstable angina. However, the use of heparin may lead to excessive bleedings and there is a need of close laboratory supervision especially in the elderly patients. Low molecular weight heparin,is easier to administer and its efficacy in treatment of unstable coronary disease has been demonstrated. However, no study included elderly patients, therefore its safety was not demonstrated in this population.

Objectives: The major objective of this study was to examine whether treatment with a low- molecular weight heparin (enoxaparin), is safe in very old patients with unstable angina. In addition, we examined whether enoxaparin is protective against new cardiac events during the first week of therapy, and after 14 days.

Methods: Ninety-eight patients over the age of 80 (average: 84 years) with unstable coronary artery disease, were randomly assigned to receive either treatment with enoxaparin (1 mg/kg subcutaneously twice daily) or continuous intravenous standard heparin (1000 IU/hr) for 7 days. Event rates were tested by chi-square analysis.

Results: During the first week the risk of bleeding (measured by decrease of the hemoglobin and the need of blood transfusions) was similar in both groups. The incidence of thrombocytopenia (platelet count < 100,000/ml) was lower in the clexane group than in the standard heparin group (0% vs 2.7%); increase in liver transaminases occurred in 4 patients (7.8%) in the clexane group and none in the standard heparin group. There were no significant differences in the rate of cardiac death, angina pectoris or EKG changes in neither one of the groups.

Conclusions: This preliminary study shows that enoxaparin, a low molecular weight heparin, can be used safely in the very elderly population. However, the safety of long-term enoxaparin treatment, in this population, warrants further assessment.

P1577 Amlodipine in post-angioplasty ischaemia: results from the Coronary Angioplasty Amlodipine Restenosis Study (CAPARES)

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Despite successful coronary angioplasty (PTCA), many patients (pts) still have ischemia early after the procedure. Ischemia may increase later on due to the luminal narrowing process occurring in most of the dilated lesions. Aims of the present study was to examine the effect of the calcium channel blocker amlodipine in reducing of post-PTCA ischemia.

Methods: 635 patients were randomly assigned to either amlodipine or placebo in a double blind prospective study. 450 pts were scheduled to perform exercise testing (ET) and 48 hours ambulatory holter monitoring (AHM) 2 weeks before, 2 (early) and 20 weeks (late) after PTCA. Of these 410 pts underwent successful PTCA, 67 had stents implanted. After PTCA 405 pts underwent ET, and 332 AHM (of whom 274 had technically readable recordings). Ischemia was defined as 1 mm ST depression at ET-ECG, and 1 mm ST depression lasting $\geq$1 min at the AHM.

Results: There were no significant differences in clinical and angiographic baseline characteristics between the groups, or the percentage of pts who had restenosis at follow-up (amlodipine: 24.0% vs. placebo: 23.8%). There were no difference in the incidence ischemia between the groups assessed by ET and AHM before PTCA. Ischemia occurred in both groups after PTCA, but was significantly reduced in the amlodipine group.

	Ischemia 2 weeks after PTCA		Ischemia 20 weeks after PTCA	
	Amlodipine	Placebo	Amlodipine	Placebo
ET	17.5%	27.7%*	46.9%	56.5%
AHM	30.6%	40.5%	28.3%	43.2%**

*p = 0.02, **p = 0.01

Multivariate logistic regression analysis revealed that amlodipine treatment exerted a positive and independent influence on freedom from ischemia on ET both 2 (p = 0.01) and 20 weeks (p = 0.03) after PTCA, when adjustment were made for age, sex, smoking, previous infarction, diabetes, restenosis, dilatation of left anterior descending, β-blockade and gain in luminal diameter.

Conclusion: Ischemia occurred after successful PTCA, and was significantly reduced by amlodipine.

P1578 Primary stenting in acute myocardial infarction: acute and short-term angiographic and clinical outcomes with a comparison of antiplatelet agents between cilostazol and ticlopidine: single center experience – Fujigaoka Antiplatelet Stent Trial (FAST study)

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Aspirin and Ticlopidine have been commonly utilized following elective coronary stenting since many studies showed the superiority of the combined antiplatelet therapy. However, the regimen of antiplatelet agents following primary stenting in acute myocardial infarction (aMI) has not yet been established. Cilostazol is an antiplatelet agent that is suggested to inhibit cyclic AMP phosphodiesterase in platelets and vascular smooth muscle and attributed to antiplatelet, vasodilation and inhibitory effect of intimal proliferation. We prospectively compared the efficacy of the combined antiplatelet therapies such as aspirin and cilostazol verses aspirin and ticlopidine after primary stenting in aMI.

Method: To elucidate the efficacy of cilostazol, patients (pts) who underwent primary stenting in aMI were randomized to receive cilostazol (200 mg/day) and aspirin (162 mg/day): (Group C), or ticlopidine (200 mg/day) and aspirin (162 mg/day): (Group T), then the angiographical and clinical outcomes were compared.

Results: Forty nine patients were randomized to Group C (n = 23) and Group T (n = 26). Angiographical f/u was performed at 4.1 $\pm$ 2.9 months and Clinical f/u was completed at 13 months after primary stenting. Primary success was achieved in all the patient and there was no major adverse cardiac event including death and CABG. Although subacute thrombpsis (SAT) did not occurre in both groups, active bleeding requiring blood trandfusion was seen in 2 pts in Group T. Quantitative coronary angiography (QCA) analysis showed as follows. Post procedural minimum lumen diameter (MLD) in both groups were similar (Group C: 2.70 $\pm$ 0.38 mm vs. Group T: 2.53 $\pm$ 0.43 mm p = ns) but f/u MLD was significantly bigger in Group C (2.38 $\pm$ 0.38 vs 1.89 $\pm$ 0.57: p < 0.05) resulting in the significant difference of the late loss between the two groups. Restenosis occurred in 4 pts in Group T while there was no restenosis in Group C, and the difference is statistically significant (p < 0.03)

Conclusion: Combined antiplatelet therapy was effective after primary stenting in aMI, however cilostazol was suggested to have better clinical and angiographical outcomes compared with ticlopidine.

P1579 Hemodynamic effect of trimetazidine during exercise in patients with coronary artery disease

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It is accepted that the beneficial effect of trimetazidine (TMZ) in patients (pts) with coronary heart disease (CHD) is due to cytoprotective action and that this drug does not alter the hemodynamic parameters.The aim of the study was to evaluate the effect of TMZ on the ECG exercise test (ET) in pts with CHD.The study group consisted of 85 pts with coronarographically confirmed two-or three vessels CHD.ET was performed twice in all pts:after single oral dose (60 mg) TMZ and without this drug.Both test were done according to Bruce protocol in identical conditions,and the sequence of them was randomly chosen.In 76.5% (65 pts) ST segment depressions were smaller after TMZ and their duration time was shorter in 54.2% (46 pts).The anginal pain during ET after TMZ occurred in 16.5% (14 pts) and in 54.2% (46 pts) during ET without TMZ.

TMZ increased the workload during ET ($p < 0.001$). TMZ also lowered asystolic ($p < 0.001$), diastolic ($p < 0.001$) and mean ($p < 0.001$) blood pressure as well as the double product (DP, $p < 0.001$) during ET.These changes were more pronounced in pts with three-vessels disease.These results suggest that in some pts TMZ may improve the exercise tolerance and attenuate the ECG signs of cardiac ischemia during ET.The lower afterload due to the decrease of DP may be one of the factors responsible for it.Thus in some CHD pts TMZ may have favourable hemodynamic effect apart from its cytoprotective action.

P1580 Effect of age on use of treatments for acute myocardial infarction

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Introduction Reports published in the literature suggest that elderly patients with acute myocardial infarction (MI) have inappropriately had thrombolytic treatment (TT) and beta blockers (BB) withheld. This is despite clear recommendations in the literature that these treatments are beneficial in the elderly. This abstract describes the current practice in a general hospital where the majority of patients are cared for by physicians without specialist training in cardiology.

Methods The records of all patients admitted with MI over 2 three month periods were examined. Patients were identified prospectively by visiting wards, examining the admissions register and discharge diagnosis system and reviewing all records of patients with a raised CK for patients with MI.

Results There were 166 patients of whom 113 were <75 years and 53 ≥75 years. The inpatient mortality was respectively: 8%, 31%. Elderly patients were less likely to fulfil the ECG criteria for TT 43% Vs 60%, $P < 0.05$. Thrombolytic treatment was received by 94% of all eligible patients with no discrimination against the elderly. Aspirin was received by 84% of all patients with no discrimination against the elderly. The elderly were less likely to be prescribed BB at discharge 33% Vs 63%, $P < 0.001$, or ace inhibitors at discharge 45% Vs 66%, $P < 0.05$.

Conclusions The historical reluctance to use TT in the elderly appears to have been overcome, but has been replaced by a reluctance to use ace inhibitors. The reluctance to use BB in the elderly patients persists. This is especially disappointing in view of the very high mortality that elderly patients with MI have.

P1581 Administration of β-adrenergic blockers at hospital discharge after acute myocardial infarction in the Greek population

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The administration of beta-adrenergic blockers (BB) has been related to improved survival after acute myocardial infarction (MI). Although the beneficial effects of BB have been recently expanded to patients (pts) with heart failure (HF), diabetes mellitus (DM) and older age, beta-blockade therapy is frequently underused.

Methods: The GEMIG study (Genetics and Epidemiology of acute Myocardial Infarction in the Greek population) is an ongoing, multicenter, prospective study which has recruited 954 men and 263 women with a mean age of 60 ± 12 and 69 ± 12 years respectively ($p < 0.001$), from May 97 to December 1998.

Results: BB were administered to 63% of the studied pts at hospital discharge. Pts receiving BB were significantly younger (59 ± 12 vs 66 ± 12 years, $P < 0.001$).

Proportion of patients under beta-blockade therapy at discharge (%)

		P
Females/Males	54/65	0.003
Age ≥ 70 years/Age < 70 years	46/70	<0.001
Diabetics/Non diabetics	22/78	<0.001
Hypertensives/Normotensives	63/63	0.998
Non Q wave MI/Q wave MI	51/65	0.003
Non thrombolysed pts/Thrombolysed pts	56/68	<0.001
LVEF ≤ 40%/Echocardiographic LVEF > 40%	49/70	<0.001

In a multivariate analysis with all the aforementioned clinical characteristics included as covariates, age ≥ 70 years, Non-Q wave MI and LVEF < 40% were significantly related to decreased administration of b-blockade therapy. Relative risks were 0.468 (0.328–667, $p < 0.001$), 0.424 (0.261–0.668, $p = 0.001$) and 0.440 (0.318–609, $p < 0.001$) respectively.

Conclusion: In this MI cohort a relatively high proportion of pts after MI received BB at hospital discharge. However, b-blockade therapy still seems to be underused in pts with older age, nontransmural MI and dysfunction of the left ventricle, despite the fact that pts with these conditions may also benefit from b-blockade therapy.

P1582 Importance of antithrombin therapy in combination with abciximab and low-dose fibrinolytic therapy: preliminary results of the GUSTO-4 pilot study

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In the GUSTO-4 Pilot trial, low-dose reteplase (5+5 U) combined with standard-dose abciximab and heparin (Hep, 60 U/kg) resulted in TIMI grade 3 flow in 63% of cases (TIMI grade 2 or 3 flow in 82%). In the dose-confirmation phase of the study, this reteplase-abciximab regimen (Combo) was compared with reteplase alone (10+10 U) with 70 U/kg heparin. During this phase, the initial heparin dose used in the Combo arm was reduced from a 60-U/kg bolus (max 6000 U) to a 40-U/kg bolus (max 4000 U). We assessed bleeding and patency before and after this reduction, to determine effects on efficacy and safety. An independent core laboratory assessed angiographic patency, and core laboratory data were available for 89% of cases.

Patency and Bleeding by Heparin Dose

	Combo, 60 U/kg Hep (n = 34)	Combo, 40 U/kg Hep (n = 75)	r-PA 10 + 10 U (n = 107)
Minutes to angiography	61 (57, 72)	65 (60, 71)	62 (60, 68)
TIMI grade 3 flow	18 (62%)	34 (51%)	47 (48%)
TIMI grade 2 or 3 flow	23 (79%)	51 (77%)	76 (78%)
Transfusion	5 (15%)	9 (13%)	12 (12%)
Max Hgb drop, adjusted	3 (1.9, 4.4)	2.8 (1.9, 4)	2.6 (2.0, 3.4)

Only one intracranial hemorrhage occurred, in the reteplase 10+10-U group. These findings suggest the need for antithrombin therapy with low-dose reteplase and standard-dose abciximab, to maximize its effect.

P1583 Brief use of ticlopidin after coronary stent implantation : a comparative study

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Many studies have demonstrated the efficiency of combined use of platelet inhibitors, as aspirin plus ticlopidin, after stent implantation, in reducing the incidence of acute thrombosis.Nevertheless, the duration of the use of ticlopidin is not well established.

The aim of our study is to compare two regimens of treatments, using long term administration of aspirin (100 mg/day), in association with ticlopidin (500 mg/day), for 15 days (201 patients) or 30 days (152 patients) after 353 consecutive Wiktor® stent-Medtronic deployement.

The principal clinical criterias at 30 days follow-up were: acute thrombosis of the stent (TH); acute myocardial infarction (AMI), unstable angina (UA), bypass surgery (BP), repeated angioplasty (RA), mortality (M), all cardiac events (ACE) and non cardiac events as cutaneous rash (CR), gastro intestinal (GI) and leucopenia (L).

	TH (%)	M (%)	AMI (%)	UA (%)	BP (%)	RA (%)	ACE CR (%)	GI (%)	L (%)	(%)
Ticlo 30 d.	1.9	0.6	1.9	1.9	0	2.6	2.6	1.9	1.9	0.65
Ticlo 15 d.	3.4	0.4	0.9	3.9	0	4.4	6.4	0	0	0
p	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

At 30 days follow-up, there is no difference between the two groups in term of incidence of thrombosis or cardiac events.

A briefer use of ticlopidin after stent implantation is possible without increasing the thrombotic risk, and is helpfull to avoid side effects of ticlopidine.

P1584 Are different angiotensin converting enzyme inhibitors identical for treatment of acute myocardial infarction? results from the Hong-Kong post-myocardial infarction trial

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Hypotension with angiotension converting enzyme inhibitors (ACEIs) during acute myocardial infarction (AMI) not only limits adequate dosing but is associated with increased mortality. ACEIs have different degrees of first dose hypotension.

Methods: We studied 212 patients with first AMI randomly assigned to receive captopril (CAP, initial 6.25 mg, upto 50 mg/day or perindopril (PER, initial 2 mg, upto 8 mg/day). Automatic blood pressure monitoring was performed every 15 minutes for 14 h, then hourly for 10 h. Echocardiography and mortality were monitored for 6 months.

Results: At baseline, there was no difference between CAP (102 pts) and PER (110 pts) in age (65 ± 1 vs 64 ± 1 yrs), sex (% male: 81.4 vs 72.7%), AMI location, peak CK and baseline mean blood pressure (MBP, 83.0 ± 1.1 vs 84.4 ± 1.1 mmHg), but PER pts tended to have a higher Killip score (1.4 ± 0.1 vs 1.2 ± 0.1, p = 0.06). Compared to PER, CAP resulted in more severe hypotension following initiation of treatment (% MBP reduction: 20.3 ± 0.9 vs 16.6 ± 1.0%, p < 0.01), a lower minimum MBP (66.0 ± 1.1 vs 70.1 ± 1.1 mmHg, P < 0.01), and a more rapid fall in MBP (time to minimum: 2.6 ± 0.1 vs 4.3 ± 0.5 h, p < 0.005). At 6 months there was no significant difference between CAP and PER in left ventricular function, need for revascularisation, and NYHA heart failure class. Significantly more patients, however, withdrew from CAP than from PER (44.1 ± 4.9 vs 28.2 ± 4.3, P = 0.016). This was also a strong tendency in favour of a mortality reduction with PER (8.1% vs 19.7% in CAP, P = 0.06).

Conclusion: In pts with AMI, PER is better tolerated and has lower hypotensive complications than conventional treatment with CAP, which may be translated into improved patient survival.

P1585 Worse short-term prognosis of myocardial infarction patients with hyperglycaemia on and during admission

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Background: Worse mortality after acute myocardial infarction (AMI) has been reported among diabetics, but patients with hyperglycaemia after myocardial infarction have received less attention.

Objective: To assess the role of hyperglycaemia in survival after AMI.

Methods: An inception cohort obtained in a population-based prospective registry of AMI patients held in the reference hospital in Girona, Spain. All consecutive AMI patients aged < 75 years registered between 1993 and 1996 were included. Patients and clinical characteristics, including history of diabetes, and glycaemia on admission, were recorded. The adjusted effect (odds ratio [OR]) of hyperglycaemia over 126 mg/dL (7 mmol/L) on survival at 28 days was analyzed with logistic regression.

Results: A total of 631 patients with AMI were included. Hyperglycaemic (n = 345) were significantly older (62.9 Vs 57.7 years) and more often diabetic (39.9% Vs 11.0%), and developed more severe AMIs than normoglycaemic: i.e. severe ventricular arrhythmias (26.3% Vs 17.5%) and acute pulmonary edema or cardiogenic shock (24.8% and 10.5%), all p < 0.02. Revascularization procedures within 28 days were performed in and thrombolysis and aspirin given to a similar proportion of both type of patients. Twenty-eight-day mortality rate was 11.0% in hyperglycemic and 1.9% in normoglycaemic patients. After adjustment, the risk of 28-day death in Hyperglycaemic patients was 3.71 (95% confidence interval 1.05–13.13) times that of normoglycaemic.

Conclusions: AMI patients with hyperglycaemia on admission develop more lethal and severe AMIs than men regardless of comorbidity, age and clinical characteristics.

P1586 Effects of oral pirenzepine on heart rate variability after acute myocardial infarction: a randomized trial

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Augmenting cardiac vagal outflow in post-myocardial infarction (MI) patients may have a favorable effect on clinical outcome. The aim of the present study was to investigate in an open-labelled randomized manner the vagotonic effects of oral pirenzepine on heart rate variability (HRV) in patients (pts) who sustained an acute MI. Pts who survived an acute MI were randomized to receive along with their standard therapy either placebo (**n** = 23, 19 men/4 women, aged 58 ± 11 yrs) or pirenzepine 25 mg bid (n = 22, 20 men/2 women, aged 59 ± 12 yrs) at the time of their discharge from the hospital. A baseline 24-h Holter recording assessing HRV was obtained prior to randomization. Baseline demographics and clinical characteristics did not differ in the two groups. MI location was anterior in 52% and 45% respectively; mean left ventricular ejection fraction was 45 ± 8% and 49 ± 6% respectively. HRV was reevaluated at 1-month and 3-month intervals while on treatment. Pts tolerated their treatment well with no reported side-effects. Baseline HRV parameters were similar in the two groups. Pirenzepine increased SDNN from 115 ± 30 to 130 ± 29 at 1 month (p = 0.045) and to 132 ± 33 at 3 months (p = 0.001); SDANN index also increased from 95 ± 24 to 106 ± 30 at 1 month (p = 0.05) and to 114 ± 32 at 3 months (p = 0.001), while no significant difference was noted in the placebo group (SDNN: 101 ± 23 vs 105 ± 30 at 1 month, vs 114 ± 31 at 3 months; SDANN index: 85 ± 19 vs 88 ± 28 at 1 month, vs 102 ± 36 at 1 month; p = NS). At 3 months there were no sudden or other cardiac deaths or arrhythmic events; there was only one cardiac death at 2 months in the placebo group.

In **conclusion,** short-term therapy with oral pirenzepine favorably affects HRV indices at 1-month and 3-month follow-up in post-MI pts. Whether this effect is further sustained or whether it influences survival remains to be seen at 6- and 12-month follow-up.

P1587 Comparative efficacy of losartan and carvedilol in patients with postinfarction left ventricular remodelling and heart failure

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Aim of the study was compare the efficacy of losartan (L) and carvedilol (C) in patients (pts) with postinfarction left ventricular remodeling (LVR) and heart failure (NYHA III) who are already on standard therapy (ST) by enalapril 10–20 mg/day, digoxin 0.25 mg/day, furosemide 20–40 mg/day at least 2 months.

Methods: After 1 week of drug (L and C) toleration determination 93 pts (age 63 ± 9 yrs, 14% female) on ST with EchoCG proved LVR and NYHA III were randomized to 2 groups in order to receive 1) L 50 mg/day (n = 47) or 2) C 12.5 BID (n = 46). 30 pts on ST served as control. 16 segment model score index contractility (SIC) on peak dobutamin-stress test, total ischemic burden (TIB) by 24 hour Holter monitoring, EF, indexes of SV and anterior and posterior segment lengths (AS; PS) on papillary muscles level in parasternal short axis view were measured in all pts by investigators without knowledge of study aims in 30, 60, 180 days after study initiation.

Results: In 30 day there were no statistically significant differences between all groups in all parameters. In 60 day TIB, SVI, SIC were significantly better in group C (TIB: C 28 ± 9 min* vs 33 ± 11 min L vs 32 ± 11 min; SVI: C 29 ± 8* vs L 24 ± 5 vs 25 ± 6; SIC: C 1.1 ± 0.2* vs L 1.3 ± 0.3 vs 1.4 ± 0.3; * – $p < 0.05$). EF was greater in the group L vs C and control (32 ± 5%** vs 28 ± 3%** vs 30 ± 4%; ** – $p < 0.01$). However in 90 day all parameters were better in L group, including LV size (SIC: L 1.2 ± 0.2* vs 1.3 ± 02 vs 1.4 ± 0.2; SVI: L 32 ± 8** vs C 25 ± 4 vs 24 ± 4; EF: L 31 ± 6%* vs 29 ± 4% vs 28 ± 4%; AS: L 6.3 ± 0.6* cm vs C 6.0 ± 0.7 cm vs 5.9 ± 0.6 cm; PS: L 3.4 ± 0.15* cm vs C 3.5 ± 0.15 cm vs 3.4 ± 0.13). TIB was significantly less in L and C groups compare to control ($p < 0.01$) and did not significantly differ between groups L and C (C: 27 ± 8 min. 24^{-1} vs L 26 ± 7 min. 24^{-1}; p = NS). In 180 day TIB also did not differ between L and C, however other better results in L group observed in 90 day became more prominent compare to C and control (SIC: L 1.1 ± 0.1*** vs C 1.2 ± 0.3 vs 1.3 ± 0.3; SVI: L 34 ± 8*** vs C 24 ± 4 vs 25 ± 4; EF: L 33 ± 6%*** vs C 28 ± 4% vs 29 ± 4%; AS: L 5.9 ± 0.6 cm*** vs C 6.1 ± 0.5 vs 6.0 ± 0.4; PS: L 3.3 ± 0.15*** vs C 3.9 ± 0.2 vs 3.8 ± 0.2; *** – $p < 0.001$).

Thus, adding C to ST in pts with LVR and HF is beneficial in first 60 days of therapy than L + ST. However in pts on L + ST effects are better after 90 day and increase up to 180 day.

P1588 Oral administration of a novel, selective and potent endothelin-A receptor antagonist (TA-0201) improves left ventricular remodelling after myocardial infarction without haemodynamic changes

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Objective: We investigated whether oral administration of endothelin-A receptor antagonist protects the LV against remodeling after myocardial infarction.

Methods: A novel, selective and potent endothelin-A receptor antagonist (TA-0201, 0.3 mg/kg) was given orally from the second day to the 6 weeks in 7 dogs subjected to the left anterior descending coronary artery ligation (TA group). Other 7 dogs served as Controls. Based on serial two-dimensional echocardiogram, the effects of TA-0201 during healing after myocardial infarction on alterations in ventricular size, shape, mass, and function were estimated. Postmortem measurements of scar size and geometry were assessed. Moreover, immunohistochemical evaluation of ET expression was performed.

Results: TA-0201 showed no significant effect on either blood pressure or heart rate. After 6 weeks of treatment with TA-0201, increases in the LV mass, end-diastolic volume, expansion index and wall motion score index were significantly reduced in the TA group as compared with those in the control group ($p < 0.05$). A thinning ratio and EF was significantly greater in the TA group than in the control group ($p < 0.05$). By immunohistochemical study, ET was detected in extracellular matrix in border zone of controls. We observed interstitial hyperplasia and myocardial cell hypertrophy in the border zone of controls. In TA group, these changes were less.

Conclusion: Endothelin-A receptor antagonist may offer a promising therapeutic approach for the protection against not only LV remodeling but also functional deterioration after myocardial infarction independently of hemodynamic changes.

ATRIA BY TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

P1589 Pulmonary venous flow patterns in a large normal population: comparison between transthoracic and transoesophageal echocardiography

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Background: Recently, increasing importance has been attributed to the pulmonary venous flow velocity (PVF) pattern for the assessment of left ventricular diastolic function or mitral regurgitation. However, normal PVF patterns have not been determined in a large population. Furthermore, it remains unclear how the normal values differ between TTE and TEE in various age groups.

Methods: A total number of 400 patients (pts) with normal Doppler echocardiography and without a history of cardiovascular disease was investigated. The flow velocity pattern of the right upper pulmonary vein was recorded in 307 pts using TTE and in 93 pts using TEE. Peak systolic (Peak S, m/s), peak diastolic (peak D, m/s) and peak reversed flow velocity at atrial contraction (peak A, m/s), systolic to diastolic peak flow velocity ratio (S/D) and duration of reversed flow (Adur, ms) were measured. Patients were divided into six age groups (table). The values were compared between TTE and TEE within the age groups.

Results:

	Age groups (years)					
	10–19	20–29	30–39	40–49	50–59	≥60
PeakS TTE	0.48±0.14 (14)	0.49±0.12 (75)	0.54±0.14 (92)	0.57±0.11 (52)	0.57±0.14* (39)	0.58±0.12 (35)
PeakS TEE	0.35 (1)	0.49±0.13 (16)	0.55±0.17 (34)	0.59±0.15 (16)	0.70±0.15* (12)	0.64±0.20 (15)
PeakD TTE	0.66±0.16 (14)	0.64±0.13 (75)	0.59±0.12 (92)	0.56±0.13 (52)	0.48±0.12 (39)	0.49±0.13 (35)
PeakD TEE	0.81 (1)	0.61±0.10 (16)	0.54±0.16 (34)	0.54±0.11 (16)	0.51±0.11 (12)	0.45±0.12 (16)
PeakA TTE	0.25±0.05 (11)	0.22±0.08 (59)	0.24±0.06* (76)	0.27±0.06 (44)	0.27±0.09 (35)	0.29±0.06* (29)
PeakA TEE	0.18 (1)	0.22±0.08 (15)	0.20±0.09* (27)	0.25±0.09 (11)	0.25±10 (11)	0.23±0.09* (10)
Adur TTE	108±10 (11)	116±32* (59)	121±27* (76)	114±31 (44)	117±33 (35)	127±42 (29)
Adur TEE	87 (1)	96±17* (15)	90±18* (27)	94±29 (11)	99±19 (11)	111±24 (10)
S/D TTE	0.75±0.23 (14)	0.81±0.30 (75)	0.92±0.22* (92)	1.05±0.31 (52)	1.24±0.30 (39)	1.24±0.32 (35)
S/D TEE	0.43 (1)	0.82±0.19 (16)	1.06±0.26* (34)	1.15±0.40 (16)	1.41±0.29 (12)	1.48±0.53 (15)

*indicates $p < 0.05$, number of patients are given in parentheses.

Conclusions: There is a considerable tendency to overestimate the duration of flow reversal at atrial contraction using TTE. This is of importance for the assessment of LV diastolic function using the PVF pattern. The S/D ratio increases later with advancing age in TTE compared to TEE. This must be accounted for in the assessment of mitral regurgitation.

P1590 Comparison of different provocation manoeuvers for echocardiographic detection of persistent foramen ovale

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Persistent foramen ovale (PFO) is found in 9.2% to 32% of echocardiographic examinations. Gold standard for the detection of a PFO is transesophageal echocardiography (TEE) and the mostly used provocation test is Valsalva maneuver. The aim of our study was to evaluate the effectiveness of Valsalva maneuver compared to other provocation tests by hemodynamic measurements of the right and left atrial pressure simultaneously.

Methods: 37 patients underwent Swan-Ganz catheterization. Right atrial pressure and pulmonal capillary wedge pressure, which nearly corresponds to the left atrial pressure, were measured simultaneously. The following maneuvers to compare were: Valsalva maneuver, coughing, deep inspiration and expiration pressure (exp.) of 20, 40 and 60 mmHg. Our interest was to compare the incidence of of appearance of pressure gradients (right atrial pressure > left atrial pressure).

Results:

Incidence of pressure gradient

Valsalva	Cough	inspiration	exp 20	exp 40	exp 60
92%	86%	86%	59%	78%	73%

Mean gradients over the time of one heart cycle (mmHg)

Valsalva	Cough	Inspiration	exp 20	exp 40	exp 60
5.6	4.0	5.1	3.7	3.8	4.1

During Valsalva maneuver the frequency of pressure gradients and the mean gradients were higher than during alternative maneuvers.

Conclusions: Valsalva maneuver is the most effective test to provoke a right to left atrial shunt for the detection of a PFO during echocardiographic examinations.

P1591 Clinical importance of a patent foramen ovale for unexpected decompression illness in divers

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Background: The presence of endogenous nitro-bubbles during dives with compressed air can lead to decompression illness (DCI) with potentially severe consequences. Symptoms and clinical presentation of decompression sickness (DCS) or arterial gas embolism (AGE) may occur even in divers adhering strictly to the recommended decompression tables. Intracardiac right to left shunting of venous bubbles through a patent foramen ovale (PFO) offers a plausible pathophysiological explanation for this kind of unexpected DCI. However, the clinical importance of a PFO in divers has not been clearly assessed.

Methods: In 48 divers with at least 200 dives, we performed a transesophageal echocardiography for detecting intracardiac shunts. By using contrast material and the Valsalva manoeuvre during echocardiography, its sensitivity was optimised. Before the exam, all divers answered to a detailed questionnaire about their diving habits and diving accidents.

Results: In 12 divers we detected a PFO. No differences were present in diving habits between divers with a PFO [PFO] and the control group [PFO/]. However, divers with a PFO reported more often major decompression illness with cerebral (blurred vision, dysarthria, loss of consciousness, hemiplegia) and spinal (impaired bowel and bladder control, limb weakness) involvement. Similarly, divers with a PFO reported more often minor decompression symptoms (headache, paresthesias, dizziness, bends) according to a score from 0 to 24.

	PFO (n = 12)	PFO/ (n = 36)	p
Number or dives (mean)	772	812	0.89
Number of dives > 40 m (mean)	57	84	0.43
Prevalence of major cerebral DCI	0.43/1000 dives	0.10/1000 dives	0.03
Prevalence of major spinal DCI	0.32/1000 dives	0.03/1000 dives	0.02
Minor decompression symptoms	4.3 ± 0.7 (SE)	2.4 ± 0.3 (SE)	0.01

Conclusions: A causal relation between PFO and unexpected DCI must be considered. Divers with major unexpected DCI should undergo transesophageal echocardiography to exclude a PFO. For divers with a PFO and episodes of major DCI, it is advisable to refrain from deep dives with high risk of bubble formation. Prospective trials are needed for further evaluation of this concept.

P1592 Transcatheter closure of atrial septal perforations under echocardiographic guidance without need for fluoroscopy

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Transcatheter closure of atrial septal perforations is presently performed under fluoroscopic guidance, but echocardiography is playing an increasingly important role in the procedure. We have now developed a technique using transesophageal echocardiography alone, without resort to fluoroscopy.

Methods: We selected 5 patients (3 to 16 years of age, bodyweight 14 to 60 kg) with atrial septal defects centrally located in the oval fossa and 5 patients (21 to 61 years of age, bodyweight 55 to 118 kg) with persistent foramen ovale after presumed paradoxical embolism for transcatheter closure. After sedation with midazolam and propofol, a diagnostic and interventional catheterization was performed in all cases under echo-cardiographic guidance without fluoroscopy. Oximetric shunt estimation and pressure recordings were taken, the defects were sized over the wire with a balloon catheter, and finally an Amplatzer Septal Occluder was placed into the defects. In 8 patients a 5 MHz monoplane transducer, and in 2 patients a 5 MHz multiplane probe was used.

Results: The patients with an atrial septal defect had a ratio of pulmonary to systemic flow of 1.6 (1.5 to 2.1). The stretched diameters of all 10 perforations ranged from 6 to 14 mm (mean 9 mm). The implantation of Amplatzer Septal Occluders led to complete closure of the defects in all patients. Mean procedure time was 92 min (45 to 130 min), no complications were encountered.

Conclusion: In selected cases with an atrial septal defect located centrally in the oval fossa and clear-cut echocardiographic findings, an Amplatzer Septal Occluder can be safely deployed under echocardiographic guidance alone.

P1593 Segmental evaluation of the left atrial appendage by anatomic M-mode: initial observations in patients with sinus rhythm and atrial fibrillation

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Background: Two-dimensional (2D) and pulsed wave (PW) Doppler echocardiography can evaluate left atrial appendage (LAA) global function but assessment of regional function is limited. The aim of this study was to test the capability of M-mode to evaluate the LAA function on a segmental basis.

Methods: An initial group of 10 patients (pts), mean age 56 9 years, 4 with sinus rhythm (SR) and 6 with atrial fibrillation (AF), was studied by transesophageal echocardiography viewing the LAA from the basal short axis and acquiring digital 2D cineloops containing 3 consecutive cardiac cycles. The Anatomic M-mode line was positioned at the base, midportion and apex of the LAA. At each level, LAA internal diameter, wall motion and thickening were related to the electrocardiogram and the PW Doppler pattern of flow.

Results: In all pts the LAA could be studied by Anatomic M-mode. In pts with SR, the basal portion of the LAA obliterated at the time of atrial systole and the lateral wall showed a clear thickening (Fig. 1, arrow) that coincided with the highest Doppler emptying flow wave. The LAA midportion and apex obliterated longer. In pts with AF, basal obliteration and thickening of the lateral wall were not observed (Fig. 2).

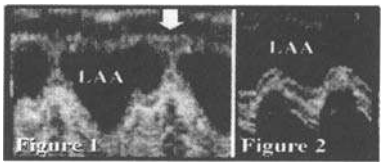

Figure 1 Figure 2

Conclusions: This initial study shows that the LAA function can be easily evaluated in M-mode format at segmental level. It also documents in pts with SR pre-systolic active contraction of the LAA, recognized for the first time by M-mode thickening of the lateral wall.

P1594 Morphologic characteristics of left atrial thrombi in patients with rheumatic mitral valve disease in relation to embolic events

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In patients with rheumatic mitral valve disease (RMVD) presence of thrombus (THR) and spontaneous echo contrast (SEC) in left atrium (LA) have been considered to be predictors for embolic events (EE). However impact of morphologic characteristics (MC) of LATHR in relation to EE has not been investigated. This study aims to evaluate whether MC of LATHR is associated with EE, and to assess the grade of LASEC in relation to MC of LATHR in pts with RMVD. Study population comprised 474 pts of RMVD (F 320, M 154, mean age 40+14.6) whom transesophageal echocardiography (TEE) was performed prior to mitral valve surgery (MVS). Pure or predominant mitral stenosis (MS) and mitral regurgitation (MR) were detected in 333 and 141 of pts, respectively. Rhythm was atrial fibrillation in 267 pts. Embolic event (n = 26) was defined as presence of emboli in last 30 days prior to TEE. Thrombus was detected in 101 (LA 13, LAA 62 and LA+LAA 26) and SEC in 128 of pts. Morphology of THR was defined as their age (organised vs nonorganised; 54 vs 47), as their surface appearence (smooth vs irregular; 69 vs 32), and largest diameter (cm) (D) and thickness (T) of THR were measured by TEE. Frequency of EE was 27%, 19.5%, 16.6% and 8.5% in pts with THR+SEC, SEC, THR and without SEC and THR, respectively. In pts with THR history of EE was found to be associated with surface characteristics (irregular vs smooth) of THR (40.6 and 18.8%, $p = 0.0001$), but not with intraatrial location and the age (24 vs 26%, $p > 0.05$), D (2.8+1.6 vs 2.8+1.8, $p > 0.05$) and T (1.6+1.0 vs 1.4+0.9, $p > 0.05$) of THR. None of the MC of THR was found to be associated with SEC grade. Multivariate analysis confirmed that surface characteristics of THR was independently associated with EE in pts with THR, and presence of THR with irregular surface, SEC and absence of MR (>2) were independent variables in overall study group.

We conclude that surface characteristics of LATHR seems to be associated with history of recent EE in pts with RMVD irrespective of intraatrial location, age, diameter or thickness of THR detected by TEE.

P1595 Cost analysis model of low-molecular-weight heparin versus unfractionated heparin for antithrombotic therapy in patients undergoing TEE-guided cardioversion from atrial fibrillation

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Patients with atrial fibrillation (AF) of >2 day's duration requiring early cardioversion (CV) are often hospitalized for antithrombotic therapy (AT) for 2 to 5 days with IV unfractionated heparin (UFH) plus initiated oral warfarin Cardioversion follows a therapeutic PTT and a negative TEE for thrombus. Self-administered low molecular weight heparin (LMWH) and warfarin will obviate the need for hospitalization and PTT monitoring, and thus potentially lower costs for these patients.

Methods: We present a cost analysis model in US$ to show the potential savings with LMWH vs. UFH for patients in AF undergoing TEE guided CV. We used ESSENCE Trial costs of LMWH at $69/day, and UFH with equipment/monitors was estimated at $35/day. Estimated total pharmaceutical costs were $276 for LMWH and $140 for UFH. Assuming a 4-day period to achieve therapeutic INR on warfarin, hospitalization costs were estimated at $800 for LMWH including instructional time and materials for home care, and $3200 for UFH. Sensitivity analyses for differences in stroke and bleeding rates were also evaluated.

Results: Assuming equivalency in stroke and bleeding rates, LMWH may lower costs from $3340/patient to $1076/patient; a 68% savings.

Conclusions: Because of the relatively low costs associated with home treatment, low molecular weight heparin may markedly lower treatment costs over unfractionated heparin for AF patients requiring early TEE guided CV. Utility analysis may show even greater advantages of LMWH for these same reasons.

P1596 Relationship between left atrial appendage flow and the outcome of cardioversion

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The aim was to search for a relationship between the mean left atrial appendage flow, measured by transoesophageal echocardiography (TEE) in patients with atrial fibrillation lasting continuously for more than 48 hours, and the success of cardioversion. A study was made of the relationships between the mean left atrial appendage anterograde peak flow (LAAPFL) and some transthoracic echocardiographic parameters (left atrial diameter and left ventricular ejection fraction). TEE was performed in 79 patients (25 females, 54 males) with atrial fibrillation before cardioversion to exclude left atrial thrombus. The mean age of the patients was 63.5 years. Following TEE, the patients underwent either electrical (36 patients) or pharmacological (43 patients) cardioversion. In 61 patients (77%) the cardioversion was successful (group 1). In 18 patients (23%), a sinus rhythm did not return (group 2). In group 1, the mean LAAPFL was 37 cm/sec; in group 2, it was 26.9 cm/sec. The two groups were compared by means of the Mann-Whitney U test and a significant difference was found ($p < 0.01$). The sensitivity, specificity, and positive and negative predictive values of LAAPFL over 35 cm/sec were considered with regard to the outcome of cardioversion. The sensitivity was 56%, the specificity 89%, the negative predictive value 37%, and the positive predictive value 94%.

Conclusion: The mean value of anterograde left atrial appendage peak flow over 35 cm/sec, measured before cardioversion by TEE, demonstrates high specificity and a positive predictive value with regard to the outcome of cardioversion.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY

P1597 Quantitative analysis of shape, area and cyclic changes of the mitral annulus in reduced left ventricular function, hypertrophic cardiomyopathy and normal controls using dynamic three-dimensional echo

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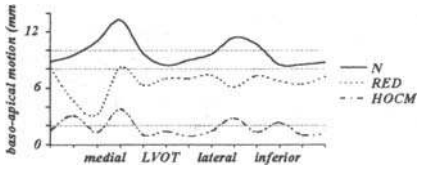
To evaluate the spatial and temporal changes of the mitral annulus (MA) during the heart cycle, transesophageal three-dimensional (3D) echo was used in 30 patients with sinus rhythm (pts, 58 ± 12 years, 14 female): 10 normal controls (N), 10 pts with hypertrophic obstructive cardiomyopathy (HOCM), 10 pts with reduced left ventricular function (RED; EF < 40%). The following parameters were measured in the 3D data set every 40 ms during one complete heart cycle: maximal baso-apical distance of highest to lowest MA points at each time-point (H_{max}), baso-apical BAM of the MA from end-systole to end-diastole (BAM) and MA area (calculated using a summation of slices technique).

Results: Non-planarity of the MA in all groups was most apparent in the portion adjacent to the left ventricular outflow tract, consistently showing displacement towards the left atrium. H_{max} averaged for the pts of every group ranged between 2 mm at systole to 7 mm at diastole for N (2–4 mm for RED and 2–3 mm for HOCM; both $p < 0.05$ vs. N).



The graph shows the averaged BAM of all circumferential points of the MA (x-axis) which was largest in N and smaller in RED and HOCM ($p < 0.01$ for every MA point). There was no significant difference between the MA areas of all groups with a minimum at end-diastole (9.8 ± 2.5 cm^2) and a maximum between end-systole and early diastole (11.8 ± 3.2 cm^2) during opening of the mitral valve.

Conclusions: Dynamic 3D echo allows a precise quantitative analysis of MA morphology and its temporal changes. Systolic left ventricular dysfunction and HOCM reduce H_{max} as well as BAM. This approach may yield further insight into mitral valve pathophysiology in a variety of left ventricular diseases and also after reconstructive surgery.

P1598 Estimation of atrial septal defect stretched diameter by 2D and 3D transoesophageal echocardiography

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In 15 patient with atrial septal defect (ASD) type II, who underwent transvenous defect closure, measurements from echocardiographical three dimensional (3D) reconstruction of the defect were compared to measurements from two dimensional transesophageal echocardiography (2D-TEE) and to the ballon stretched diameter of the defect. The data acquisition for 3D-recontruction was performed with a Hewlett Packard Sonos 5500 ultrasound and a 5 MHz multiplane transesophageal probe. Using 2D-TEE the maximum diameter of the defect was obtained by rotating the imaging plane to the appropriate position. In the 3D reconstruction the longest diameter and a diameter perpendicular to that, als well as the defect area were each measured in the phase were maximum or minimum defect cross sectional areas were visualized. The maximum diameter of the defect was 15.3 ± 6.6 mm using 2D-TEE as compared to 17.7 mm ± 6.6 mm using 3D-TEE ($p < 0.001$). The difference between 2D-TEE and the stretched diameter was 4.8 ± 3.4 mm as compared to 2.4 ± 3.4 mm when 3D reconstruction was used ($p < 0.005$).

The mean fractional change of the defect area (3D reconstruction) was 30 ± 20% (1–60%). In patients with a high fractional area change (>40%) the difference between the maximum diameter from 2D-TEE and the maximum streched diameter was significant larger than in patients with a fractional area change less than 40% (7.6 mm vs. 3.0 mm, $p < 0.01$).

Conclusions: The stretched diameter of the ASD can be more accurately estimated by 3D-TEE as compared to 2D-TEE. The difference of 2D-TEE maximum diameters and strechted diameter is larger in patients with a higher fractional change of defect area.

P1599 Real-time three-dimensional echocardiographic evaluation of mitral annular characteristics in myocardial hypertrophy

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It has been shown that systolic excursion of mitral annulus (MA) has good correlation with left ventricular (LV) systolic function. Evaluation of complicated shape and dynamics of mitral annulus, however, may require rigorous methodology, such as 3 dimensional echocardiography (3DE) and reconstruction. We previously reported that hypertrophic cardiomyopathy (HCM) has large basal LV cavity with small volume in midcavity while secondary LV hypertrophy (LVH) has basal LV cavity narrowing by 3DE. The aim of this study was to investigate differences in mitral annular motion between HCM and LVH using real-time 3DE.

Methods: We studied 12 HCM and 12 secondary LVH patients to observe 3 dimensional structure and motion of mitral annulus. Real-time 3DE images were acquired from apical views and stored on optical disks. After the 3DE datasets were transferred into a computer, each 3D volume data was segmented in 9 consecutive rotational apical planes (20° between each plane). Subsequently, the coordinates of the two mitral leaflet insertion points were identified in each plane. MA geometry was reconstructed from these coordinates (x, y, z) and mitral area change, circumference (CF) change and long axis motion between end-diastolic and end-systolic frames were calculated.

Results: The motion and area change of MA from ED to ES were smaller in HCM comparing with other groups.

	% CF	% Area	Excursion (mm)
HCM	10 ± 4.3	10.1 ± 4.3***	6.6 ± 4.9*
SEC LVH	14.4 ± 8.2	28.1 ± 14.8	11.9 ± 4.5

*$p < 0.05$, ***$p < 0.001$

In conclusion, real-time 3D imaging and digital reconstruction accurately display complicated MA geometry and dynamics during cardiac cycle. Annular excursion and sphincter action is reduced in HCM, while LVH had remarkably smaller end-systolic mitral annular area. This may be a consequence of altered myocardial function in HCM and dominant LV basal hypertrophy in LVH.

P1600 Real-time 3-D dobutamine stress echocardiography in quantitative assessment of ischaemia

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Preliminary observations during Real-time 3-D Dobutamine stress echocardiography (RT-3D DSE) revealed the extent of the stress induced LV wall motion abnormality (WMA) was greater in extent in parallel or C-scans compared to the orthogonal 2-D images. We prospectively examined a set of 30 pts (mean age 58.2 ± 10.6 yrs) with both RT-3D and conventional 2-D images obtained during DSE. Nineteen pts had cineangiographic evidence of CAD and 1 pt. was post heart transplant. All 30 pts had evidence of new WMA by RT-3D DSE compared to only 19 pts by 2-D DSE. LV wall motion score at peak DSE was 1.56 ± 0.41 for RT-3D and 1.23 ± 0.25 for 2-D ($p < 0.0005$).

Orthogonal apical 4 and 2 chamber views along with C-scans were assessed for segmental LV wall motion by RT-3D. The length of the induced WMA at peak DSE was measured in orthogonal apical 4 or 2 chamber views by defining the outer edges of the abnormal LV segment and then measuring its length in cm. WMA was then visualized in the corresponding C-scans and longitudinally measured by identifying the upper and lower slices of the abnormal segment. Mean ± SD length of the WMA was 2.57 ± 1.27 cm in orthogonal apical views compared to 3.33 ± 1.23 cm in C-scans ($p < 0.0001$).

Conclusions: C-scan mode in RT-3D identifies a larger area of LV WMA when compared to the same segments in orthogonal images. These findings may in part explain the higher sensitivity of RT-3D in detection of ischemia and provide the basis for quantifying the extent of ischemia by RT-3D.

P1601 Left ventricular and left atrial volumes during the heart cycle assessed by three-dimensional echocardiography

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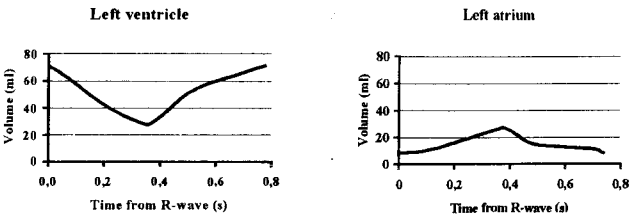
We assessed the dynamic changes in left ventricular (LV) and left atrial (LA) volumes by three-dimensional echocardiography (3DE). The maximal and minimal volumes and the LV mass were compared with the results obtained by magnetic resonance imaging (MRI).

Methods: Thirty healthy children (aged 8 to 13 years, 15 boys and 15 girls) underwent examination by 3DE and MRI. Three-dimensional echocardiography of LV was performed using rotational acquisition of planes at 18-degree intervals from the transthoracic apical view with ECG gating. Imaging of LA was performed from the parasternal window. LV and LA volumes were measured at every frame (median 54, range 33–72 frames) during one heart cycle. Left ventricular mass was assessed in end diastole. Ejection fraction was calculated

Results: The average values obtained by 3DE and MRI were equal for LVmax, LVmin, and LVmass. However, the two methods produced slightly diverging results for LA size.

	LVmax (ml)	LVmin (ml)	EF (%)	LVmass (g)	LAmax (ml)	LAmin (ml)
MRI	65.2 ± 15.6	26.6 ± 7.0	59.2 ± 3.9	74.1 ± 16.3	26.7 ± 7.4	14.5 ± 4.4
3DE	69.3 ± 14.9	27.1 ± 6.3	60.9 ± 1.9	75.4 ± 17.3	29.1 ± 6.7	9.0 ± 2.0
r	0.80	0.88		0.82	0.48	0.72

As 3DE imaging is performed with high frame rates, curves reflecting changes in LV and LA volumes during the heart cycle can be calculated (figure).



Conclusions: Three-dimensional echocardiography detects the different phases of left ventricular and left atrial emptying and filling during the heart cycle.

P1602 Quantitative assessment of prosthetic valve area with three-dimensional transoesophageal echocardiography

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Aims: The currently used methods for prosthetic effective orifice area (EOA) assessment based on transthoracic Doppler pressure half time and continuity equation (EOA-Doppler) have their own known limitations. A new method of direct 3 D planimetry for EOA (EOA-3 D) is compared with EOA-Doppler and with the EOA's provided by Doppler literature (EOA-L) and with the manufacturer's values (EOA-M) for the corresponding valve types and sizes.

Methods: With HP 2500 transesophageal multiplane TEE 3 D acquisition was performed and processed off-line with Tom-Tec 4.0 EchoView. From the long axis of the mechanical valve, short axis anyplane images with the EOA at maximal valve opening were generated. Three D TEE with Doppler measurements was performed in 14 consecutive patients: 9 patients after mitral valve replacement (MVR); (6 St Jude and 3 Medtronic Hall, sizes 27–33) and 5 after aortic valve replacement (AVR); (4 St Jude, 1 Carbomedics, sizes 21–27).

Results: 3 D planimetry was possible in all 14 patients. The means (± SD) of EOA's after MVR, AVR and the total group for EOA-3 D, EOA-Doppler, EOA-L and EOA-M are shown in the table. There were no statistical differences between these 4 methods, only EOA-M in the MVR and total group was larger ($P < 0.001$; ANOVA). Correlations for all 4 methods ranged between 0.76–0.82.

EOA (cm^2)	3D	Doppler	Literature	Manufact.
MVR	3.06 ± 0.65	2.61 ± 0.74	2.98 ± 0.35	4.46 ± 0.72
AVR	1.95 ± 0.45	1.65 ± 0.77	1.72 ± 0.47	2.76 ± 0.85
Total group	2.66 ± 0.79	2.50 ± 0.71	2.53 ± 0.73	3.85 ± 1.12

Conclusion: 3 D effective orifice area (EOA-3D) is comparable with Doppler-and literature derived EOA assessment in normal functioning mitral and aortic mechanical prosthetic valves with good correlations between all EOA's. The manufacturer's EOA's were consistently larger than the Doppler-and 3 D planimetry EOA's, possibly due to pannus/thrombus formation in vivo.

P1603 Real-time three-dimensional echocardiographic assessment of acute haemodynamic changes during ventricular and atrioventricular sequential pacing

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Previous studies have reported variable hemodynamic changes during different pacing modes. Real-time 3-D echocardiography (RT-3D, VOLUMETRICS) measures LV volumes accurately and rapidly during pacing; 21 pts (age 64.7 ± 14.5 yrs) with permanent pacemakers had sequential RT-3D measurements of LV volumes (ml), cardiac output (CO, l/min), LV ejection fraction (EF, %) and systolic blood pressure (SBP, mmHg) at baseline and at paced rates of 80, 100 and 120/min in AV sequential (DDD) and ventricular paced (VVI) modes. AV interval was fixed at 150 ms in DDD mode. Mean ± SD hemodynamic parameters were:

	EDV	ESV	CO	EF	SBP
Baseline	108.2 ± 46.9	63.7 ± 36.7	2.8 ± 1.5	42.6 ± 12.7	130.9 ± 30.8
DDD 80	100.7 ± 40.5*	60.2 ± 33.5	3.3 ± 1.8	42.1 ± 14.2	122.3 ± 21
DDD 100	94.4 ± 45.8*	59.8 ± 38.6	3.5 ± 1.9*	39.2 ± 14.7	124.2 ± 22.4
DDD 120	89 ± 45.3*	60.5 ± 41.1	3.4 ± 1*	36.2 ± 12**	122.1 ± 26.3*
VVI 80	96.2 ± 41.8*	57.4 ± 36*	3.2 ± 1.4	43.2 ± 13.5	114.2 ± 22.5*
VVI 100	93.7 ± 44.6*	57.3 ± 37.7*	3.7 ± 2.1*	41.3 ± 14.5	118 ± 21.6*
VVI 120	88.2 ± 42.8*	62.6 ± 42.1	3.1 ± 1.6	32.7 ± 14.8**	111.1 ± 27.9*

(*$p < 0.05$, **$p < 0.001$, comparisons of VVI and DDD to baseline) EDV decreased with increasing rate in both pacing modes; ESV decreased VVI 80, 100; CO increased DDD 100, 120, VVI 100, 120 due to increased heart rate; EF decreased DDD 120, VVI 120; SBP decreased DDD 120, VVI 80, 100, 120.

Comparisons between VVI and DDD modes showed no significant differences in the parameters except for a higher SBP in DDD mode ($p < 0.05$). In 6 pts with baseline LV dysfunction (EF < 40%) the results of comparisons between the two modes were similar.

Conclusions: 1) RT-3D is useful in accurate measurement of volumetric changes during pacing. 2) DDD pacing does not offer significant hemodynamic advantage over VVI in pts with either preserved or depressed LV function.

DIASTOLIC FUNCTION

P1604 Influence of alteration in preload on the pattern of left ventricular diastolic filling as assessed by Doppler tissue imaging.

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Pulsed Doppler indexes of diastolic filling have been used as measures of diastolic function. However, various hemodynamic factors and loading conditions independent of the intrinsic properties of the hart also influence the pattern of LV filling. Doppler Tissue Imaging (DTI) is a new technique currently under investigation for assessment of regional systolic and diastolic left ventricular function. The aim of the present study has been to evaluate whether the diastolic mitral annular velocities by Doppler tissue imaging is affected by changes in preload conditions.

Methods: Doppler transmitral inflow velocities (E, A), diastolic mitral annular velocities at the lateral (LatE, LatA) and septal (SepE, SepA) side of the mitral annulus by pulsed DTI, and the ratio of peak early to peak atrial filling velocities (E/A, LatE/A, SepE/A) were assessed in 42 subjects (age 56 ± 9 years) with coronary artery disease at the baseline and after nitroglycerine administration. All the measures were performed at end expiration and averaged over three cardiac cycles.

Results: Heart rate slightly increased from 68 ± 10 to 77 ± 12 beats/min ($p < 0.001$). The E, LatE, and Sep E velocities (cm/sec) decreased from 68.7 ± 25.6 to 54.2 ± 18.7 ($p < 0.0001$), from 9.2 ± 3.2 to 8.1 ± 2.6 ($p < 0.001$), and from 7.4 ± 2.8 to 6.6 ± 2.6 ($p = 0.001$), respectively. The A, LatA, and SepA velocities were not significantly changed (68.6 ± 21.2 vs. 71.3 ± 21.4; $p = 0.518$, 9.4 ± 2.4 vs. 9.5 ± 2.5; $p = 0.721$, 8.8 ± 2.0 vs. 8.7 ± 2.0; $P = 0.521$, respectively). The E/A, LatE/A, and SepE/A were decreased from 0.98 ± 0.33 to 0.87 ± 0.36 ($p = 0.0001$), from 1.07 ± 0.59 to 0.92 ± 0.44 ($p = 0.0002$), and from 0.87 ± 4.2 to 0.78 ± 3.2 ($p = 0.0049$), respectively.

Conclusions: In the present study, alterations in preload significantly altered the pattern of diastolic filling as assessed by DTI of mitral annular velocities in a similar manner to the Doppler transmitral flow velocity profile. These results suggest that DTI of mitral annular velocities must also be interpreted cautiously when used as indexes of diastolic function.

P1605 Unmasking significantly elevated filling pressure in patients with an impaired left ventricular with relaxation pattern using the Valsalva manoeuvre

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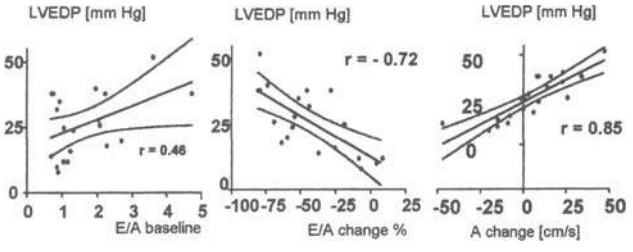
Impaired relaxation is frequently masked by elevated filling pressures resulting in a pseudonormal flow pattern (E/A > 1.0) which can be unmasked using the Valsalva maneuver. Because the E/A wave ratio increases as filling pressures rises it is generally assumed that patients with an E/A ratio < 1.0 (impaired relaxation pattern) have lower or even normal filling pressures when compared with patients who have a pseudonormal or restrictive filling pattern. However, based on individual observations, we hypothesized that patients with an E/A ratio < 1.0 can nonetheless have severely elevated filling pressures. Since left ventricular enddiastolic pressure (LVEDP) essentially determines atrial afterload, the response of the A-wave velocity to a reduction of aftrial afterload by a standardized Valsalva maneuver should be best suited to estimate LVEDP. This was tested in 20 patients at the time of diagnostic cardiac catherization:



Conclusion: Just as elevated filling pressures can mask impaired relaxation, the impaired relaxation pattern can mask the presence of elevated filling pressures. This can be revealed by testing the response of the A-wave to the Valsalva maneuver allowing estimation of LVEDP independent of the baseline E/A ratio.

P1606 Validation of five non-invasive Doppler methods for the assessment of left ventricular filling pressure

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Background: There are several non-invasive Doppler methods to estimate left ventricular end-diastolic pressure [LVEDP]. So far, it has not been evaluated which one most accurately predicts LVEDP in an unselected patient population.

Methods: In 50 consecutive patients with sinus rhythm, undergoing elective coronary angiography, transthoracic Doppler echocardiography was performed during or at least within 10 hours before/after cardiac catheterization. LVEDP was estimated by Doppler measurements of – if present – the mitral regurgitant peak gradient [A], the mitral regurgitant gradient at aortic valve opening [B] or the end-diastolic gradient of aortic regurgitation [C] in combination with blood pressure measurement with an oscillometric cuff. LVEDP was additionally estimated using regression equations of transmitral inflow parameters [D] and of mitral A-wave and pulmonary vein A-wave duration [E]. All estimates were compared with invasive LVEDP.

Results: Echocardiography was performed 4 ± 7 hours after the invasive exam with mean systolic and diastolic blood pressure unchanged. Angiographic mean LVEDP was 17 mmHg (range 4–36 mmHg). For each method a regression equation was calculated (see table). A dependence of the method from ejection fraction [EF] was postulated, if its unexplained variation in a multivariate regression model using EF as predictor variable, was significantly reduced.

	Valve regurgitant methods			Regression equations	
Method:	A	B	C	D	E
n patients (total 50)	18	16	7	42	40
Intercept	5.7	0.61	5.4	3.6	16
Slope	0.6	1.0	0.63	0.78	0.1
Regression coefficient	0.58	0.71	0.53	0.21	0.01
EF dependent	no	no	no	yes	yes

Conclusions: The estimation of LVEDP using valve regurgitant jets is EF independent. For clinical use, regression equations of mitral inflow or pulmonary vein flow are not reliable. In half the patients, estimation of LVEDP can be done using regurgitation gradients (A–C). Under these circumstances, the mitral regurgitation gradient at aortic valve opening (B), allows the most reliable estimate.

P1607 Diastolic pulmonary artery pressure evaluation by continous wave Doppler in patients with tricuspid regurgitation: proposal of a new method

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Background: In patients (pts) with tricuspid regurgitation (TR) the diastolic pulmonary artery pressure (dPAP) can be estimated using the right ventricular-right atrial pressure gradient (RV-RA_{grad}), measured on the continuos wave doppler (CWD) TR velocity curve at the opening of the pulmonary valve and adding it to the value of the right atrial pressure (RAP) at that moment. In order to locate, beat by beat, the TR velocity just before the onset of the right ventricular ejection into the pulmonary artery (RVE_{PA}), when the right ventricular and the pulmonary artery pressure are alike, we often observed two different areas of echo gray level distribution into the CWD spectrum of TR, with increased echoreflectivity in the proximal one. As the intensity of the spectral recording is influenced by the number of red cells passing through the regurgitant orifice, the onset of RVE_{PA} may produce a reduction of the spectral echo-density. The initial point of the boundary line between the two areas could coincide with the onset of RVE. Purpose: to locate the onset of RVE_{PA} on the CWD-TR velocity curve and calculate dPAP.

Methods: we studied 12 consecutive pts (8 men, age 50–73 years), presenting TR and submitted to right heart catheterization, using a balloon flotation (Swan-Ganz) catheter, for heart failure, in recent myocardial infarction. The echocardiografic (RV-RA_{grad} at the onset of RVE_{PA}) and hemodynamic measurements (mean RAP_{hemo} and RAP_{hemo} at the onset of RVE_{PA}) were performed by two independent observers. The PAP at the onset of RVE_{PA} was calculated adding the RV-RA_{grad} to the RAP_{hemo} (both measured at the onset of RVEPA). The values of PAP at the onset of RVE_{PA} vs $dPAP_{hemo}$ and the values of the mean RAP_{hemo} vs RAP_{hemo} at the onset of RVE where compared.

Results: The initial point of the boundary line between the two areas of different echodensity into the CWD-spectrum of TR was detected in 10/12 pts (83.3%). In these pts we observed a good correlation between the values of dPAP estimated by CWD-echo and hemodinamic data ($R = 0.98$, $P < 0.0001$). There was also a good correlation between the mean value of the RAP at the onset of RVE_{PA} and the mean RAP (9.63 ± 4.33 mmHg versus 9.5 ± 4.65 mmHg) ($R = 0.98$, $P < 0.0001$).

Conclusions: diastolic PAP can be calculated adding the value of the right ventricular-right atrial pressure gradient, measured on the CWD-TR velocity curve at the opening of pulmonary valve, to mean RAP.

P1608 Opposite to standard Doppler parameters, the difference of duration of pulmonary and mitral A-wave is independent of mitral regurgitation and may reliably estimate left ventricular filling pressure

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Mitral (MV) and pulmonary vein (PV) parameters have extensively been used to predict left ventricular (LV) filling pressure (LVfp). Elevated LVfp causes increased MV early diastolic and decreased systolic PV flow. However, mitral regurgitant volume (RVol) modifies MV and PV pattern exactly in the same direction. Therefore, measurements independent of RVol have to be identified in order to reliably predict LVfp.

Methods: 69 pts (age: 56 ± 23), who underwent left heart catheterization with end-diastolic pressure recording (pTD), had a complete echocardiographic evaluation. Patients had a broad range of pTD (12–36 mmHg), LV EF (19–72%) and mitral regurgitant volume (RVol) (0–65 ml). The only esclusion criteria were presence of mitral stenosis or unsatisfactory PV flow recordings (9.5%). E (Emax), A wave velocity, E/A, E (Dte) and A (Dta) deceleration time, PV systolic (S), diastolic (D), S/D were measured. MV A wave and PV A wave duration were measured and their difference (A-A′) calculated. A quantitative assessment of RVol was also obtained.

Results: Doppler parameters more strongly associated with pTD were: Emax (0.52; $p < 0.0001$), Dte ($r = 0.53$; $p < 0.0001$), E/A ($r = 0.56$; $p < 0.0001$), S/D ($r = 0.55$; $p < 0.0001$), LV EF ($r = 0.47$; $p = 0.0002$), and A-A′ (0.58; $p < 0.0001$). RVol was not significantly associated with pTD. Among Doppler parameters only A-A′ and DTa were not correlated with RVol. Multivariate analysis showed that A-A ($p < 0.0001$) and DTe ($p = 0.04$) were independent predictors of pTD. A A-A′ cut-off > 30 msec predicted a pTD > 20 mmHg with a positive predictive value of 91% and negative predictive value of 78%.

Conclusion: A-A′ is an accurate parameter to estimate LVfp independently of Rvol. This method could be enhenced by contrast technology, which can markedly improve PV flow recording.

P1609 Comparative accuracy of pulmonary venous flow velocity variables and mitral flow velocity variables in predicting pulmonary wedge pressure in the presence of atrial fibrillation

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We have previously demonstrated that pulmonary wedge pressure (PWP) could be estimated in patients with either sinus rhythm and atrial fibrillation (AF) from transthoracic Doppler analysis of pulmonary venous flow (PVF) velocities. Other investigators have found excellent correlation between PWP and mitral velocity variables in patients with sinus rhythm. Because sampling PVF velocities by transthoracic Doppler is technically more difficult in presence of dilated atria, such as those found in presence of chronic AF, we sought to compare the accuracy of PVF and mitral Doppler in predicting PWP in patients with AF. In 48 consecutive patients (32 M/16F aged 46 to 82 years) with chronic AF, suffering mainly from dilated cardiomyopathy, PWP was compared with PVF and mitral velocity parameters. For both PVF and mitral flow the best correlation was found for deceleration time (DT). In patients with normal (≤12 mmHg) PWP mitral DT (295 ± 54 ms) was longer than in patients with elevated PWP (215 ± 53 ms), but this difference was not statistically significant. PVF DT was significantly longer in patients with normal PWP (264 ± 45 ms) as compared with patients with elevated PWP (145 ± 20 ms $p < 0.0001$). The correlation between PVF DT with PWP was significantly stronger ($r = -0.91$, SEE 0.03, F ratio 158.2) than the correlation between mitral DT and PWP ($r = -0.54$, SEE 22.17, F ratio 13.25). The equations derived from mitral and PVF variables were prospectively tested in 32 additional patients. When estimating PWP using the PVF-derived equation the measured and predicted PWP agreed with a mean difference of −0.88 mmHg. When using the mitral-derived equation the mean difference was significantly larger (−3.11 mmHg; $p < 0.01$).

Possible explanations are: the presence and continual variations in the degree of mitral regurgitation following changes in the R-R interval; the stronger dependence of mitral variables on the position of the Doppler sample volume, and finally the fact that the theoretical simplification that left atrial stiffness is very low (assumed when considering the relation bewteen mitral flow velocity pattern and left ventricular filling pressures) may be not true in presence of chronic AF.

In conclusion PVF DT is more accurate than mitral DT in predicting PWP in presence of chronic AF.

P1610 Left ventricular relaxation patterns and their relation with P-wave duration in ankylosing spondylitis

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Valvular involvement with aortic insufficiency, increased myocardial fibrosis and conduction system disturbances are known complications of ankylosing spondylitis (AS). In this study P wave analysis and echocardiographic measurements of systolic and diastolic functions were studied in patients with AS and compared with healthy controls.

Methods and Results: The study included 88 AS patients with no cardiac symptom (44 M, 44 F; age 19–64, mean 32.9 ± 11.1) and 31 healthy subjects (16 M, 15 F; age 19–60, mean 32.7 ± 8.5). Recordings for P wave analysis were obtained with Kardiosis ars-LP high resolution ECG analysis system and filtered P wave duration (PWD) was calculated. Left ventricular systolic and diastolic diameters and ejection fraction were used as systolic parameters whereas A peak, E peak, E/A ratio, E deceleration time (Edec) and isovolumic relaxation time (IVRT) were used as diatolic parameters. AS patients and controls were similar according to age and sex characteristics ($p > 0.05$). Systolic functions and left atrial (LA) diameters of both groups were similar ($p > 0.05$) but diastolic functions were found to be impaired in AS group (Table). Mean PWD in AS was 102.4 ± 13.4 ms which is higher but not significantly different than controls (100.1 ± 6.2 ms) ($p > 0.05$). PWD in AS patients was positively correlated with LA diameter ($p < 0.05$, $r = 0.27$) and negatively correlated with E peak ($p < 0.05$, $r = -0.24$) and E/A ratio ($p < 0.05$, $r = -0.23$). LA diameter of AS patients was also found to be correlated with IVRT ($p < 0.05$, $r = 0.25$).

	Anklosing Spondylitis	Control	P Value
E Peak (m/s)	0.73 ± 0.17	0.81 ± 0.15	$p < 0.05$
A Peak (m/s)	0.61 ± 0.14	0.53 ± 0.12	$p < 0.05$
E/A Ratio	1.27 ± 0.38	1.57 ± 0.54	$p = 0.001$
DT (ms)	217.91 ± 38.26	193.39 ± 23.54	$p < 0.001$
IVRT (ms)	94.38 ± 16.73	79.35 ± 13.95	$p < 0.001$

In conclusion myocardial involvement may be seen in asymptomatic AS patients and parameters of left ventricular diastolic functions can be used in this period. Further studies are needed to clarify the value of P wave analysis in cardiac evaluation of patients with AS.

P1611 Pulsed Doppler tissue imaging in assessing regional myocardial function changes associated with ACE inhibitor decreased left ventricular mass

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The aim of the study was to evaluate the regional systolic and diastolic myocardial velocities (mv) changes associated with pharmacologically reduced left ventricular mass (LVM).

Methods: Thirty-two hypertensive patients (pts, 22 male, 10 female; mean age 56.7 ± 10.1 years) with increased LVM index (LVMI > 110 g/m^2 in F, >134 g/m^2 in M), free of coronary artery disease were treated with ACE inhibitor (enalapril or ramipril) for a period of 24 weeks. Before and after treatment in all pts LVMI was calculated and in the pulsed wave Doppler tissue imaging (PW DTI, Acuson-Sequoia) examination of LV interventricular septum (IVS) and posterior wall (PW) in the short axis view we calculated peak velocities of systolic (S), early (E) and late (A) diastolic waves and their ratio E/A.

Results: At the end of the treatment period in 19 (59.4%) pts LVMI significantly decreased (from 161.7 ± 22.5 to 137.7 ± 24.1 g/m^2; $P < 0.005$), while in 13 (40.6%) pts LVMI was not changed significantly (from 158.2 ± 21.7 to 150.5 ± 22.1 g/m^2; NS). In pts with regression of LVM, mv of IVS and PW showed: increased E by 13% and 10.5%, decreased A by 8.2% and 4.2%, increased ratio E/A by 22.8% and 16%, and slightly increased S by 2.5% and 1.2% compared with baseline values. In pts without significant LVM reduction, evaluation of mv of IVS and PW showed slightly changes: increased E by 6.2% and 5.4% and ratio E/A by 7.2% and 6%, while A and S were unchanged compared with baseline values.

Conclusion: Our data showed that PW DTI allows quantification of regional myocardial function changes associated with LVM regression. Increased regional E/A ratio and E wave are the most prominent changes in pts with ACE inhibitor decreased LVM.

P1612 Diastolic function in hypertrophic cardiomyopathy: pulmonary venous flow assessment as an adjunct to mitral valve inflow patterns

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Background: Abnormalities of diastolic function are common in hypertrophic cardiomyopathy (HCM). Although Doppler patterns of mitral valve inflow (MVI) can be used to assess diastolic function, pulmonary venous flow (PVF) analysis has been shown to supplement this assessment, and several PVF parameters correlate with left ventricular end-diastolic pressure.

Methods: We studied 69 patients (pts) with HCM (37 men, mean age 41 (19–70)). Transthoracic pulse-wave Doppler tracings of MVI and PVF were taken and the following parameters measured: early (E), late (A), E/A ratio and A duration (Ad) of MVI; systolic (S), diastolic (D), atrial systolic wave (PA) and duration of PA (PAd) of PVF. The pts were divided into 4 groups (Gp): Gp 1 (normal) with an E/A 1–2.1, a PA < 35 cm/s and a negative PAd-Ad, Gp2 (impaired relaxation) with E/A < 1, Gp 3 ("pseudonormal") with an E/A 1–2.1 but a PA > 35 cm/s or a positive PAd-Ad, and Gp 4 (restrictive) with an E/A > 2.2.

Results: See table

Pulmonary venous flow parameters by group

Group	No.	S	D	S/D	PA	PAd-Ad
1	10	74	40	1.7	27	−20
2	21	64	34	1.7	34	53
3	25	60	50	1.3	41	45
4	13	38	72	0.7	27	24

Gp 4 when compared with the combined other groups has larger left atria(47 vs 41 mm, $p < 0.1$), a higher mean end diastolic diameter (46 vs 42 mm, NS), and a higher mean end-systolic diameter (28 vs 22 mm, $p < 0.1$). The maximal LV wall thickness, pattern of hypertrophy and outflow tract gradient were similar in all groups. Patients in gp 3 were more likely to be in NYHA class II or III than those in gp 1 (40 vs 10%, $p < 0.05$). Chest pain was also more common in gp 3 than in gp 1 (40 vs 30%, NS).

Conclusions: 1) PVF identifies HCM patients with a "pseudonormal" pattern of diastolic dysfunction. 2) Abnormal PVF correlates with diastolic function and clinical parameters.

P1613 Regional left ventricular myocardial function in hypertrophic cardiomyopathy: assessment by tissue Doppler imaging and ^{123}I-β-methyliodophenyl pentadecanoic acid scintigraphy

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Background: Myocardial velocity gradient (MVG) obtained by tissue Doppler imaging (TDI) is a new noninvasive index in evaluating regional myocardial thickening or thinning. On the other hand, ^{123}I-β-methyliodophenyl pentadecanoic acid (123I-BMIPP) myocardial scintigraphy has been established as a technique for evaluating the myocardial fatty acid metabolism. We assessed the relationship between diastolic MVG and 123I-BMIPP scintigram findings in patients with asymmetric septal hypertrophic cardiomyopathy (HCM).

Methods: We recorded the left ventricular (LV) M-mode color-coded TDI in 20 patients with HCM and age-matched 15 normal controls (NC), and calculated maximal MVGs in the ventricular septum (VS) and posterior wall (PW) during early diastole and atrial systole by off-line analysis. We also performed 123I-BMIPP myocardial scintigraphy in all patients, and calculated the washout ratio (WR) of SPECT imaging in the VS and PW.

Results: 1) Early diastolic MVGs in the PW and VS, particularly VS, were significantly lower in the HCM group than in the NC group. 2)Atrial systolic MVG in the PW was significantly greater, whereas that in the VS was significantly lower in the HCM group than in the NC group. 3) WR in the PW and VS, particularly VS, were significantly greater in the HCM group than in the NC group. 4)There were negative correlations between early diastolic MVG and WR in both PW and VS.

Conclusions: There was a close relationship between early diastolic MVG and WR of the hypertrophied VS in patients with HCM. The regional myocardial wall motion abnormality detected by MVG may reflect the regional metabolic abnormality in this disease.

P1614 Reversibility of ischaemic diastolic left ventricular disfunction by successful coronary angioplasty: follow-up of 70 patients 3 months after percutaneous transluminal coronary angioplasty

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The aim of the study was to assess the relation between the left ventricular diastolic function and myocardial viability 3 months after percutaneous transluminal coronary angioplasty (PTCA).

Material: 70 patients (pts), 61 men (87.1%), mean age 52.6 ± 9.06 years, with coronary artery disease: unstable angina (91.4%) and stable angina (8.6%), who underwent PTCA. Most of our pts had one-vessel disease (58.5%), the others having two-vessel (21.5%) and three-vessel disease (20%). None had evidence of mitral stenosis, severe mitral regurgitation, atrial fibrillation or conduction disturbances such as second- or third-degree heart block.

Methods: All patients underwent successful PTCA, and were prospectively followed over a 3-month period by Doppler echocardiography. Diastolic transmitral flow variables were recorded 1 day before PTCA and 1 week, 1 and 3 months after the procedure. We measured the following variables of diastolic function: peak E and A velocities (cm/s), E wave deceleration time (Edt, ms), A wave deceleration time (Adt, ms), E/A ratio, isovolumetric relaxation time (IVRT) (ms), and the ejection fraction (EF). The measurement of left ventricular end-diastolic pressure (LVEDP) was done by left heart catheterization.

Results: According to the Doppler transmitral flow velocity profile, as expressed by the E/A ratio, the study pts were assigned to the following 3 groups: group 1 with E/A $\leq$ 1, with impaired relaxation filling pattern (35 pts, 50%),; group 2 with 1 $\leq$ E/A < 2 which may signify a normal or "pseudonormal" filling pattern (30 pts, 42.8%); group 3 with E/A $\geq$ 2 representing "restrictive" filling pattern (5 pts, 7.1%). LVEDP was 10 to 35 mmHg. In all three groups, we found a very good correlation between Adt and LVEDP (r = 0.95) and between Edt and LVEDP (r = 0.89) before PTCA. In all study pts, Adt showed a significant increase at 1 week as well as at 1 and 3 months. In both group 1 and 2, the E/A ratio showed significant improvement after PTCA (0.76 ± 0.19 vs 1.28 ± 0.28, $p < 0.001$ in group 1; 1.23 ± 0.26 vs 1.44 ± 0.30, $p < 0.001$ in group 2), which was more marked in the subgroups that did not present clinical restenosis signs. In group 3, the E/A ratio decreased significantly (2.15 ± 0.32 vs 1.56 ± 0.21; $p < 0.001$). At the same time, all study pts showed a significant improvement of the EF (51.57 ± 8.82 vs 56.21 ± 5.93, $p < 0.001$), more important in the subgroups without clinical restenosis.

Conclusions: Left ventricular diastolic filling variables, altered in patients with coronary artery disease, were improved after percutaneous transluminal coronary angioplasty: significant improvement of the E/A ratio, Adt and Edt, as well as increase of the ejection fraction. This amelioration was more marked in patients who did not show clinical restenosis.

P1615 Abnormal diastolic filling patterns are related to the left ventricular function and remodelling after first acute myocardial infarction

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Data regarding the contribution of diastolic dysfunction on left ventricular (LV) remodeling after acute myocardial infarction (MI) are limited. Aim of this study was to evaluate the impact of the abnormal LV filling patterns on the echocardiographically detected LV function and size after acute MI.

Methods: 98 consecutive patients (pts) with first, acute MI (mean age: 58, M = 85, Killip I–II) underwent echo-Doppler examination 10 days after the admission. The following parameters were considered: 1) End-diastolic and end-systolic LV transverse diameters (EDD, ESD: mm); 2) LV ejection fraction (EF, modified Simpson rule: %); 3) Wall motion score index (WMSI, 16 segments); 4) Early-and late LV filling peak velocities (E, A: cm/sec); 5) E/A ratio; 6) Deceleration time (EDT, msec); 7) Isovolumic relaxation time (IVRT: msec). Based on LV diastolic filling pattern, pts were divided as follows: Group 1, 12 pts, with a restrictive (E/A > 2 or E/A > 1 and EDT < 140 msec) pattern; Group 2, 46 pts, with a pseudonormal (E/A > 1 and EDT > 140 msec) pattern; Group 3, 40 pts, with an impaired relaxation (E/A < 1) pattern. Moreover, EDD and ESD were calculated three months after MI and their changes were compared.

Results: Group 1 pts had larger infarct size (peak of creatine kinase: 4227 vs 2055 and 2035 U/l, $p < 0.001$), higher WMSI (1.74 vs 1.50 and 1.54, p = 0.005), lower EF (35% vs 44% and 47%, $p < 0.001$) and shorter IVRT (98 vs 108 and 136 msec, $p < 0.001$) in comparison with Group 2 and 3 pts, respectively. All other demographic and clinical variables were comparable among the three groups. At three months, LV EDD and ESD appeared significantly increased in comparison with the first evaluation both in Group 1 (+5.5 ± 2.7, +6.6 ± 3.3 mm, respectively; $p < 0.0001$) and Group 2 (+2.0 ± 2.7, +2.7 ± 3.4 mm, respectively; $p < 0.0001$), while a significant reduction was observed in Group 3 pts (−3.1 ± 3.0, −3.7 ± 3.3 mm, respectively; $p < 0.0001$).

Conclusions: A restrictive filling pattern is present in pts with impaired LV function after MI. Both the restrictive and pseudo-normal filling patterns identify pts with LV dilatation after MI, while in pts showing an impaired relaxation pattern the LV remodeling phenomenon seems to be absent.

P1616 The restrictive left ventricular filling pattern: configuration, frequency and underlying heart disease

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The restrictive left ventricular filling pattern (RFP) offers typical Doppler findings, indicating abnormal compliance. It was our aim to show frequency, underlying heart disease and configuration of the RFP in a great group of patients.

Methods: M-Mode, two-dimensional and continuous wave/colour flow Doppler echocardiograms were obtained in a total of 8704 Patients (PT) with conventional systems. Pulsed wave Doppler ultrasound examination of the transmitral (early [E] and late [A] diastolic) Doppler flow velocities (DFV), E-deceleration time (E-D) pulmonary venous DFV (systolic [S], diastolic [D], atrial reversal flow [ARF]), and the isovolumic relaxation time (IVRT) was performed in an apical four- or five-chamber view. Pt with more than mild mitral regurgitation, after cardioversion of atrial fibrillation and young healthy subjects were excluded.

Results: In 74 PT (0.85%) with a mean age of 57.5 ± 11.3 years a RFP was detected. In this group the left ventricular diameter at end-diastole (LVEDD) was 62.5 ± 8.9 mm, at end-systole (LVESD) 49.1 ± 10.3 mm, left atrial diameter at end-systole (LAESD) 49.8 ± 6.7 mm, ejection fraction (EF) 26.1 ± 11.1%. The PT were in NYHA class 2.7 ± 1.1. The table shows the comparison of the Doppler parameters with an age-matched control group with left ventricular dysfunction (LVD) (LVEDD: 64.0 ± 9.7 mm, LVESD: 49.9 ± 10.7 mm, LAESD: 45.8 ± 12.1 mm, EF: 28.2 ± 13.4%)

Group	E (m/s)	A (m/s)	E-D (ms)	S (ms)	D (m/s)	ARF (m/s)	IVRT (ms)
RFP	0.91	0.34	107.4	0.27	0.65	0.30	55.8
	±0.18	±0.09	±23.4	±0.13	±0.13	±0.08	±10.2
LVD	0.60	0.73	165.8	0.46	0.40	0.27	111.4
	±0.21	±0.18	±54.8	±0.14	±0.14	±0.07	±44.7

$p < 0.001$ for all mean values between the two groups; except ARF: $p < 0.04$

Underlying heart disease: dilated cardiomyopathy (n = 12), anterior (n = 38) and inferior (n = 8) myocardial infarction, hypertensive heart disease aortic valve disease (n = 3), amyloidosis (n = 3) myocarditis (n = 1), endomyocardial fibrosis (n = 1).

Conclusion: The RFP was found in a minority of PT. This type of diastolic dysfunction is not reflected by LVEDD or EF, in our group it is dominated by ischemic heart disease. Because the RFP is associated with a worsened prognosis, it is an important echocardiographic sign.

P1617 Response of the restrictive left ventricle diastolic filling pattern to valsalva manoeuvre is the predictor of the future symptomatic status in patients with left ventricle systolic dysfunction

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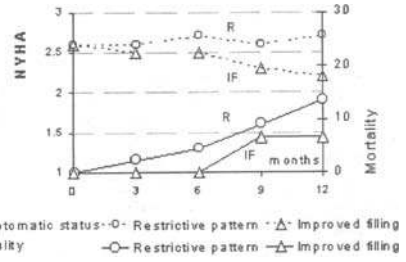
The aim was to evaluate the prognostic value of the response of restrictive transmitral inflow pattern to standardized Valsalva manoeuvre, in patients with an advanced left ventricle systolic dysfunction and EF < 30%.

Methods: Fifty nine patients with ischemic and dilated cardiomyopathy (mean EF 23 ± 3%), who showed restrictive left ventricle diastolic filling pattern (E/A > 2, DT < 150 msec) were examined. Mitral inflow velocities were recorded first at the end of the normal expiration and then during the strain phase of standardized Valsalva manoeuvre. Patients symptomatic status were assessed using NYHA classification.

Results: In 44 (75%) patients Valsalva manoeuvre induced decrease of both E and A velocity during the 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 Improved (E/A < 2) and pseudonormalized. At the end of the follow up 11.0 ± 3.2 months period in patients, who showed no reversion of the restrictive filling pattern during Valsalva manoeuvre, there was no improvement of the symptomatic status (from 2.6 ± 0.3 NYHA to 2.7 ± 0.3) and there were 6 deaths (13.6%). In patients with improvement of the diastolic filling pattern during manoeuvre there was also improvement of the symptomatic status (from 2.6 ± 0.2 NYHA to 2.2 ± 0.3 p < 0.01) and there was only 1 death (6.7%,NS)



Conclusion: Restrictive filling pattern represents an advanced left ventricular diastolic dysfunction. Unimprovement of the filling pattern in response to preload reduction by Valsalva manoeuvre can detect patients with more adverse prognosis.

ECHOCARDIOGRAPHY IN CORONARY ARTERY DISEASE

P1618 Colour Doppler sonographic detection of artery puncture site complications after invasive cardiac procedures

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Peripheral artery puncture site complications after diagnostic cardiac catheterization (DC) or PTCA have been described at a rate between 0.21% and 6.25% with surgical repair rates of up to 2%. Diagnostic suspicion of vascular pathology on physical examination was found to be less reliable.

Therefore, 2101 unselected consecutive pts subjected to invasive procedures (DC: 1700 pts; PTCA 401 pts) during an 11-month-period underwent Colour-Duplex-Ultrasonographie (CDS) within 24 h after sheath removal, hand-compression and application of a compression bandage for 18 to 24 h. Baseline demographic and clinical characteristics and laboratory variables were collected prospectively. Primary end point was a composite of CDS-defined vascular complications: artery thrombosis (ATH), arteriovenous fistula (AVF), pseudoaneurysm (PSA) and open puncture channel (OPS) and echogenic haematome (HAM). OPC was observed in 1.19%, PSA in 4.28%, AVF in 0.48%, ATH in 0.19% and HAM in 3.9% at first CDS. OPC was found in 0.69% of males and in 2.3%% of females; PSA was found in 3.3% of males and in 6.6% of females. In the majority of pts prolonged compression was successful for resolution of puncture site pathology. Surgical repair was performed in 0.9%. Multiple logistic regression analysis identified female gender, advanced age, elevated bodymass and a platelet count of less than 120.000 as risk factors for OPC and PSA. Only in males risk of puncture site complications was higher after PTCA in comparison with DC. Sheath size did not influence the rate of puncture site complications.

P1619 Significance of resting wall motion abnormalities in two-dimensional echocardiography in patients without previous myocardial infarction referred for pharmacologic stress testing

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Background. Resting wall motion abnormalities (WMA) in 2 dimensional echocardiography may be encountered in patients without previous myocardial infarction or known coronary artery disease (CAD) referred for stress testing. However, resting WMA are not established criteria for the diagnosis of CAD. Additionally, the functional significance of these abnormalities has not been evaluated by an independent technique.

Aim of the study is to assess the value of resting WMA in the prediction of an ischemic response and abnormal perfusion during dobutamine stress test.

Methods. We studied 116 patients (mean age 57 ± 13 years, 50 men) without known CAD or a history of myocardial infarction by dobutamine (up to 40 μg/kg/min) stress echocardiography and simultaneous stress and rest technetium sestamibi SPECT imaging. Ischemia was defined as new or worsening WMA and reversible perfusion defects respectively.

Results. Resting WMA were detected in 24 patients (21%). Patients with resting WMA had a higher prevalence of abnormal perfusion (75% vs 25%, p < 0.001) and ischemia by SPECT (50% vs 24%, p < 0.05) and by echocardiography (42% vs 9%, p < 0.001) compared to patients without resting WMA respectively. Stress and rest perfusion defect scores were higher in patients with than those without rest WMA (3.25 ± 2.67 vs 0.88 ± 1.77, p < 0.0001 and 1.46 ± 1.69 vs 0.21 ± 0.70, p < 0.0001 respectively). Independent predictors of the occurrence of ischemia by echocardiography were the presence of resting WMA (p < 0.01, Chi^2 = 6.7), ST segment depression (p < 0.005, Chi^2 = 11.3) and angina during the test (p < 0.05, Chi^2 = 5.3). The presence of resting WMA was the only independent predictor of an abnormal perfusion (p < 0.0001, Chi^2 = 20).

Conclusion. In patients without known CAD referred for pharmacologic stress testing, resting WMA are powerful independent predictors of an ischemic response during dobutamine stress test and identify a population with a higher prevalence and extent of myocardial perfusion abnormalities.

P1620 Automatic backscatter analysis of regional right ventricular systolic function in patients with inferior wall acute myocardial infarction using colour kinesis

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Color kinesis (CK) is a recently developed echocardiographic method based acoustic quantification (AQ) that automatically tracks and displays endocardial motion in real time. We studied whether AQ and CK may provide quantitative assessement of global and regional right ventricle (RV) function in patients with inferior acute myocardial infarction (AMI) since the evaluation of RV function has important prognostic implications in these patients.

Methods: Thirty two consecutive patients with recent (within one week) inferior AMI and 15 age- and gender-matched controls were studied. RV AQ and CK images were acquired in the apical four-chamber view. After image quality was optimized, the acquistic quantification system for endocardial border detection was activated. Once the region of interest (ROI) was drawn around the RV, all gains compensation were adjusted to optimize tracking of the blood-endocardial interface. AQ vaweforms of RV fractional area change and ejection fraction were displayed along with the electrocardiogram and the concurrent cross sectional image. CK digitized RV end-systolic images were evaluated by rewiewing the stored loops obtained in all normal subjects and patients. To evaluate the entire spatial temporal histories of RV systolic endocardial excursion, further quantitative CK analysis was performed by measuring the systolic segmental endocardial motion (SEM) and the time of systolic segmental endocardial motion (tSEM).

Results: Compared to controls, inferior AMI patients had reduced RV fractional area change (21 ± 7 vs 45 ± 6%, p < 0.01), reduced EF (26 ± 16 vs 44 ± 18%, p < 0.01), reduced mean SEM (11 ± 5 mm vs 21 ± 3 mm, p < 0.01) and reduced mean tSEM (150 ± 38 msec vs 290 ± 30 msec, p < 0.01).

In conclusion, our data suggest that RV systolic functions are influenced in inferior AMI and AQ and CK are feasible technique for investigating RV regional systolic functions in these patients.

P1621 Early detection of myocardial ischaemia during dobtamine stress echocardiography using color coded tissue Doppler imaging

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Background: Color coded tissue Doppler imaging has been used to detect early acceleration in ventricular contractility during low dose dobutamine (DOB) stress tests. Since wall motion abnormalities (WMA) are known to occur following myocardial ischemia, it was recognized that color coded tissue Doppler imaging may enable the detection of myocardial ischemia before WMA induced by DOB stress echocardiography.

Subjects and Methods: Seven patients with severe stenosis of left anterior descending coronary artery were enrolled in this study. DOB stress echocardiography (3, 6, 12 mcg/min/kg step-wise every 5 min) was performed using SSA 370 Echo-Doppler equipment (Toshiba, Tokyo). Wall motion was determined from 4 different view angles acording to the procedure of American Society of Echocardiography. Color coded tissue Doppler images (CCTDI) were obtained from the parasternal short axis view at an early point during the systolic cycle when posterior wall velocity was highest as defined by the M-mode tissue Doppler method. Endocardial and epicardial velocities were measured by two-dimensional CCTDI in both the anterior septum (ischemic region) and the posterior wall (non-ischemic region). Each Myocardial velocity gradient (MVG) was calculated by the subtraction of epicardial velocity from endocardial velocity. MVG ratio [(MVG at stress − MVG at baseline)/MVG at baseline] between the two segments were determined.

Results: All patients showed significant MVG during infusion of the maximum dose of DOB (12 mcg/min/kg). In the non-ischemic region (posterior wall), MVG and MVG ratio during the highest dose of DOB increased significantly from 2.90 ± 0.32 to 5.62 ± 0.48 ($p < 0.05$) and from 0 to 0.966 ± 0.25 ($p < 0.05$), respectively. In contrast, in the ischemic region (anterior septum), MVG and MVG ratio values increased until 6 mcg/min/kg DOB and then decreased significantly during the highest dose of DOB (MVG, from 3.46 ± 0.32 to 0.76 ± 0.54; $p < 0.01$: MVG ratio, from 2.48 ± 0.77 to −2.20 ± 0.58; $p < 0.01$) before WMA was detected.

Conclusion: Real time determination of MVG and MVG ratio using CCTDI makes possible the detection of myocardial ischemia prior to the appearance of WMA, suggesting that this technique is a useful and safe means for detecting myocardial ischemia during DOB stress testing.

P1622 Short term prognostic value of a non geometric global Doppler index of diastolic and systolic performance in first myocardial infarction

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Objective: To assess in an unselected population with first myocardial infarction (MI) the ability of a nongeometric global Doppler index (GDI) of combined left ventricular systolic and diastolic function, to predict in-hospital congestive heart failure (CHF), and cardiac mortality 35 days after MI.

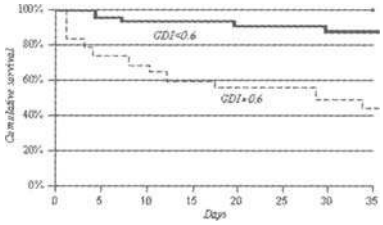
Background: Recently a nongemetric global doppler index has shown prognostic value in patients with dilated cardiomyopaty and cardiac amyloidosis, only limited data are avaliable in patients with MI.

Methods: Echocardiography was performed within 24 hours of arrival to CCU. During hospitalization Killip-class was determined on daily basis.

Results: Of 72 eligble patients aged 67 ± 11 years sustaning first MI, 70 patients (97%) were enrolled the study, 1 patient was excluded due to aortic stenosis and 1 due to dementia.

35 of 70 patients (50%) had signs and symptoms of CHF (Killip ≥ II) during hospitalization. Univariate analysis identified age, heart rate, peak creatine kinase B, GDI, E-wave deceleration time (Dt) < 140 msec, E/A ratio and WMI as predictors of CHF. Multivariate logistic regression analysis dentified GDI ($p = 0.0001$) and peak creatine kinase B ($p = 0.03$) as independent predictors of CHF.

16 patients (23%) died of cardiac causes within 5 weeks of MI. Of 24 patients with GDI > 0.6 at admission 12 patients (50%) died, of 46 patients with GDI < 0.6 4 patients died (9%), Log-Rank test $p < 0.0001$ (figure). Cox hazards analysis identified GDI ($p < 0.0001$) and Dt ($p = 0.04$) to be independent predictors of cardiac death, when compared with age, heart rate, CHF, peak creatine kinase B, and WMI.



Conclusion: A nongeometric global Doppler index (GDI) of left ventricular global function has significant prognostic value in MI.

P1623 The value of echocardiography in assessing patients post myocardial infarction

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The AIRE study showed that clinical signs of heart failure (HF) post myocardial infarction (MI) indicate an increased risk of death which is reduced by angiotensin converting enzyme inhibitors (ACE-I). The TRACE study showed that patients with echocardiographic evidence of LV dysfunction also benefited from ACE-I, whether or not clinical HF was present. Asymptomatic LV dysfunction (ALVD) can be suspected clinically in the presence of a large anterior or repeat MI, and/or large enzyme rise. How accurate are clinicians in predicting ALVD?

Methods: The senior CCU clinician completed a short questionnaire for patients with MI. The presence of heart failure was recorded, as was any clinical suspicion of ALVD. Current or planned use of diuretics, ACE-I, and B-blockers was noted. All patients then had echocardiography within 3 days. EF was estimated visually and then calculated using the wall motion score (WMS) method as used in the TRACE study.

Results: 67 consecutive patients with definite MI were studied. Their mean EF was 43% and mean WMS 1.5. 21 had clinical evidence of heart failure, and 29 had EF < 40%. Mean EF of those with clinical evidence of heart failure was 37% range 13–60. Mean EF of those with no clinical evidence of heart failure was 45% range 7–60. 13 had EF < 40% and clinical evidence of heart failure.16 had EF < 40% but no clinical evidence of heart failure. Only 18 of the 29 patients with EF ≤40 were thought on clinical grounds to need ACE-I, and 13 of the 38 patients with EF > 40 were thought to need ACE-I. 21 patients had no clinical features to suggest ALVD and no clinical plan to start ACE-I. Their mean EF was 48.5%, range 17–60. 3 of these patients had EF < 40%. The technician estimate of EF agreed with the EF calculated from the WMS in all but 2 cases. In these 2 cases the calculated EF was only 1% point outside the range given by the technician.

Conclusions: The "Eye-ball" method of determining LV function by an experienced echocardiographer agrees well with the WMS (TRACE) method. Patients who have clinical signs of HF, often have preserved left ventricular function, whereas those with no signs of heart failure often have significant LV dysfunction. It seems difficult to define a group of patients in whom preserved LV function or ALVD can be predicted clinically. Therefore all MI patients without evidence of HF should have echocardiographic assessment of LV function to allow more rational and cost effective use of ACE-I.

P1624 Myocardial viability detected by dobutamine echocardiography in patients with chronic coronary artery disease, and long-term outcome after coronary angioplasty

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Background: Viable but dysfunctional myocardium (VM) detected by dobutamine echocardiography (DE) predicts a post-PTCA improvement in regional left ventricular (LV) function. However, whether or not DE can predict the long-term (>2 years) outcome, including LV function, after PTCA is still unclear.

Methods: Fifty patients (age 60.4 ± 9.5 yrs) with chronic coronary artery disease and regional LV dysfunction who underwent DE 1 week before PTCA to assess myocardial viability were followed for 4.0 ± 0.8 yrs. VM by DE was defined as improvement in systolic thickening in a dysfunctional segment (in a 16 segment LV model) by ≥1 grade in a 4 point wall motion score (1 = normal to 4 = dyskinesis). Follow-up coronary artery angiography was performed at 3 months after PTCA. Regional LV function (regional wall motion score index, RWMSI) in revascularized area and LV ejection fraction (LVEF) were evaluated by two-dimensional echocardiography at 1 week, 3 months and at >2 yrs (late follow-up) after PTCA in patients remained event (cardiac death or myocardial infarction or unstable angina pectoris which required myocardial revascularization)-free.

Results: Thirty-six patients had VM and 14 had non-VM by DE. The rates of restenosis and re-PTCA were similar between patients with VM and non-VM (restenosis, 50% vs 36% and re-PTCA 19.4% vs 21.4%, p = NS, respectively). At late follow-up, 29 patients showed improvement in RWMSI (1.9 ± 0.5 to 1.4 ± 0.4, p < 0.001), 15 showed no improvement (2.2 ± 0.8 to 2.2 ± 0.8), 3 showed worsening (2.6 ± 0.2 to 2.9 ± 0.0) and 3 had cardiac events (1 non-fatal myocardial infarction and 2 unstable angina pectoris). Of the 29 patients with improvement, 27 (93%) had VM, while only 3 (20%) of the 15 with no improvement had VM and all 6 of those with poor outcomes (3 with cardiac events and 3 with worsening) had VM (Chi-Square = 28.9, p < 0.001). LVEF improved (0.53 ± 0.1 to 0.58 ± 0.1, p < 0.001) in patients with VM and improved RWMSI while deteriorated (0.38 ± 0.03 to 0.30 ± 0.03) in 3 Patients with worsened RWMSI. Patients with VM and a poor outcome had a lower mean LVEF before PTCA, and at 1 week and 3 months after PTCA (p = 0.004, < 0.001, and = 0.001, respectively), and a higher restenosis rate (p = 0.007) than patients with VM and without a poor outcome.

Conclusion: We conclude that, in patients with chronic coronary artery disease, VM detected by DE may predict long-term improvement in regional and global LV function after PTCA. However, patients with VM and persistent low LVEF and restenosis are at risk for cardiac events or worsening of LV function.

P1625 Myocardial viability by echocardiography predicts long-term survival after revascularisation in patients with symptomatic ischaemic cardiomyopathy

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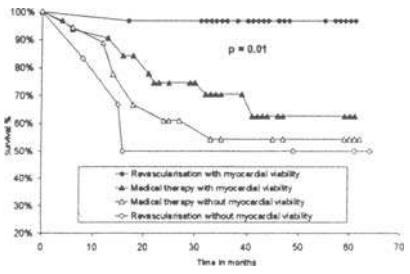
Resvascularisation (Rev) improves survival in CAD pts with angina and LV systolic dysfunction however, there are insufficient long term data regarding survival benefit of Rev in pts with predominant symptoms of CHF.

Methods: Follow-up was obtained in 87 consecutive pts with CHF due to ischaemic LV systolic dysfunction (NYHA Class II–IV; LVEF: 0.25 ± 0.09) who were investigated with low dose dobutamine echocardiography (DE). Myocardial viability (MV) was defined as having either normal function or mild dysynergy at rest or severe resting dysynergy that improved or worsened on DE.

Results: 37 pts underwent Rev based on clinical grounds. At a mean follow up of 40 ± 17 months there were 22 (25%) cardiac related deaths. Multivariate analysis was performed using clinical data, drug therapy, LVEF, number of diseased vessels, number of viable segments. Results showed that the independent predictor of survival was when Rev was performed in patients with ≥5 segments of viability) from a 12 segment model); hazard ratio (95% CI): 0.39 (0.17–0.91), p = 0.01. The latter group also showed significant improvement in NYHA class (p < 0.001) and LVEF (p < 0.01) compared to the other groups.



Conclusion: Rev produced a clear survival benefit in patients with CHF due to ischaemic cardiomyopathy who have significant MV and was associated with improved symptoms and LV function.

P1626 Coronary artery disease in allograft: dobutamine echocardiography detection

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Allograft coronary artery disease (ACAD) is the leading cause of mortality after cardiac transplantation (CT). Although angiography (angio) is considered the gold standard for diagnosis, it tends to understimate the extent of vasculopathy. Dobutamine stress echocardiography (DSE) identifies myocardial hypoperfused areas inducing local hypokinesia or akinesia.

From 1990 to 1998, 221 patients (pts) underwent CT in our Institution. Since 1993 DSE is utilized for ACAD detection in our laboratory. In the period '93–'98 sixty pts (mean age 45.2 ± 6 years, mean duration since CT 58.2 ± 32 months) had a standard DSE evaluation (dobutamine infusion schedule 5, 10, 20, 30, 40 mcg/kg/min at 5 minutes step). An 11 segments wall motion score model was used (modified ASEC's criteria) and positive DSE was defined as a new or worsening LV regional wall motion abnormality. EF%, EDV, ESV, WMSI were calculated at rest and each step. Results were compared with angio (Gao's criteria) and EMB data.

Three groups of pts were identified (values are expressed as mean ± SD):

Groups	Angio	WMSI basal	WMSI DSE	EDV% var.	ESV% var.	EF% var.
G I (48 pts)	–	1.02 ± 0.09	1.02 ± 0.09	−44.4 ± 13	−60.4 ± 24	30.2 ± 16.6
G II (9 pts)	+	1.53 ± 0.45	2.22 ± 0.50	+0.96 ± 20	84.79 ± 80	−38.16 ± 13
G III (3 pts)	–	1.15 ± 0.21	1.6 ± 0.00	−40.25 ± 14.5	−14.55 ± 2.8	−45 ± 2.8

In 48 pts (G I) angio, EMB and DSE were negative for ACAD. In 10 pts (G II) angio and DSE were positive for ACAD. In 2 pts (G III) angio was negative and DSE positive for ACAD and EMB showed intramyocardial proliferative lesions.

In conclusion: 1) Results suggest that DSE is reliable non-invasive test to detect epicardial vascular involvement; 2) Probably DSE can be a highly reliable test in the assessment of microvascular ACAD involvement which can be identified by EMB but not be predicted by angiography; 3) DSE can be used for the diagnosis and follow up of ACAD.

MISCELLANEOUS

P1627 Perivalvular complications in native valve endocarditis

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The aim of this multicenter study was to assess the clinical course, predisposing risk factors, microbiological profile, and echocardiographic manifestations of patients (P) with native, left-sided valve endocarditis and perivalvular complications demonstrated by transesophageal echocardiography (TEE) or at pathology.

Methods: We have studied prospectiely 94 p (70 men; mean age 56 ± 15 years) of left-sided endocarditis (85 p had definitive and 9 p had probable Duke Criteria). The infection was on the aortic valve in 45 p, on the mitral valve in 48 p, and on both valves in one p.

Results: Periannular complications (abscesses, pseudoaneurysms or fistulae) were detected in 27 p (group I). In the remaining 67 p (group II) none of these complications were found. The latency period between the onset of symptoms and the diagnosis of endocarditis of both groups was not different. Pre-existent heart disease and predisposing risk factors had no association with peniannular complications. There were no significant differences between microorganisms of gr I and II [*staphylococcus aureus* (n = 16, 2 gI and 14 gII), *staphylococcus coagulase negative* (n = 8, 3 gI and 5 gII), *streptococci* (n = 32, 11 gI and 21 gII), *enterococci* (n = 12, 4 gI and 8 gII)]. TEE demonstrated vegetations in 86 p (26 gI and 60 gII, p = NS). No significant differences were found in the vegetation size of both groups. Atrioventricular block developed in 7 p (5 gI and 2 gII, p < 0.05). Systemic embolism occurred in 35 p (9 gI and 26 gII, p = NS). Forty five P underwent surgery (22 gI and 23 g II, p < 0.05). Twenty five p died (7 gI and 18 gII, p = NS).

Conclusions: 1 Periannular extension complicates aortic more frequently than mitral endocarditis; 2 The type of microorganism, time to diagnosis, preexisting heart disease, and predisposing risk factors were not related to the existence of these complications; 3 The frequency of systemic embolism was not higher in p with periannular extension of the infection; 4 Surgery was more frequent in these p; 5 Global mortality was similar in both groups.

P1628 Echocardiographic prognostic markers in patients with severe mitral regurgitation: ejection fraction versus dp/dt of the left ventricle

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The echocardiographic evaluation of left ventricular (LV) contractility in patients with severe mitral valve regurgitation (SVMR) can sometimes be misleading especially when based on the ejection fraction of the left ventricle (LVEF). Moreover, LVEF is poorly correlated to long-term prognosis of patients with SVMR The aim of this study was to examine the clinical importance of the rise of the LV pressure per time unit (dp/dt) as a marker of ventricular contractility with prognostic value in patients with SRMV.

Methods: We examined 86 patients (52 men and 34 women, 56 with coronary artery disease, 15 with dilated cardiomyopathy and 15 with valvular heart disease, mean age 72 ± 11 years) which were presented in the hospital with SRMV during the years 1992–95. The LVEF was calculated according to the Teicholz method and the dp/dt from the mitral regurgitation signal obtained by continuous wave Doppler. All patients were followed until December 1998. Sixty-one out of the 86 patients (71%) had died due to progressive congestive heart failure. Patients who died due to acute ischemic episodes or due to extracardiac causes were not included in the study.

Results:

	Deceased (n = 61)	Survivals (n = 25)	P value
Age (years)	73 ± 11	69 ± 10	0.128
LVESD (mm)	564 ± 112	528 ± 90	0.157
LVEDD (mm)	667 ± 90	654 ± 63	0.530
LVEF (%)	33 ± 15%	37 ± 16%	0.353
dp/dt (mmHg/sec)	659 ± 243	900 ± 256	<0.001

In multivariate analysis with age, sex, etiology of SVMR and LVEF < 35% as covariates, only dp/dt values lower than 730 mmHg/msec were significantly associated with poor prognosis [p = 0.038, odds ratio 12.1 (1.1 to 129.9)].

Conclusions: Contrary to LVEF, dp/dt was significantly increased in patients with improved long-term prognosis. Although further, specifically designed prospective studies are needed to clarify this issue it could be postulated that in patients with SVMR the echocardiographic evaluation of dp/dt is an informative prognostic tool, presenting superior prognostic value compared to LVEF.

P1629 Prediction of the situations in which the proximal flow convergence method estimates better than the regurgitant jet area the degree of angiographic severity in the mitral regurgitation

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Background: The regurgitant jet area (RJA) and the proximal flow convergence (PFC) are two valid methods in the cuantification of the mitral regurgitation (MR), however its application in the daily clinical practice is not widespread due to its complex and time-consuming calculation. Nevertheless, there are situations in which its application is essential bearing in mind the limitations of the RJA.

Methods and results: We studied 82 patients (pats) with MR by the RJA and the PFC. In one patient the RJA could not be determined {angiographic severity degree (ASD) I} and in 6 pats it was not possible to calculate the maximum regurgitation flow (MRF) (5 pats were labeled with ASD I and 1 with degree II). The values of RJA (cut points in 6, 9.4 and 15.2 cm^2) and the MRF (cut points 16, 56 and 160 ml/sec) were determined through ROC curves, that gave the best predictions of the degrees of angiographic severity from I to IV. The correlation between severity of the MR by RJA and by angiography (A) was $r_s = 0.74$, with a degree in agreement (weighed Kappa) $\kappa_p = 0.75$. The PFC method gave a $r_s = 0.92$ with $\kappa_p = 0.91$ (a significative difference of correlation with p = 0.01). In the group of pats with eccentric jet and increased valvular mobility, as well as in those with left atrial size more than 7.5 cm, we could not find a significative statistical correlation of the RJA with the (A), however we could find it between the PFC and the (A) with $r_S = 0.92$ (p = 0.0001). In 75 pats we could compare the severity of MR through the three methods (RJA, PFC and A), in 30 pats (40%) of them there was agreement among these three methods, in 31 pats (41.4%) the severity of the MR by the PFC was in agreement with (A), however both were in disagreement with the severity by the RJA; in 6 pats (8%) the RJA was in agreement with the (A) (all of them had rheumatic valvular disease) and in disagreement with PFC; in 6 pats (8%) the RJA and the PFC were in agreement, and in disagreement with the (A), and finally in 2 pats (2.6%) the three methods were in disagreement.

The multivariable analysis of logistic regression showed the jet eccentricity as the only independent predictor (odds ratio 5.08) for a higher accurancy of the PFC versus the RJA (the PFC is in agreement with the (A) but the RJA is in disagreement with both of them).

Conclusions: 1) The PFC method presents a better correlation with the (A) than one of the RJA. 2) For the pats with eccentric jet and increased valvular mobility, as well as in those with left atrial size more than 7.5 cm, it is essential the use of the PFC bearing in mind the lack of correlation between RJA and (A). 3) The jet eccentricity is an independent predictor that provides a better estimation of the severity of the MR by the PFC, than by using the RJA.

P1630 Echocardiographic characteristics of diastolic mitral regurgitation

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Diastolic mitral regurgitation (DMR) is rarely seen. We tried to evaluate the hemodynamic characteristics of DMR by typical Doppler findings and to consider the meaning of DMR according to these parameters.

DMR was analysed in an apical four-chamber view by M-mode colour Doppler (M/Q) tracing of the mitral regurgitant jet. From these M/Q tracings the flow of DMR was calculated by the method of the proximal isovelocity surface area (F), the duration (DU) of DMR and of diastole (DD) and the beginning (BEG) of DMR after the onset of the QRS-complex in the electrocardiogram were obtained. The regurgitant volume (RV) of DMR was calculated according to F and DU. By pulsed Doppler the stroke volume (SV) was obtained at the aortic or pulmonary valve.

DMR was found in 13 patients (mean age 53.5 ± 13 years). The underlying disease was severe aortic regurgitation (n = 5), idiopathic dilated cardiomyopathy (n = 1), cardiac amyloidosis (n = 1), hypertensive heart disease (n = 2), myocardial infarction (n = 2), high degree atrioventricular block (n = 2). The mean left ventricular diameter at end-diastole was 62.0 ± 10.3 mm (30.7 mm/m^2), at end-systole 40.2 ± 11 mm (19.9 mm/m^2), left atrial diameter at end-systole 48.8 ± 4.8 mm (24.2 mm/m^2), ejection fraction 44 ± 15%. The Doppler pattern of transmitral and pulmonary venous flow were typical for pseudonormalization with increased flow velocity during diastole. The mean heart rate was 75.3 ± 30.0 beats/minute; blood pressure: systolic 131.7 ± 26.7 mm Hg, diastolic 67.0 ± 16.6 mm Hg. Specific results are shown in the table:

DD (ms)	DU DMR (ms)	BEG (ms)	SV (ml)	RV (ml)
654.5 ± 353.9	140.3 ± 174.4	335.8 ± 86.3	110.8 ± 25.8	12.6 ± 8.7

p = n.s. for RV in the case of long or short DU DMR

A positive left ventricular-to-left atrial pressure gradient in diastole generates DMR and raises the left atrial pressure in addition to impaired left ventricular function. In some clinical situations DMR might induce deterioration of left atrial and consecutive left ventricular filling. The long diastole should be avoided in the presence of DMR, dual-chamber pacing and valve repair should be considered in the treatment strategies besides conventional medical treatment.

P1631 Association between mitral annulus calcification and aortic atheroma: a prospective transeophageal echocardiographic study

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Background: Although mitral annulus calcification (MAC) has been reported to be a significant independent predictor of stroke, no causative relationship was proven. It is also known that aortic atheromas, especially those ≥5 mm thick and/or protruding and/or mobile, are associated with stroke. Therefore, we sought to determine whether an association exists between MAC and aortic atheroma.

Methods: The records of 195 consecutive patients who underwent transesophageal echocardiography (TEE) for various indications were followed prospectively. The 79 patients in whom a diagnosis of MAC was made on prior transthoracic echocardiography (TTE) were compared with 116 sex-and age-matched patients without MAC. MAC was defined as a dense, localized, highly reflective area at the base of the posterior mitral leaflet. We measured MAC thickness with two-dimensional-TTE in four-chamber view, and aortic atheroma thickness, calcification, protrusion and mobility with TEE. Aortic atheroma was defined as localized intimal thickening of ≥3 mm. A lesion was considered complex if there was plaque extending ≥5 mm into the aortic lumina and/or if it was protruding, mobile or ulcerated.

Results: No differences were found between the groups in risk factors for atherosclerosis or in indications for referral for TEE but atrial fibrillation which was more prevalent in the MAC group (13% vs 4%, p = 0.032). Significantly higher rates were found in the MAC group for prevalence of aortic atheroma (95% vs 38%, p < 0.001), atheromas ≥ 5 mm thick (73% vs 17%, p < 0.001), protruding atheromas (49% vs 11%, p < 0.001), mobile component (11% vs 3%, p = 0.021), and complex atheroma (80% vs 19%, p < 0.001). Forty-six patients had MAC thickness ≥ 6 mm and 33 <6 mm. Aortic atheroma thickness was significantly greater in the patients with a MAC ≥ 6 mm (6.9 ± 2.4 vs 5.1 ± 2.7 mm, p < 0.003). On multivariate analysis, MAC, diabetes, hypertension, age and sex were the only independent predictors of aortic atheroma (p = 0.0001, 0.01, 0.02, 0.014 and 0.029, respectively).

Conclusions: There is a significant association between the presence and severity of MAC and aortic atheroma. MAC may be an important marker for atherosclerosis of the aorta. This association may explain the high prevalence of systemic emboli and stroke in patients with MAC.

P1632 Aortic regurgitation in acute aortic dissection type A. The value of transoesophageal echocardiography in aortic valve repair/replacement decision making. 9 years study

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Aortic regurgitation (AR) frequently associates type A aortic dissection (AAD). Transoesophageal Echocardiography (TEE) can identify the mechanism of AR in pts with AAD. The mechanism of AR in AAD pts is the main guide for the decision of the surgical method for AR operation – aortic valve repair/replacement.

The results of TEE were assessed in consecutive 58 pts (M – 49, F – 9, mean age 52 (6.7) with acute AAD who underwent an operation at the period 1990–1998. 2 pts with prior aortic valve replacement were excluded from the analysis. The degree of AR was estimated on the grounds of the proximal AR jet height to annular diameter ratio. 12 pts with AAD had no or trace AR – Group (G) I. In 14 pts mild AR (II) was found – G II. In 30 pts moderate or severe AR was detected – G III. The predominant mechanism of AR was independent on AAD in 29 pts (bicuspid aortic valve or leaflet thickening) and dependent on AAD in 20 pts (geometric distortion of the valve support structures resulting in incomplete valve closure or leaflet prolapse, intimal flap prolapse.

Results:

Mechanism of AR	Group I (n = 14)	Group II (n = 14)	Group III (n = 30)
Independent on AAD (n = 29)	11 (79%)	10 (71%)	5 (17%)
Leaflet thickening	9	7	2
Bicuspid valve	2	3	3
Dependent on AAD (n = 20)		4 (29%)	25 (83%)
Incomplete valve closure		3	13
Valve prolapse		1	7
Intimal flap prolapse		0	5

Surgical procedure for AR was planed both by cardiac surgeon and echocardiographer on the grounds of TEE – Aortic valve repair or replacement was decided to be performed in 37 pts. These were all 30 pts from G III and 7 pts from G II – 4 pts with AR dependent on AAD and 3 pts with bicuspid valve. In 8% the planed procedure must have been changed intraoperatively.

Conclusions: 1. In pts with AAD the severe AR is frequently a result of AAD dependent factors, whereas in pts with mild AR it is more often due to the prior organic changes of the valves. 2. In pts with AAD and AR TEE is a helpful method in aortic valve repair/replacement decision making.

P1633 Three-year clinical follow-up of patients with spontaneous echocardiographic contrast in the thoracic aorta

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It has been suggested that spontaneous echocardiographic contrast in the thoracic aorta (SEC) is associated with an increased risk of future cardiovascular events.

Methods: To further elucidate this issue, the transesophageal echocardiograms (TEE) of 717 consecutive patients (pts) who were examined in our laboratory between January 1995 and December 1996 were reviewed for the presence of SEC. Pts in whom the finding was confirmed were reexamined clinically or their attending physicians were contacted by telephone and information were collected regarding the occurrence of the following events: Cardiac death, noncardiac death, stroke, peripheral embolic events and acute myocardial infarction (AMI).

Results: SEC was confirmed in 58 (8.1%) of the reviewed cases, none of whom regarded aortic dissection or thoracic aortic aneurysm. Follow-up information were collected in 45 of these pts (33 men, 12 women, aged 70 ± 10 years). The time elapsed between the index TEE and the follow-up was 38 ± 6 months (range, 25–48 months). During this period, 20 pts (45%) died, 11 of whom due to cardiac causes (6 by sudden cardiac death, 1 because of congestive heart failure, and 4 because of an AMI), 3 due to a cerebrovascular accident, and 4 due to non cardiac causes. The cause of death was not defined in 2 cases. Furthermore, 2 pts experienced a non-fatal stroke during follow-up, while no non-fatal myocardial infarctions or peripheral embolic events were reported. Five of the pts with SEC consented to undergo repeat TEE at follow-up. Four of them who underwent repeat TEE had coronary artery disease and one had chronic atrial fibrillation. All 5 pts had been receiving chronic aspirin therapy (160–325 mg o.d.), whereas no one received oral anticoagulants. Thoracic aortic SEC was shown to persist in all cases.

Conclusions: The data of the present report support the suggestion that thoracic aortic SEC is associated with considerable cardiovascular morbidity and mortality. Conventional-dose aspirin was shown not to influence the presence of SEC over a 3-year period in a small group of patients

P1634 Effectiveness of intra-venous rt-PA in the treatment of massive pulmonary and right atrial floating thrombus

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Occurrence of right atrial floating thrombus (RAFT) during the course of pulmonary embolism (PE) is a rare but probably overlooked event. Positive diagnosis is based upon echogardiographic features. Surgery is the current treatment and consists of thrombectomy during extracorporeal circulation. Therapeutic uncertainity dominates medical management and very few studies focused on effectiveness of intravenous (IV) fibrinolysis in this condition. 8 consecutive patients admitted for massive PE in whom echocardiography showed RAFT prolapsing across the tricuspid valve in diastole were eligible for fibrinolitic treatment. Echocardiographic signs of pulmonary hypertension were found in all cases. 1 patient (pt) treated by Heparin alonde died before starting fibrinolysis. 7 patients were trated with 100 mg IV of rt-PA. We gave rt-PA at the dose of 10 mg IV bolus, then 40 mg for two hours, followed by 50 mg for five hours. Rt-PA was associated with a bolus of 5000 units of Heparin. Rt-PA determinated the dissolution and dissappearence of RAFT on hour 12 of treatment, and the cocomitant disappearence of the echocardiographic signs of pulmonary hypertension. However, 2 pts needed adjunctive surgery because of evidence of persistant thrombus in pulmonary artery. At a 24 hours later evaluation, both scintigraphy and angiography showed an improvement of pulmonary perfusion. No side effects occurred during and after rt-PA infusion. Our results indicate that rt-PA acts rapidly and is save. IV fibrinolysis could be proposed as a firts line therapy for RAFT associated with PE.

P1635 Acute improvement of aortic mechanics following haemodialysis in patients with chronic renal failure

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Aortic distensibility (AoDist) represents an important determinant of left ventricular pulsatile load and coronary blood flow. While AoDist seems to undergo marked impairment in patients (pts) with chronic renal failure (CRF), little is known regarding the potential effects of hemodialysis (HD) on this parameter.

Methods: We measured the distensibility of the proximal ascending thoracic aorta (AoDist) in 48 CRF pts (31 men, 17 women, aged 45 ± 14 years) undergoing regular HD, before and immediately after a mid-week dialysis session. Aortic distensibility was calculated as a function of changes in aortic diameter and pulse pressure, using the formula: 2 × (pulsatile change in diameter)/([diastolic diameter] × [pulse pressure]). Aortic diameters were measured by transthoracic echocardiography, while arterial pressure was measured simultaneously by sphygmomanometry at the brachial artery. All data were compared with those of a group of subjects with normal renal function (17 men, 10 women, aged 44 ± 14 years), matched to the CRF pts with respect to age and prevalence of risk factors for atherosclerosis.

Results: Aortic distensibility was significantly lower in CRF pts vs controls. A significant improvement of AoDist was noted following completion of the HD session (table).

Parameters	Controls	Pts pre-HD	Pts post-HD
Diastolic aortic diameter (cm)	2.9 ± 0.4	3.7 ± 0.6†	3.6 ± 0.6†‡
Systolic aortic diameter (cm)	3.3 ± 0.4	3.9 ± 0.5†	3.9 ± 0.5†‡
Pulsatile change of diameter (cm)	0.3 ± 0.1	0.2 ± 0.1†	0.2 ± 0.2†
Diastolic aortic pressure (mmHg)	73 ± 10	87 ± 17†	76 ± 14‡
Systolic aortic pressure (mmHg)	118 ± 14	141 ± 29†	115 ± 26‡
Arterial pulse pressure (mmHg)	47 ± 11	53 ± 19	39 ± 18‡
Aortic distensibility ($cm^2\ dyn^{-1} \times 10^{-6}$)	3.8 ± 1	1.9 ± 0.7†	2.6 ± 1.2†‡

†$p < 0.05$ compared with controls; ‡$p < 0.05$ compared with pre-HD value.

In conclusion, our data confirm the impairment of aortic mechanics in CRF and provide the additional information that AoDist is acutely improved to a significant extent immediately after an HD session. This effect, most likely passive in nature and possibly of limited duration, may however add considerably to the overall hemodynamic benefit offered by regular HD in CRF pts.

SYSTOLIC FUNCTION AND HEART FAILURE

P1636 Midwall mechanics and left ventricular geometry

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Asymptomatic hypertensive patients exhibit subnormal left ventricular (LV) midwall fiber shortening (MWS) at rest and this finding predicts morbid events independently of age and blood pressure levels. Still unclear are the relationships between LV structure and midwall mechanics, in particular the influence of LV geometry on systolic performance.

To explore this issue, we evaluated by M-mode-2D Doppler echocardiography 1076 patients with stage I hypertension (604 F and 472 M, mean age 62 ± 11 ys). Exclusion criteria were: valvular heart disease, dilated cardiomyopathy, coronary artery disease. LV hypertrophy (LVH) criteria were LV mass index (LVMI) >134 g/m^2 in males and >110 g/m^2 in females.

355 patients had a normal LV, 88 had remodeling, 195 a concentric hypertrophy and 438 an eccentric hypertrophied ventricle. Patients with a normal LV were younger (58 ± 12 ys) and had higher MWS (19.6 ± 2.8%). Ejection fraction was normal in all groups. MWS was significantly reduced in patients with concentric remodeling (16.6 ± 2.0%) and with concentric LVH (16.0 ± 2.4%) ($p < 0.01$ in all cases). An abnormal MWS (<14%) was present in 84 patients (33 F and 51 M, age 67 ± 9 ys), 3.1% with normal ventricles, 9.1% with remodeling, 19.5% with concentric LVH, and 6.2% with eccentric LVH. 38 of these patients showed in addition a reduced fractional shortening (<26%). In a multivariate analysis only age, LVMI, systolic and diastolic blood pressure were independent predictors ($p < 0.05$) of MWS.

In conclusion: about 8% of hypertensives exhibit a depressed midwall fractional shortening despite a normal ejection fraction. Midwall fractional shortening is prevalently reduced in hypertrophied hearts with increased relative wall thickness (concentric remodeling or concentric hypertrophy patterns) as compared to normal or eccentric ventricles.

P1637 Left ventricular function by echocardiography and mortality: a population-based study

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Echocardiography is frequently used to determine the presence of left ventricular systolic dysfunction (LVD). However, there are many different quantitative measures of LV in clinical usage. They are often assumed to be equivalent. A meaningful measure of abnormal LV function should give prognostic information. We report the mortality of LVD, assessed by several echocardiographic techniques, in a random, geographical sample of men and women aged 25–74

1640 attendees were studied in 1992/3. LV function was assessed by a left ventricular ejection fraction (LVEF) using the apical Biplane Simpson's Rule and Bullet methods fractional shortening (FS) and a left ventricular end diastolic dimension (LVEDD). Cut-off points for abnormality for each method were defined as being outwith or equal to two standard deviations from the mean for "normal" subjects within the population. We report all cause mortality at 4 years of follow up.

The Simpson's Rule LVEF was obtained in 89% of subjects, a Bullet LVEF in 60%, FS in 62% and an LVEDD in 63%.

LV Function Measure	4 yr. mortality rate	p value
Simpson's LVEF ≤ 34%	23%	<0.0001
Bullet LVEF ≤ 33%	5.7%	0.76
FS ≤ 0.19 (men) ≤ 0.23 (women)	7.8%	0.06
LVEDD ≥ 6.2 (men) ≥ 5.6 (women)	9.1%	0.1

By Cox Survival Regression Analysis only an abnormal LVEF by the Simpson's Rule technique predicted mortality: it remained significant in a multiple regression analysis, including age with an odds ratio of 1.5 (95%CI 1.2–2.0), p = 0.002.

In this large epidemiological study, LVEF according to the Simpson's Rule was the best predictor of mortalityand the most widely obtainable. The main reason for its lack of use clinically is its time-consuming nature. We contend that the measurement of LV function accurately is important in determining both therapeutic strategies and prognosis in patients with chronic heart failure and LV dysfunction and as such, the measurement should be as robust as possible. Simpson's Rule should be applied more frequently.

P1638 Harmonic versus fundamental echocardiography imaging for endocardial border definition

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Background: Harmonic imaging has recently been developed in order to improve endocardial border definition.

The purpose of this study was to compare 2nd harmonic with fundamental echocardiographic imaging for endocardial border definition and assessment of segmental wall motion of the left ventricle.

Methods: 60 consecutive patients were studied during routine transthoracic echocardiography in both harmonic (H) and fundamental (F) modes. Apical (4- and 2-chamber) and parasternal long axis views were acquired using a Vingmed System 5, in both fundamental and harmonic modes. Images were digitally stored and reviewed blindly by two experienced observers for endocardial segment and wall motion contractility score. A total of 960 segments were analyzed. Quality of endocardial border delineation (EBD) was scored in a 0 to 2 scale (0 = inadequate/not seen, 1 = satisfactory, 2 = excellent).Wall motion (WMS) was scored in a 1–4 scale using the standard ASE 16 segments.

Results: In the harmonic mode 945 of 960 segments were visualized (98%) vs 851 of 960 (89%) segments in the fundamental mode ($p < 0.001$). The scores of harmonic imaging significantly showed an improvement in EBD (harmonic = 26 ± 3.8 vs fundamental = 18.6 ± 5.2; $p < 0.001$). The wall motion score also showed a statistically significant difference (harmonic = 22.9 ± 8.2 vs fundamental = 20.6 ± 7.03; $p < 0.05$). A total of 46% of all studied segments showed a significant improvement when the harmonic mode was used. Of 443 segments classified as satisfactory or not seen, 361 (81.5%) improved to excellent with the harmonic mode.The lateral, apical-septal and inferior walls showed a greater improvement with the harmonic imaging. The WMS was also altered in 118 of 960 segments (12.3%) when the harmonic mode was used.

Conclusions: Harmonic imaging markedly enhances endocardial border definition, more significantly seen in the lateral, inferior and apical-septal segments. The differences in the wall motion score are most likely the result of a better EBD, resulting in a more accurate assessment of segmental contractility. Therefore, harmonic imaging is potentially becoming an indispensable tool for the correct assessment of wall motion.

P1639 Pulmonary venous flow velocities assessed by transthoracic doppler echocardiography: relation to left ventricular systolic function

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Background: During ejection LV long axis shortening causes a corresponding increase in left atrial capacity due to motion of the atrioventricular plane towards the apex. This effect is likely to influence pulmonary venous flow.

Methods: To assess possible relations between pulmonary venous flow velocities and systolic left ventricular function we studied 37 patients, age 56 ± 10 years, 23 male, using transthoracic Doppler echocardiography. Left ventricular systolic function was assessed from minor axis systolic and diastolic dimensions and long axis amplitude of motion and peak shortening velocities.

Results: None of the patients had significant mitral regurgitation. The systolic component of pulmonary venous flow correlated with both LV end-systolic diameter (r = −0.62) and peak long axis shortening velocity (r = 0.61). 15/37 patients had severe LV disease and raised left atrial pressure (transmitral E/A ratio > 1.0 and short E wave deceleration time < 120 ms). In them, the systolic pulmonary venous flow velocity held similar correlation with LV end-systolic diameter (r = −0.62) and peak long axis shortening velocity (r = 0.63). Diastolic component of the pulmonary venous flow however, did not correlate with any of LV diastolic measurements.

Conclusion: In the absence of significant mitral regurgitation the systolic component of pulmonary venous flow correlates with systolic left ventricular function. This close association seems to be independent of transmitral filling pattern and left atrial pressure.

P1640 Correlation between left ventricular systolic function and aortic dilatation in marfan syndrome and Marfan related disorders

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In inherited disorders of Fibrillin 1, like MASS (Mitral valve prolapse-Myopia, Aortic dilatation, Skeletal involvement, Skin striae) and more consistently Marfan Syndrome (MFS) the cardiovascular involvement is characterized by mitral valve prolapse and aortic dilatation.

Subclinical alterations of diastolic function have already been described, but no alterations of systolic function have been reported. Since the aortic impedance influences the afterload and consequently the ejection force of the left ventricle (LV), we investigated the possible relationship between aortic dilatation and LV systolic function.

LV systolic function was studied in 24 patients, 16 MFS and 8 MASS with aortic dilatation by echocardiography. Significant valvular regurgitation or other cardiac alterations were absent and no patient was on cardiovascular therapy.

In the presence of normal LV-systolic parameters, a significant correlation between aortic diameter and ejection fraction (EF), fractional shortening (FS) and LV-end systolic volume (LVESV) was observed. No correlation was found between aortic diameter and LV-end diastolic volume and LV-mass (table).

Results:

	r	p
EF (%)	0.81	<0.01
FS (%)	0.64	<0.05
LVESV (ml)	−0.72	<0.01

These findings put into evidence a reduced resistance against which the left ventricle contracts and a consequent enhanced shear force during ejection of blood into the aorta in MASS and MFS. These alterations, associated with abnormal aortic wall structure, may affect the progressive dilatation and underline the relevance of negative inotropic therapy.

P1641 Non-contrast octave tissue imaging improves assessment of echocardiographic left ventricular ejection fraction: preliminary results from a multicenter study

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Background: Echocardiographic visual estimation of left ventricular ejection fraction (LV-EF) is performed routinely in clinical practice to provide a rapid assessment of global LV function but it is limited by non-optimal image quality. The aim of this study was to assess the incremental value of noncontrast harmonic imaging (Octave Tissue Imaging, OTI) in evaluation of EF compared with conventional imaging (CONV).

Methods: A) In 13 patients (pts) unselected for image quality and with distorted LVs who underwent a clinically indicated nuclear study, the standard apical 4- and 2-chamber views were acquired in a high frame rate cineloop format by both OTI and CONV modalities. Digital cineloops were transferred to a computer, separated, renamed, mixed in a pool and sent to 5 observers for analysis. Echo image quality was assessed using a 4 point scale (1 = poor and 4 = excellent); EF was visually evaluated as a continuous variable, for a total of 65 estimates for each 2D modality. B) In addition, 2 observers compared quantitative EF by biplane Simpson's method for OTI vs CONV.

Results: A) In 80% of CONV studies image quality was poor (grade 1–2) while in 71% of OTI studies it was good (grade 3–4). The EF values obtained by OTI showed a higher correlation with the nuclear measures than values obtained by CONV (0.63 vs 0.49, $p < 0.01$ by Z-transformation) with a trend for a decrease in the standard deviation of the mean error (8.8% vs 10.4%). Interobserver variability was lower by OTI than by CONV (6.5% vs 7.7%, $p < 0.05$ by F-test). B) Quantitative EF values by OTI showed a higher correlation with nuclear than those obtained by CONV (0.87 vs 0.76, $p < 0.01$) with a smaller standard deviation of the mean error (7.4% vs 13.1%, $p < 0.01$) and a lower observer variability.

Conclusions: In this initial group of pts, OTI enhanced visualization of the LV (expecially in pts with worse image quality by CONV), increased correlation of EF with nuclear and reduced interobserver variability. These benefits are even more prominent when EF is calculated by the biplane Simpson's method.

P1642 Accurate determination of cardiac output and ejection fraction by real-time three-dimensional echocardiography: comparison with gated SPECT-thallium

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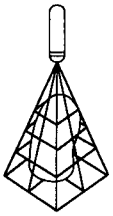
Background: The purpose of this study was to determine the accuracy of real-time 3-D echocardiography (RT3DE) for quantification of left ventricular volume parameters and function.

Methods: In 10 patients with coronary heart disease comparative measurements of the cardiac output (CO) and the left ventricular ejection fraction (LVEF) were performed within 72 h using a VOLUMETRIX Model 1 und gated SPECT-thallium. For RT3DE a matrix phased array transducer (2.5 MHz, 512 elements) and a 16.1 receive/transmit parallel processing scheme to develop 4096 line scans interrogating all positions in a 60° pyramidal volume at 18 frames/s. Volume calculation was performed summing up 7 subvolumes previously created by manual tracing of the endocardial border in the cut planes of the data set. All measurements were carried out by 2 blinded observers and averaged.

Results: The mean difference for CO was calculated to be of about 14 ± 0.81 l/minute and for LVEF 4.3 ± 10.9%. Data acquisition took about 3 to 7 min.



Method	CO ± SD (range) l/min	LVEF ± SD (range) %
RT3DE	5.2 ± 1.2 (3.7–7.4)	53.2 ± 18.3 (26–86)
SPECT	5.1 ± 0.8 (3.5–6.2)	48.9 ± 18.6 (18–73)
r	0.72	0.83
p	0.016	0.003

Conclusions: Echocardiographic determination of CO and LVEF using RT3DE is valid. Measurements do not take up a great deal of time and, therefore, can be employed alternatively if hemodynamic monitoring is not available.

P1643 Effects of different pacing modes on left ventricular systolic function as determined by echocardiography

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Backgrond: The effect of heart rate control resulting from AV node ablation with pacemaker implantation for atrial fibrillation (AF) is believed to improve LV systolic function. Purpose: We evaluated the difference in LV systolic function resulting from different pacing conditions using a canine AF model.

Methods: Epicardial echocardiography was performed in 8 healthy mongrel dogs during induced rapid AF or right ventricular (RV) pacing. Rapid AF was induced by programmed random rapid atrial pacing. Heart rate was slowed during AF by vagus nerve stimulation (VNS). The AV junction was subsequently ablated by radiofrequency energy and random slow rate RV pacing was performed. The LV end-diastolic volume (EDV) and ejection fraction (EF) was obtained from 2D echocadiography, and the stroke volume (SV) was calculated using LV outflow Doppler velocity profile. The maximum value of the first derivative of the LV pressure curve (+dP/dt) was obtained by Millar catheter. Data were expressed as an average of more than 20 consecutive beats.

Results: 1) During rapid AF, the RR interval shortened while LVEF, SV and +dP/dt significantly decreased compared to baseline. 2) During AF with VNS, the RR interval significantly prolonged, while LVEF, SV and +dP/dt significantly increased compared to AF without VNS. 3) After ablation of the AV junction with RV pacing, the RR interval significantly prolonged, SV slightly increased, while LVEF and +dP/dt significantly decreased compared to AF without VNS. 4) There was a significant difference in the LVEF, SV and +dP/dt between AF with VNS versus ablation with RV pacing.

	Baseline (sinus)	Rapid AF	AF + VNS	Ablation + RV pace
RR (msec)	377 ± 25	348 ± 121*	583 ± 167*	527 ± 208*
EDV (ml)	29.3 ± 2.3	18.2 ± 7.0	26.3 ± 4.3*	26.3 ± 3.3*
EF (%)	60 ± 6	42 ± 25	55 ± 16*	36 ± 24*#
SV (ml)	18.2 ± 2.8	10.8 ± 8.2	17.2 ± 7.9*	11.6 ± 10.4#
+dP/dt (mmHg/s)	2727 ± 28	2644 ± 1256	2945 ± 1256*	2471 ± 1253*#

*$p < 0.0001$ vs Rapid AF, #$p < 0.0001$ vs AF with VNS

Conclusions: LV systolic function improved by reducing heart rate, while the LVSV and +dP/dt was significantly greater during AF with VNS than ablation with RV pacing. We conclude that antegrade pacing can be more physiologic than retrograde pacing, highlighting the importance of the atrial contribution to filling.

P1644 Non-invasive estimation of right atrial pressure by combined echo-Doppler measurements of the inferior vena cava in patients with congestive heart failure

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Background: In patients with congestive heart failure (CHF), the evaluation of right atrial pressure (RAP) provides useful therapeutic, functional and prognostic information.

Objective: To investigate whether a combination of inferior vena cava variables, measured by echo-Doppler, can provide a reliable non-invasive estimate of RAP.

Methods: One hundred consecutive pts with severe CHF (EF: 24 ± 6%) due to dilated cardiomyopathy were evaluated by simultaneous echo-Doppler and hemodynamic studies. RAP, end-expiratory (IVCDmax), end-inspiratory (IVCDmin) diameters of inferior vena cava, its index collapse (IVCIC = (IVCDmax − IVCDmin/IVCDmax) * 100) and systolic fraction of forward inferior vena cava flow (SFivcff) were measured and correlated by both single and multilinear regression analysis. The accuracy of the generated equations was tested in a separate group of 60 patients at baseline and a subgroup of 20 patients after loading manipulations, prospectively studied in the same methodological setting.

Results: All echo-Doppler variables were correlated to RAP. The IVCDmin showed the best correlation ($r = 0.84$ $p < 0.0001$). Stepwise regression analysis identified two equations for predicting RAP: 1) RAP = (6.4 * IVCDmin + 0.04 * IVCIC − 2) ($r = 0.82$ $p < 0.0001$ SEE = 1.7 mmHg) in all pts and 2) RAP = (4.9 * IVCDmin + 0.01 * IVCIC − 0.2) ($r = 0.92$ $p < 0.0001$ SEE = 1.2 mmHg) in pts without tricuspid regurgitation. In the testing group estimated and measured RAP were strongly correlated at baseline ($r = 95$ SEE 1.3 mmHg $p < 0.00001$) and after loading manipulations ($r = 0.96$ SEE 1.2 mmHg $p < 0.00001$). The agreement between invasive and non-invasive measurements of right atrial pressure in identifying patients with normal (RAP ≤ 5 mmHg), moderately increased (<5 RAP < 10 mmHg) or markedly increased (≥10 mmHg) right atrial pressure was 81% and 93% when using equation 1 or 2, respectively.

Conclusions: Our results show that in patients with congestive heart failure, indices derived from the inferior vena cava can be used to provide an accurate, non-invasive estimate of right atrial pressure.

P1645 Non-invasive estimation of pulmonary vascular resistances in patients with chronic heart failure

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Pulmonary vascular resistance (PVR), by right heart catheterization (RHC), is of important clinical and prognostic value in patients (pts) with chronic heart failure (CHF), particularly for possible candidates to heart transplantation. Thus, a noninvasive estimation of PVR is desirable. We hypothesized a strict correlation between Doppler systolic pulmonary flow (PF) and PVR.

Methods: 50 consecutive pts with CHF (39 males, 57 ± 3 yrs, EF 22 ± 4%, NYHA class II–IV) underwent simultaneous hemodynamic monitoring (Swan-Ganz cath.) and echo-Doppler study. The following Doppler parameters were evaluated on PF: pre-ejection period (PEP), acceleration time (AcT), ejection time (EjT), total systolic time (Tt) and peak flow velocity (Vmax).

Results: mean PVR value was 2.8 ± 2.1 Wood. At univariate analysis all variables, except Vmax, showed a significant, although weak, correlation with PVR. The best correlation was found between AcT and PVR ($r = -0.68$). By multivariate forward stepwise analysis only PEP, AcT and Tt entered in the final equation with a cumulative $r = 0.87$. On the basis of these results and pathophysiological background, we combined these three variables in a single function to verify whether their interaction could define a closer relation with PVR: PEP to AcT ratio, normalized for Tt showed the highest correlation with PVR ($r = 0.95$).

In conclusion: although PVR is a complex parameter resulting from the interaction of several hemodynamic variables, Doppler systolic pulmonary flow signal is strictly related to PVR. PEP to AcT ratio, normalized for Tt of pulmonary systolic flow represents a reliable tool for predicting PVR in pts with CHF. This finding strongly support the contention that most CHF pts can be noninvasively investigated by echo-Doppler examination to accurately predict PVR.

P1646 Dobutamine stress echocardiography can predict extent of myocardial fibrosis in patients with dilated cardiomyopathy

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In order to assess relationship between dobutamine stress echocardiography (DSE) and myocardial fibrosis (MF) we have analyzed 24 consecutive pts with endomocardial biopsy (EMB) proven idiopathic dilated cardiomyopathy (DCM) in whom both DSE and EMB were performed in the same hospitalization.

DSE was performed using 5, 10, 20, 30 and 40 mcg/kg/min infusions, in progressive stages lasting 5 minutes each. DSE was considered positive if there was an increase >0.22 between resting and peak left ventricular (LV) wall motion score index (WMSi) that was calculated using 16-segment model. LV end-systolic (ESVi) and end-diastolic (EDVi) volume indexes, as well as EF, were calculated from apical 2- and 4-chamber views using Simpson's biplane formula. LV EMB specimens (3–5 per pt) were routinely processed and stained with Masson-trichrome. MF was calculated quantitatively using commercially available software for a representative field in each specimen, averaged and dichotomized in respect to median value. Logistic regression model, that included clinical (NYHA class, duration of symptoms, presence of 3rd heart sound, and heart rate), hemodynamic (LV end-diastolic pressure) and echocardiographic data (DSE, EDVi, ESVi, EF, and early filling deceleration time), was used to identify predictors of the extent of MF.

Results: Pts with positive DSE (14/24) had lesser extent of MF compared to pts with negative DSE (32.8 ± 6.2 vs. 20.8% ± 7.3, $p < 0.001$). Additionally, these patients had more favourable clinical, hemodynamic and echocardiographic data ($p < 0.01$, for all), except heart rate and duration of symptoms which were similar between the groups. Logistic regression model identified DSE as the only independent predictor of the extent of MF (beta −2.7, $p = 0.04$). When DSE was removed from the model, none of the variables were predictive of MF.

Conclusion: Our data indicate that wall motion improvement during DSE in pts with DCM, in contrast to other clinical, hemodynamic and echocardiographic parameters, may identify pts with lesser extent of MF. This observation may provide rationale for routine use of DSE in the assessment of pts with DCM.

P1647 Contrast-enhanced Doppler echocardiography allows a complete haemodynamic assessment in patients with congestive heart failure

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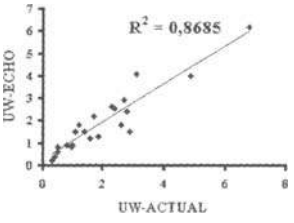
In patients (pts) with congestive heart failure (CHF) Doppler echo provides relevant hemodynamic information. In some pts, poor quality Doppler signals may limit feasibility and accuracy of measurements.

Methods: to assess whether contrast-enhanced DE can improve noninvasively hemodynamic estimation, we investigated 30 consecutive CHF pts by simultaneous right heart catheterization and DE performed before and after IV injection of 5- 10 ml of contrast agent (Levovist®). Cardiac output (CO)was estimated by PW-Doppler of left ventricular outflow tract; pulmonary wedge pressure (PWP) by previously validated equations including PW-Doppler mitral and pulmonary venous flow variables; right atrial pressure (RAP) by 2D-echo inferior vena cava expiratory and inspiratory diameters. Systolic and diastolic pulmonary artery pressures (PAP) were calculated by adding RAP to the pressure gradients derived from the CW-Doppler peak velocity of tricuspid regurgitation and from the end-diastolic velocity of pulmonary regurgitation, respectively. Mean PAP and pulmonary vascular resistance were then derived from these measurements.

Results: PWP was 18.3 ± 7.7 before and 17.9 ± 6.8 mmHg 30" after contrast injection. A complete assessment could be obtained only in 20 pts without using contrast while with contrast-enhanced DE it was obtained in 30. By this method, strong correlation between invasive and noninvasive variables were found: r = 0.94, SEE 0.4 l/min for CO; r = 0.98, SEE 1.6 mm Hg for PWP; R = 0.98, SEE 1.6 for mean PAP and r = 0.93 SEE 0.6 Wood units for pulmonary vascular resistance.



Conclusion: in pts with CHF contrast-enhanced DE allows complete noninvasive hemodynamic assessment and may reduce the need for right heart

P1648 Prognostic value of contractile reserve as assessed by high-dose dobutamine Doppler echocardiography in patients with severe heart failure

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Background: In patients (pts) with heart failure (HF) the contractile reserve is impaired and the assessment of the severity of this impairment may add valuable prognostic information to baseline data.

Methods: To prove this hypothesis, we prospectively investigated 56 pts with severe HF due to dilated cardiomyopathy. Maximal cardiac power output (PO) was assessed by means of both right heart catheterization and Doppler echocardiography (D-E) simultaneously performed during a high-dose Dobutamine test. Invasive PO was calculated from the formula PO = (mean arterial pressure- right atrial pressure) cardiac output*2.22/1000. The same formula was applied for D-E but right atrial pressure was estimated from the inspiratory collapse of the inferior vena cava and cardiac output from Doppler of the left ventricular outflow tract.

Results: D-E maximal PO was strongly correlated with invasive PO (r = 0.98; SEE = 0.1 Watt). During a follow-up of 13 ± 6 months 13 pts (23%) died. At baseline, no differences were found between survivors and non-survivors in left ventricular ejection fraction (23 ± 8% vs. 21 ± 8%), cardiac index (2.1 ± 0.5 vs. 1.9 ± 0.5 l/min/m^2), and PO (0.7 ± 0.1 vs. 0.6 ± 0.1 Watt). In contrast, 11/13 pts who had a reduced contractile reserve during high-dose Dobutamine (D-E PO < 1 Watt) died; while only 2/31 pts who had a maximal PO > 1 Watt had events (p < 0.001).

Conclusions: In severe HF high-dose Dobutamine D-E allows a reliable non-invasive estimation of maximal PO. This index adds strong prognostic information to baseline indices of systolic dysfunction.

P1649 Low-dose dobutamine stress echocardiography in patients undergoing high dose potentially cardiotoxic chemotherapies

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Background: Patients undergoing high dose chemotherapies with potentially cardiotoxic drugs can develop both acute and chronic heart failure. The study evaluated heart response to low dose dobutamine infusion, in order to define the effect of various chemotherapic regimens (CT) on myocardial contractile reserve.

Population: We studied 38 patients, all females, aged 44 ± 8 (mean ± SD) years, with no cardiovascular diseases and normal left ventricular ejection fraction (EF).

Methods: EF measurements were obtained in basal conditions and after continuous infusion of dobutamine at increasing doses (0.5 mcg/kg/min, 2.5 mcg/kg/min and 5 mcg/kg/min for 10 minutes each step). Each patient underwent a basal study before the first CT and again one month later, before a second CT cycle.

Results: Before CT mean EF was 69 ± 6% in the baseline and increased to 76 ± 5% (p < 0.01) at the end of third step of dobutamine infusion (5 mcg/kg/min). One month after CT, baseline EF decreased to 64 ± 6%; the difference between pre- and post-CT is statistically significant (p < 0.01) but clinically not relevant. After CT, dobutamine infusion caused a more consistent increase in EF (74 ± 6%). Surprisingly after 5 mcg/kg/min dobutamine infusion EF did not show any significant difference between pre- and post-CT values (76 ± 6% vs. 74 ± 6%, respectively).

Conclusion: High dose chemotherapy can lead to significant, although not clinically relevant, decrease of baseline EF but no decrease in inotropic response after low-dose dobutamine infusion. We can argue that this pattern can be related not to permanent structural damage but to some kind of atypical "hybernated-like" myocardial condition.

P1650 Echocardiographic determinants-predictors of mortality rate in patients with severe congestive heart failure

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The aim of the study was to estimate different echocardiographic parameters in order to characterize high-risk patients (pts) with severe congestive heart failure (CHF) and severe left ventricular dysfunction.

Methods: We studied 108 consecutive patients aged 63 ± 0.9 years, 90 man and 18 woman in sinus rhythm, with heart failure, NYHA class II–IV and ejection fraction (EF) echocardiographically estimated <30%.

Results: After period of 20 months of follow up there was 21 (19.4%) cardiac deaths. We applied univariate Cox regression analysis X^2, p, and multivariate Relative Risks witk CI 95%, to estimate significant predictors of mortality in pts with severe CHF. Our results showed that age > 65 years (p = 0.037), EF (p = 0.005), left ventricular end diastolic diameter (LVEDD) (p = 0.0031), fractional shortening (p = 0.006), left ventricular ejection time (p = 0.0015), E/A (p = 0.012), ejection time (p = 0.0125), A wave integral (p = 0.004), deceleration time of E, DT (p = 0.000), DT < 125 ms (p = 0.000), E > A (p = 0.007) were significant predictors of mortality.

In conclusion, EF < 30%, LVEDD > 7 cm, age > 65, and DT < 125 ms were independent predictors of mortality.

CARDIAC REHABILITATION: FITNESS AND EXERCISE TRAINING

P1651 Rehabilitation programme effects on congestive heart failure patients taking β-blockers

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Background: Training is now well accepted in stable congestive heart failure (CHF). Since few years beta-blockers (βB) are used in the treatment of CHF. The aim of this study was to compare the training response of CHF with and without beta-blockade therapy.

Methods: 34 CHF stable patients (Ejection Fraction: 31 ± 1.3%, NYHA II–III) were included consecutively in a 4 weeks training program: 45 min/6 times/week at the ventilatory threshold (Vth). Sixteen patients were taken βB and 18 not. Before and after training the subjects underwent a cardio-pulmonary exercise test. We compared the parameters of aerobic capacity before and after training by repeated measures ANOVA adjusted with ejection fraction and VO_2.

Results:

With βB	Before training	After training
VO_2 Vth (ml min^{-1})	1040 ± 28	1237 ± 28
VO_2 max (ml min^{-1})	1382 ± 32	1575 ± 32

Without βB	Before training	After training
VO_2 Vth (ml min^{-1})	1183 ± 30	1443 ± 30
VO_2 max (ml min^{-1})	1544 ± 34	1811 ± 34

VO_2 at peak exercise and at Vth increased in both groups ($p \leq 0.0001$) without any differences between the groups ($p = 0.2444$ and $p = 0.182$ respectively). Same results were found after adjustment with EF and VO_2 at the start of the training program. Comparison of the Vth increased ($p = 0.0104$) in term of VO_2 utilization percentage was the same in both groups.

Conclusion: βB therapy does not impair functional improvement induced by rehabilitation program in CHF patients.

P1652 Oxidative stress in chronic heart failure: effects of exercise

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In this study, we measured plasma nitrite, L-arginine, asymmetrical dimethylarginine (ADMA; an endogenous nitric oxide synthase inhibitor), hypoxanthine (pro-oxidant substrate for xanthine oxidase), and uric acid (putative free radical scavenging properties) to assess whether levels can be altered by exercise.

Twenty-one patients and 9 controls were randomly assigned to 8 weeks of exercise (EX; >5 d/wk, ergometer training, 30 min/d; calisthenics 9 min/d) followed by 8 weeks of detraining, and vice versa (cross-over study). L-arginine, ADMA, hypoxanthine, and uric acid were measured by high performance liquid chromatography and nitrite concentrations by Griess reaction.

Maximal exercise time increased in both groups ($p < 0.005$). Uric acid levels were highest in CHF ($p < 0.005$) but did not change after training. However, there was an inverse correlation between uric acid levels and maximal exercise time ($r = -0.32$, $p < 0.02$). Hypoxanthine levels were significantly higher in patients than in controls ($p < 0.02$), and were normalized by chronic exercise. Nitrite levels were significantly lower in CHF patients than in healthy controls. Although nitrite levels were highest after EX, changes did not reach statistical significance (p = n.s.). There were no baseline differences detected for L-arginine and ADMA; levels were not altered by exercise.

Chronic heart failure is associated with increased levels of hypoxanthine and decreased levels of nitrite. This imbalance can be beneficially modulated by chronic exercise training. Furthermore, uric acid levels are elevated in CHF and associated with diminshed exercise capacity, reflecting an impairment of oxidative metabolism.

P1653 Positive effects of metoprolol on the functional capacity, during exercise conditioning in patients with the ischaemic left ventricular dysfunction can be demonstrated after discontinuation of β-blocker

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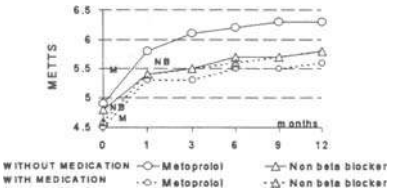
Beta blocker treatment has been shown to improve prognosis in patients with dilated and ischemic cardiomyopathy. There are questions about possibility to achieve training effect in patients who are treated with beta blockers, because sympathetic stimulation with adequate cardiovascular response is necessary for the exercise tolerance and attainment of the training effect.

The aim of this study was to estimate the influence of chronic metoprolol treatment added to conventional heart failure therapy, in patients with the post infarction left ventricular dysfunction, on the effects of one year physical training.

Methods. Eighty nine post-myocardial infarction patients (3.4 ± 1.7 months after infarction), with left ventricular dysfunction (EF ≤ 40), without congestion, were examined. After 1 month residential exercise training program, patients continued home based unsupervised physical activity 3 times per week, during 11.1 ± 2.7 months. 47 patients (EF % 32.4 ± 1.9) received Metoprolol 50.3 ± 28.2 mg/day and 42 patients (EF% 31.7 ± 2.0) (without difference in baseline characteristics from metoprolol group) did not receive beta blocker. Patients functional capacities were examined by exercise stress testing on treadmill, before entering the training, at the end of the residential rehabilitation, on three month intervals, and also at the end of the program. Patients performed exercise tests while receiving complete medication, and these tests were used for physical training prescriptions. Exercise tests were repeated two days after stopping medication and these results were used for functional capacity measurements.



Results After the physical training program was completed, the functional capacity increased in Metoprolol group from 4.9 ± 1.6 to 6.3 ± 1.7 METs ($p < 0.001$) in significantly greater degree (28.7%, $p < 0.01$) than in the Non beta blocker group (4.8 ± 1.8 to 5.7 ± 1.9 METs ($p < 0.01$), 18.8%). In metoprolol group exercise tolerance examination perform during medication show significantly lower functional capacity than assessment after discontinuation of the beta blocker $p < 0.01$.

Conclusion Patients treated with metoprolol showed greater functional capacity improvement due to physical training than patients without the beta blocker. A few days after discontinuation of the beta blocker, heart rate and cardiac output increment during exercise is unrestricted and a real degree of the functional capacity improvement due to physical training can be assessed.

P1654 Improved exercise capacity after endurance training with theraband in patients with chronic heart failure

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Background: In chronic heart failure (CHF) there is an inability to adequately increase cardiac output during exercise. To circumvent the central cardiovascular stress of this limitation during exercise training and thereby to improve the training effect on the local muscle, is to train a minor muscle mass at a time

Aims: To test the hypothesis that comprehensive endurance training applying the concept of a minor muscle mass training can improve physical exercise capacity as well as quality of life.

Methods: 24 habitually active men and women (63 ± 9 years) with moderate CHF (left ventricular ejection fraction < 40%) were studied in a randomized controlled study with a training group of 16 patients and a control group of 8 patients. The training was performed for 8 weeks, 3 times/week with TheraBand activating one functional muscle group at a time.

Results: Peak oxygen uptake (8%, $p < 0.03$), noradrenaline level at rest (26%, $p < 0.008$), the distance walked in a six minute walking test (11%, $p < 0.002$), and the health-related quality of life measured with the Minnesota Living with Heart Failure questionnaire ($p < 0.001$) showed improvement in the training group, while no improvement was found in the control group.

Conclusions: Endurance training activating a minor muscle mass at a time markedly improves physical exercise capacity and quality of life and can be recommended for medically stable CHF patients under supervision of a physical therapist. This training method can easily be applied at home for these patients.

P1655 The improvement in peripheral vasodilatory capacity improves oxygen uptake kinetics after physical training in cardiac patients

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It is well documented that the physical training improves oxygen uptake kinetics during exercise through the improvement of the cardiac output response. Since this phenomenon is noted even after the short-term training, we designed this study to clarify the contribution of peripheral vasodilatory capacity to the increase in cardiac output during exercise.

Method: Thirty two patients (mean age of 64 years) 1 week after the cardiac surgery or myocardial infarction who joined 2-week supervised aerobic training course entered the study. They underwent symptom-limited cardiopulmonary exercise tests with a cycle ergometer using a ramp protocol before and after the training. The peak hyperemic calf blood flow (CBF) was measured after 5-min. arterial occlusion with a strain gauge plethysmography before each exercise test. Peak oxygen uptake (peak VO_2), VO_2/WR, and the time constant of VO_2 at the beginning of 20 W constant work (TC) were calculated.

Results: CBF before the training was 14.6 ± 4.2 ml/min/100 ml tissue and it was significantly lower than those in normal subjects (26.5 ± 5.8). CBF showed significant correlations to peak VO_2, VO_2/WR, and TC before the training. All these parameters increased significantly by the physical training (CBF: 14.5 ± 4.2 – 15.6 ± 4.6 ml/min/100 ml tissue, peak VO_2: 15.7 ± 3.1 – 17.6 ± 3.2 ml/min/kg, VO_2/WR: 8.0 ± 2.3 – 9.2 ± 1.9 ml/min/W, TC: 53.6 ± 21.1 – 43.4 ± 17.0 sec), while the increase in CBF by the training reveled a strong positive correlation to that of TC ($r = 0.75$, $p < 0.0001$).

Conclusion: These data suggest that the blurred cardiac output response, especially at the beginning of exercise, is caused partly by the impaired peripheral vasodilatory capacity in patients after the cardiac surgery or myocardial infarction. The aerobic training improves attenuated oxygen uptake kinetics and vasodilatory capacity in these patients even it is short-term.

P1656 Improved physical fitness and quality of life in elderly patients recovering from an acute coronary event after three months of aerobic group training: a one-year follow-up, randomized controlled study

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Cardiac rehabilitation including exercise training is of proven value in ischemic heart disease. Still, elderly patients are frequently not encouraged to participate in such programmes. The aim of this prospective randomised controlled study was to evaluate the physiological effects and self-reported health-related quality of life after an aerobic outpatient group-training programme in subjects >65 years of age.

Methods: The study included a consecutive series of 101 patients, 20 women and 81 men, aged 65–84 (mean 71) years recovering from an acute coronary event. The patients were randomised to either a supervised outpatient group-training programme, 50 minutes three times a week during three months (n = 50) or to a control group (n = 51).

Results: The two groups were well balanced as regards clinical characteristics at randomisation. In all 101 patients completed the 3 months follow-up and 100 the 12 months follow-up. The compliance in the training group was 87%, and there were no complications during training. Exercise tolerance increased in the trained group from 104 to 122 ($p < 0.001$) and 111 watts ($p < 0.05$) after 3 and 12 months respectively. The corresponding values were 102, 105 and 105 watts among controls (ns). Parameters as quality of life, self-estimated level of physical activity, fitness and wellbeing were graded higher by the trained patients than those who served as controls at the two occasions of follow-up.

Conclusion: Organised aerobic group-training of elderly patients recovering from an acute coronary event has significant effects on physical fitness as well as self-reported health-related quality of life one year after discharge. Great care has to be taken to preserve the initial effects by continued training.

P1657 Effects of long-term exercise training in female cardiac patients aged 40–69 years

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Women have traditionally been under-referred to cardiac rehabilitation services and under-represented in cardiac research. This study examined the physiologic response of selected variables in 330 women between the ages of 40 and 69 years referred for outpatient cardiac rehabilitation. Variables were measured during cardiopulmonary exercise assessment using cycle ergometry at entry (A1) and after 12 months of participation (A2) in a walk/jog exercise rehabilitation programme following MI, CABG or PTCA. For analysis purposes, the women were grouped into decades of age, as indicated.

Results:

Variable	40–49 yrs (n = 43) Δ%	50–59 yrs (n = 116) Δ%	60–69 yrs (n = 171) Δ%
HR_{rest}	−6.4**	−5.7**	−3.8**
SBP_{rest}	−1.2	+1.5	+2.5*
DBP_{rest}	−1.7	−2.1	−2.6*
RPP_{200}	−9.8**	−6.8**	−3.4
HR_{peak}	+2.1	+1.6	+4.1***
Kpm $min^{-1}{}_{peak}$	+18.4***	+15.9***	+12.7***
$\dot{V}O_{2peak}$ (mL kg^{-1} min^{-1})	+5.4*	+10.1***	+8.3***
$\dot{V}O_{2peak}$ (L min^{-1})	+8.7***	+12.0***	+8.4***
RER_{peak}	+1.3	+3.6**	+6.4***
$\dot{V}_E$ (L min^{-1})	+14.2**	+14.9***	+13.7***

*$p < 0.05$; **$p < 0.001$; A2 vs. A1 within groups.

Conclusions: After 12-months of exercise training, these women demonstrated physiologic benefit from long-term exercise training with significant improvements in many cardiorespiratory variables across all 3 decades of age including physical work capacity.

P1658 Predictors of response to exercise training in chronic heart failure

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Physical training is an effective strategy to improve exercise tolerance in patients (pts) with chronic heart failure (CHF). Nevertheless, baseline patients factors which determine this beneficial effect are still debated.

In order to assess predictors of response to exercise training in CHF, we included succesive 118 pts (55.6 ± 12.1 years) with radionuclide left ventricular ejection fraction (LVEF) < 0.40 referred for a cardiac rehabilitation program (CRP). Pts were evaluated by clinical examination and symptom limited exercise test with gas analysis before and at the end of CPR. Patients were submited to training program during 23 ± 10 sessions.

Results: The mean improvement of peak VO_2 was 2.6 ± 3.0 ml/kg/mn (+19%), and of VO_2 at aerobic threshold (98 pts) was 2.2 ± 3.7 ml/kg/mn (+39%). Responders pts were defined by an improvement of VO_2 > 10%.

	Responders (n = 70)	Non responders (n = 48)	p
Age (years)*	56.0 ± 11.9	55.0 ± 12.4	NS
NYHA class*	2.20 ± 0.8	2.26 ± 0.8	NS
LVEF (%)*	26.0 ± 7.5	24.9 ± 7.6	NS
Peak VO_2 (ml/kg/mn)*	16.8 ± 3.8	19.5 ± 6.5	0.005
Peak VO_2/theoretical VO_2*	0.60 ± 0.13	0.71 ± 0.21	0.001
Compliance (%)	84.5 ± 12.7	78.7 ± 17.2	0.04

(*: baseline characteristics).

In multivariate analysis initial VO_2 and compliance are statistically ($p < 0.05$) related to post CRP improvement of VO_2.

In Conclusion, clinical status and LVEF cannot predict response to exercise training. Significant improvement of exercise tolerance in CHF is correlated with a low exercise capacity before training. Higher compliance to CRP improve the results. Patients with CHF and very low exercise capacity are target candidates for exercise training.

P1659 Combined maximal O_2-pulse and heart rate by cardiopulmonary exercise testing and ^{99m}Tc sestamibi myocardial imaging in evaluation of ischaemia in trained and untrained patients with coronary artery disease

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The effect of controlled exercise training in patients (pts) with coronary artery disease (CAD) is well known. The aim of the study was to evaluate and compare the ischemic degree in controlled trained vs untrained pts with documented CAD by ^{99m}TC Sestamibi myocardial perfusion imaging (MIBI-SPECT) while assessing the contribution of maximal oxygen pulse (O_2P) along with the maximal heart rate (HR) achieved during exercise by cardiopulmonary exercise test (CPET).

Methods: Forty-four male pts, aged 40–83 years, with recent angiogram underwent a MIBI-SPECT and CPET using one exercise test for both studies. Pts were divided into 3 aged matched groups: I: n = 9; normal angiogram; control group. II: n = 20; 1–3 vessel disease in angiogram; untrained group; and III: n = 15; 1–3 vessel disease in angiogram; trained group for 3–6 months by HR at the ventilatory anaerobic threshold. The degree of ischemia by MIBI-SPECT was scored as follows: 0-no ischemia; 1-mild; 2-moderate; 3-severe reversible ischemia.

Results:

	I	II	III
N°. occluded vessels	0	1.95 ± 0.83	1.93 ± 0.85
Ischemic degree	0	1.79 ± 0.95***	0.8 ± 0.65
VO_2max (ml/min)	2171 ± 536*	1608 ± 296***	1989 ± 422
O_2Pmax (% of predicted)	125 ± 24*	94 ± 11***	139 ± 29
HRmax (% of predicted)	89 ± 7**	84 ± 9***	70 ± 11

*p < 0.01 group I vs group II; **p < 0.01 group I vs group III; ***p < 0.01 group II vs group III; all values = mean ± SD.

Conclusion: Controlled exercise training in CAD pts reduces significantly the degree of ischemia at maximal achieved exercise testing probably by the improvement in maximal O_2P (related to stroke volume) along with significantly lower maximal HR but with significantly higher VO_2 max (HR × O_2P). Such an exercise training effect is considered energetically metabolic efficient for the myocardium and may explain the significant decrease of ischemic response in the trained CAD pts.

COMPUTERS IN CARDIOLOGY: INTERNET APPLICATIONS

P1660 Remote access to medical records via the Internet: is it feasible?

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This study investigated the feasibility of using Internet technology to provide access to our department's computerised medical records. The purpose of this was twofold: to share data with other departments within the same institution and to allow physicians in other regions or countries to see the clinical data of patients of theirs who may have been treated in our cardiology clinic. The study was part of a larger project to create virtual electronic healthcare records for patients on the island of Crete.

Methods: A flexible approach was chosen, designed to take full advantage of the existing database system, while retaining compatibility with available Internet software and avoiding the need for a specific computing environment on the part of the remote user. The database package employed extracts information from patients' data archives and uses it to create a hierarchical tree of linked temporary files that may be viewed using Internet browser software. These "web pages" can contain not only textual information but also digital and image data, such as ECG recordings. For security reasons, the temporary files are deleted once the transaction is completed.

Results: The above approach has led to the development of a fully functional system, which allows easy and rapid access to medical data by authorised users, through an Internet connection employing a variety of computer platforms. A demonstration version, using fictitious data, can be seen on the Internet at http://lorien.ics.forth.gr:8080/cardioS, or http://cardio.med.uch.gr/DBdemo.

Conclusions: The use of the Internet for remote access to medical records is feasible and is a useful step towards the realisation of the virtual electronic healthcare record.

P1661 A web-based multicenter multitrial coordination service

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Multi-center clinical trials require a reliable communication between participating hospitals and the coordinating center. The Internet could form the ideal medium, provided the security and integrity of data could be guaranteed. To evaluate the application of the Internet for data collection in a multicenter trial, involving percutaneous transluminal myocardial revascularization using a laser catheter, a webserver was created outside the hospital's firewall. Centers participating in this trial received a unique username and password, required to access the home page of the multicenter trial coordination center, which was protected using HTAccess software. Although this webserver currently is able of maintaining a number of trial simultaneously, the username/password combination will limit access to those pages related to the specific trial. In the above-mentioned revascularization trial a questionnaire per intervention was presented, that could be filled out by the participating investigator. After completion of the form the answers were encrypted and sent to the coordinating center by e-mail. For encryption a Java applet for the Complete Columnar cipher method was used with a key provided to the investigator together with the experimental laser catheter. In a second clinical trial, performed simultaneously on this webserver, Pretty Good Privacy (an implementation of the RSA algorithm) was used as encryption tool with one public key per participating center. Due to legal regulations only 512 bit keys could be generated. An advantage of the RSA algorithm is formed by the possibility to create digital signatures or fingerprints offering more security about the sending center. In the near future this web based multicenter multitrial data server will migrate to Secure Socket Layer as the platform for data communication, based on a Trusted Third Party. However, this will require that both the coordinating center as well as all participating investigators obtain a class-3 certificate from a Certificate Authority to be able to participate in such web based clinical trials. For hospitals without such a certificate alternative modes of communication should remain available.

P1662 A web-based cardiology tutor incorporating dynamic hypertext mark-up language

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Purpose: Recent advances in internet technology provide exciting opportunities for computer-based cardiology education. An assessment-linked cardiology multiple choice question (MCQ) tutor was created that is web-based and also fully reproducible on CD-ROM. The tutor utilises dynamic Hypertext Mark-up Language (HTML) to optimise interactivity with the user and is rapidly accessible from any internet-connected computer.

Methods: A randomly accessible bank of cardiology MCQs, categorised according to subspecialty was created. The pool of questions was derived from standard textbooks and recent articles in major journals such as the European Heart Journal, Circulation, and the New England Journal of Medicine. The tutor was designed to be an up-to-date, dynamic teaching aid for cardiologists and cardiologists in training. It avails of the latest internet technology to provide an instantly responsive and dynamic system. Javascript, a powerful scripting language is integrated with dynamic HTML to enhance the speed and interactivity of the teaching aid. It automatically adapts itself to the level of expertise of the user. The answers include detailed explanations and are widely referenced and linked to relevant articles on the web. Images are used extensively to complement the information provided and image-mapping further enhances the interaction between the user and the tutor.

Results and conclusion: A web-based cardiology tutor is presented that is universally accessible and personalised in an innovative fashion to the user. Utilising Javascript and dynamic HTML, it provides an up-to-date, dynamic teaching aid in cardiovascular disease.

P1663 Remote access to medical records via the internet: how to solve the language problem?

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The purpose of this study was to investigate the possibility of allowing physicians in other countries to access our department's computerised medical records relating to their patients. Since this hospital is in a touristic region, a significant number of foreign patients are treated in our cardiology clinic. The study was part of a larger project to create virtual electronic healthcare records for patients on the island of Crete.

Methods: A system we have developed uses information from patients' medical records to create temporary files that may be viewed by an Internet browser. An authorised user may view the information not only in Greek, the language in which the data are stored, but also in English, through an automated translation process. This is accomplished by means of a system of lookup tables which contain the equivalent terms for, say, cardiological diagnoses in both languages. This has the advantages that other languages can easily be added if necessary and that existing or future codification systems may be freely incorporated into the design. Names, addresses, etc., are transliterated from the Greek to the Latin alphabet using a specially created algorithm.

Results: The system as designed successfully displays a patient's medical data in either Greek or English, according to the user's choice, without a significant delay. A demonstration version, using fictitious data, can be seen on the Internet at http://lorien.ics.forth.gr:8080/cardioS, or at http://cardio.med.uch.gr/DBdemo.

Conclusions: Access to medical records across national boundaries can be hampered by language differences. We believe that the data translation system we have developed is a step towards solving this problem and making it possible to use the Internet for access to medical records on an international level.

P1664 CARDIOnet program, education – information program in cardiovascular medicine on Internet

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Cardiovascular diseases are leading health problem in most countries. In developing countries, there has been an epidemiological transition from infectious diseases to cardiovascular diseases. Modern cardiology requires continuing education. Internet offers a lot of cardiology sites, but numerous programs cannot help in systematic, update and standardized education.

CARDIOnet Program has been developed as an international education – information program on Internet in cardiovascular medicine for cardiologists, especially for the countries where continuing education is missing.

The program has its own Internet computer center and developed original software for administration of documents and data bases. It is dynamic interactive program supported by data bases. Searching through data bases and documents is structured by Microsoft SQL Server and Microsoft Index Server. System is based on combined Microsoft NT and Unix platform.

CARDIOnet consists of Journal and Exhibition. CARDIOnet Journal presents educational topic volumes with 2,500 pages on Feb. 1999. Editorial policy is to present state-of-the art topic volumes in an outline, lecture-like presentation, extensively illustrated, with figure magnifications, large number of the links and prepared indexes (Authors Index, Key Word Index, Subject Index, Equipment Company Index, Trial Index, etc.) for rapid and easy navigation through texts.

CARDIOnet Exhibition (2,000 pages) has the goal to present various bussiness information (medical-scientific institutions, bibliography, publishers, meetings, government-non government organizations, associations, fairs, drug-equipment companies, etc.). The content has a standard format of presentation, making easy insight and navigation. Address Directory is suported by data bases with 800 addresses in 28 activity and 150 categories.

Program has free acess, with 20,000 registered users from 64 countries since Sep. 1997 to Feb. 1999. CARDIOnet proved to be helpful and practical site for update cardiology education.

COMPUTERS IN CARDIOLOGY: IMAGE PROCESSING

P1665 Comparison of two- and three-dimensional image reconstruction methods for the non-invasive visualization of coronary artery stenoses by contrast-enhanced electron-beam computed tomography

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Electron beam computed tomography (EBCT) has been shown to permit non-invasive visualization of coronary artery stenoses after intravenous injection of contrast agent. Several forms of 2- and 3-dimensional image reconstruction can been applied, they have so far not been comparatively assessed concerning their ability to visualize coronary artery stenoses.

Methods: In 40 patients investigated by EBCT, 40 to 50 axial cross-sections of the heart were acquired after intravenous injection of contrast agent (3 mm slice thickness, 2 mm table feed). Next to evaluation of the original transaxial cross-sections (source images), 2-dimensional reconstructions (maximum intensity projextion [MIP] and curved multiplanar reconstruction [MPR]) as well as 3-dimensional shaded surface display reconstructions (SSD) were independently assessed concerning the presence of high-grade stenoses and occlusions in the mid and proximal segments of the coronary arteries. Results were compared to invasive coronary angiography in a blinded fashion.

Results: A total of 34 high-grade stenoses were present in the investigated patients. If all forms of reconstructions were jointly evaluated, sensitivity of EBCT was 92%, and specificity was 94%, while 22% of all coronary segments could not be assessed due to impaired image quality:

	Sensitivity	Specificity	Evaluation impossible
Source Images	91% (21/23)	93% (96/103)	21% (34/160)
SSD	58% (15/26)	95% (100/105)	18% (29/160)
MIP	92% (22/24)	90% (96/107)	18% (29/160)
MPR	81% (17/21)	88% (94/107)	20% (32/160)
Joint evaluation	92% (22/24)	94% (95/101)	22% (35/160)

In conclusion, analysis of the unprocessed source images seems to be sufficient for evaluation of contrast-enhanced EBCT data sets of the coronary arteries. Of the available image reconstruction methods, maximum intensity projections yield the highest accuracy.

P1666 A comparison of echocardiographic findings using videotape and digital recording compressed by MPEG (moving picture expert group)-2

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Background: To utilize moving images (angiogram and echocardiogram) on inter-and intra-hospital computer networks, we have developed a multi-modality digitized moving picture central archiving system. Echocardiographic moving images are compressed by MPEG-2 encoder and sent to the center server via the Fibre Channel (sustained data rate = 26.6 megabyte/sec). We evaluated echocardiographic findings on videotapes and this digitized system.

Methods: Thirty patients underwent echocardiography using Sonos 5500 (Hewllet Pacard), Sequoia C256 (Acuson), SSA 370 (Toshiba) and SSD5500 (Aloka). Two-dimensional (2D) and M-mode (M) Echocardiographic moving images were recorded into S-VHS tape and sent to the central server simultaneously. All digital echocardiograms were analyzed blindly. We compared the parameters as following; wall motion score (WMS) according to American society of echocardiography, end-diastolic left ventricular major and minor axial dimension (LVMD and LVmD) at apical four-chamber view, intraventricular septum thickness (IVST), end-diastolic and end-systolic left ventricular dimension (EDD and ESD) obtained from M mode echocardiography between analogue data from videotape (AG) and digital data from central server (MPEG-2).

Results: WMS obtained from MPEG-2 agreed well with that from AG ($R = 0.998$, $p < 0.0001$). The parameters measured by M and 2D obtained from MPEG-2 also agreed with those from AG. The mean difference between AG and MPEG-2 was greater in 2D measurement than in M measurement.

Correlation between AG and MPEG-2

Measurements	LVMD (mm)	LVmD (mm)	IVST (mm)	EDD (mm)	ESD (mm)
AG	73.5 ± 9.8	40.6 ± 10.6	12.7 ± 3.5	48.4 ± 9.4	30.9 ± 8.6
MPEG-2	75.0 ± 10.6	43.2 ± 13.6	12.4 ± 3.8	47.9 ± 10.1	30.0 ± 9.4
Mean difference	1.0 ± 2.5	2.6 ± 6.6	−0.3 ± 1.1	−0.7 ± 2.9	0.0 ± 1.5
Correlation	0.969	0.891	0.953	0.959	0.988
p value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Conclusions: Digital recording compressed by MPEG-2 is suitable for echocardiographic measurements in clinical setting.

P1667 A novel method to validate true 3-dimensional imaging of the coronary artery lumen

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Three-dimensional imaging of the coronary artery lumen would be of value in the assessment and treatment of coronary artery disease. We are investigating the utility of a lesion moulding balloon catheter, which provides a 3-D luminal mould. In order to study this method in post-mortem and animal work we have developed a computer based technique to allow comparison of the balloon mould with a luminal cast.

Method: The technique was validated using a selection of straight and curved guiding catheters and sheaths of known diameters (1.96–3.63 mm) and radii of curvature. The objects were vertically mounted in a stand, designed to rotate by 22.5 degrees per turn, to give 9 views (0–180). Each image was captured with a CCD camera (JVC KY-F55B) and digitising board (Snapper) onto a computer (Sun Ultra-5), and spatially calibrated at a resolution of 0.135 millimetres per pixel. Brightness thresholding of the image was performed to identify the image edges. This information was then used to reconstruct true 3-D co-ordinates of 16 points on the perimeter of each horizontal cross-section. The orthogonal diameters (D), orthogonal cross-sectional areas (XSA), volume, centreline co-ordinates and centreline curvatures were calculated from this data, and compared with the known values. Reconstructed 3-D shapes may be viewed in any orientation.

Results: The technique takes approximately 20 seconds to analyse 1 object. The correlation coefficient (r) for the measurement of curvature was 0.99.

Results Table

	A	P	E
D (mm)	−0.01	0.10	0.07
XSA (mm sq)	−0.26	0.34	0.29

The accuracy (A (mean signed difference)), precision (P (1SD of A)) and the absolute error (E (unsigned mean difference)) of these validation studies are shown in the table.

In conclusion, we have developed a fast, accurate method of 3-D imaging and analysis of luminal casts. This method describes the true 3-D co-ordinates of the lumen border, centreline, and measures curvature of the centreline, and would therefore be an appropriate "gold standard" to use in validation studies of 3-D coronary artery imaging.

P1668 Mean echocardiographic intensity must be integrated by other grey level distribution features to characterise myocardial structure of hypertensive patients

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So far, most of the studies on myocardial structure by 2D echocardiography have been based on the assessment of mean myocardial echo intensity (MEI) and on its systo-diastolic cyclic variations (CV). Despite disproportionate connective tissue growth which can occur in the myocardium of hypertensives (HT), studies performed on HT have failed to show differences in MEI and its CV, when compared to normal subjects. The aim of the present study was to evaluate whether statistical analysis of 2D echo grey level distribution may provide further parameters able to characterise myocardial structure in HT patients. Thirty-one uncomplicated essential HT with mild LV hypertrophy were studied; thirty-three age and sex-matched normotensive subjects were the control group (NL). Settings of the echoscanner were fixed and kept constant throughout all the recordings. Images, frozen on the echoscanner at end-diastole in the 4 chamber apical approach to obtain the best view of the iv septum, were digitised and converted in matrices of 256*256 pixels. A region of interest of 15*15 pixels was drawn inside the iv septum for the subsequent analysis. After first order statistical analysis to quantitatively describe the shape of the echo-generated grey level amplitude distribution, the following parameters were obtained: mean (index of overall echo intensity of the image), uniformity (index of tonal homogeneity) and entropy (the disorder of the grey level distribution)

Results: LV myocardium of HT showed an echo intensity comparable to that of NL (mean: 73 ± 16 vs. 71 ± 16); on the contrary HT showed an evident tonal inhomogeneity (uniformity: 0.016 ± 0.003 vs. 0.018 ± 0.004, p = 0.02) associated to a greater disorder in the grey level distribution (entropy: 4.4 ± 0.2 vs. 4.1 ± 0.2, p = 0.02). In conclusion, the recognition of this peculiar histologic condition by quantitative analysis of 2D echocardiograms needs to integrate the mean intensity by parameters related to tonal homogeneity and disorder.

P1669 Realistic geometry cartographic imaging in evaluating patients with coronary artery disease – during pre and post intervention phase

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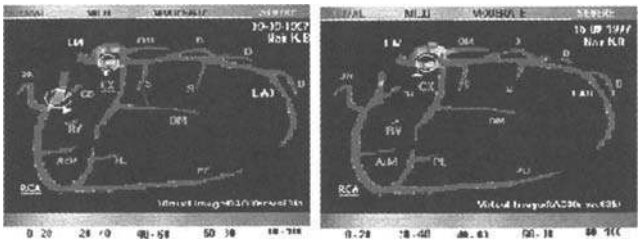
Based on a realistic geometry coronary artery model (RGCAM), we proposed an approach to localise abstraction in different coronary artery branches. Using kinetic modeling (k-model), we get disease dependant cartogram of cardiac haemodynamic variability. The beat-to-beat haemodynamic variability behavior, its deviation difference and correlation was calculated and a three-dimensional (3D) array was constructed and embedded on a RGCAM. The resultant images are the realistic geometry cartographic image (RGC-Imaging) representing coronary artery stenosis. This study was to assess the feasibility of using such RGC-Imaging technique in evaluating patients with coronary artery disease, during pre and post intervention phase.

Methods: Using the signals obtained and by real time simulation of the data thereof, 33,600 coronary unit three-dimensional array was generated in 8 patients (all male). The array was then embedded into the RGCAM, obtaining a realistic geometry two dimensional view in the classic LAO and RAO projection with the chosen angulation of 60 and 30 degrees respectively.

Results: All the 8 RGC-Imaging showed that the intervened vessels had reduced or no disease after intervention.



Pre and Post Intervention RGC-Images.

In conclusion: Our Modeling and Imaging studies have shown its potential in using haemodynamic variability realistic geometry cartographic Imaging techniques to assess patients during pre and post intervention phases. As the data of model simulation and reconstruction may pose some errors from the real one, the results may still be needed to be confirmed in mega clinical trials.

COMPUTERS IN CARDIOLOGY: DATABASES/DICOM

P1670 Integration of different cardiology information sources into an electronic patient record: the need for a central hospital-wide index repository

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Background: Medical review stations (MRS) available in the clinic and outpatient clinic allow access to data from the Hospital Info System (HIS). In order to access data stored in a local Cardiology Information System (CIS) (cathlab reports, echolab reports, ECG's, images) from the HIS-MRS, the present functionality needs to be extended. An important aspect of this is the need for an index database where the MRS can find which information in a local CIS is available for a specific patient.

Methods and results: In our depatment, all information about cathlab studies performed is stored in a self-developed CIS ("CARIS"), based on a traditional client/server architecture. When a cathlab study has been finished and authorized, the CARIS system sends a HL7 message with index information about the study (patient ID, study date and time, procedures performed, etc) to a central HIS repository. An Integration Engine (CAI-TDM) translates the index information from CARIS and forwards it to the HIS. With this information, the HIS-MRS can display the index items to the cardiologist. Then, by launching the CARIS client application from the MRS, a full-disclosure view on all cathlab data can be achieved. The X-ray images acquired in the cathlab are stored on a local image server. The images can be viewed on the MRS using a dedicated DICOM viewer application. Information about the available images, and the images themselves can be retrieved by the MRS via the DICOM query/retrieve (Q/R) protocol.

Presently, integration in the MRS of echolab reports and ECG's is being implemented. In the same fashion as for the cathlab data, index information will be stored in a central repository. However, the index repository will be stored on a system outside the HIS database, allowing easier implementation and modification. Access to echolab reports and ECG's is possible using a standard web-browser interface, which allows the cardiologist to experience the benefits (and drawbacks) of an universal HTML browser compared to a traditional dedicated client application.

Conclusion: The approach resulted in a robust and powerful application that provides integrated access to patient information from different sources. A central index repository is crucial for the MRS to know which information is available and where it is stored. In the future, this database might be implemented as a virtual repository, with the MRS querying the local information systems via the hospital network for all information of interest, comparable to the DICOM Q/R protocol.

P1671 Deficard – a new concept of patient management after ICD-implantation

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Background: Due to an increased number of patients receiving ICD therapy patient management and the control of patient and device realted data will become difficult. To improve patient management the DEFICARD concept was introduced in clinical cardiology. This concept consists of a database on a personal computer and a multifunctional chip card that is carried by the patient. In our phase-1 study we have followed 102 patients (pts.), mean age 57 + 11 years, after ICD implantation. The acceptance of the DEFICARD was extremely high (98%).

Results: Patients attended the outpatient clinic every two months. The DEFICARD reduced the visit significantly from 45 + 20 minutes to 23 + 12 minutes ($p < 0.05$). All data were stored and reevaluated on the card and, therefore, relevant up-to-date information was always available about the ICD and the state of health of the patients. According to our phase-2 protocol we have invited 3 additional hospitals to participate in the DEFICARD project. We will study the cooperation in patient management between our hospital and these referring centers.

Conclusion: The DEFICARD has proven suitable for all pts. after ICD implantation. It reduces the time needed in the outpatient clinic and thereby costs when treating pts. with implanted cardioverter-defibrillators.

P1672 Cardiac image communication based on the DICOM application profile: comparison with new options for lossless and lossy image data compression

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Background: The DICOM XA (x-ray angiographic) standard for coronary angiography allows for only one mode of lossless data compression. Advanced lossless methods or 'clinically lossless' compression may offer higher compression ratios (CR), thus potentially reducing the communication and archiving problems.

Methods: 75 difficult cases were selected from the 520 digital cine runs collected for the recent ACC/ ESC compression viability study (CVS). They were rated (scale with 5 quality scores) by 13 clinical experts from Europe and the US using a side-by-side display (fixed contrast and brightness settings) of uncompressed and compressed (JPEG6: lossy JPEG at CR = 6) cine runs. The same 75 cine runs were also compressed with lossless methods: lossless JPEG with Predictor 1 (LJPEG1, as applied in DICOM) and Predictor 7 (LJPEG7), LS-JPEG (LOCO, presumably successor for LJPEG), lossless Wavelet (LWAVE from the SPIHT algorithm) and with PNG using freely available compression software on an UltraSparc computer.

Results: The 13 reviewers considered the images compressed with lossy JPEG6 to be indiscernible from non-compressed cine runs in 78.5% of the cases and to be different, but fully equivalent in 20.9%. The remaining 0.6% (2/325) showed larger aesthetic quality differences, but still no diagnostic errors were detected. Lossy JPEG6 compression (CR = 6) is therefore regarded as 'near-lossless'. For the lossless methods, the compression ratios CR for the 75 cine runs were:

Method	LJPEG1	LJPEG7	LOCO	LWAV	PNG
Mean CR, SD	2.74 ± 0.40	2.90 ± 0.40	3.80 ± 0.81	3.56 ± 0.55	2.70 ± 0.34
Max CR	3.96	4.02	5.79	4.87	3.66
Min CR	2.01	2.13	2.41	2.38	2.10
CTIME (sec)	0.7/0.6	0.8/.0.6	0.2/0.2	1.1/1.2	1.0/0.3

where SD is the standard deviation of the mean and CTIME is time for compression/ decompression (derived for the image with maximum entropy).

Conclusion: Near-lossless image compression (JPEG6) provides compression up to CR = 6 or 7. This is an improvement by a factor of about 3 over the present DICOM standard (LJPEG1) and of about 2 over the best lossless method (LOCO).

P1673 A digital echo laboratory: clinical application of the DICOM standard

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A digital echo laboratory according to Feigenbaum's suggestions has been implemented. For each study, ten at least ECG-synchronized standard projections are acquired over a single cardiac cycle on a HP Sonos 2000 and recorded on magneto-optical (MO) disc. A dedicated software was developed in order to 1) review the sequences from the MO disc on a standard PC, 2) convert the files from HP TIFF proprietary format to DICOM format, 3) masterize a multisession DICOM CD-R, 4) Review the sequences from the CD-R on a standard PC. Using standard RLE lossless compression, real time playback of full resolution echo color images can be obtained on a Pentium II, 266 MHz with 32 Mb RAM and CD to DMA capabilities.

Two kinds of digital archives are used. A sequential digital archive, maintaining the HP proprietary format, is obtained by file copy of the magneto-optical disc to the CD-R. This kind of storage permits review of echo loops on a PC-based workstation as well as reversal to MO-disc for visualization on the echo machine. The second archive consists of multisession DICOM CD containing the echo history of the individual patient as well as an autoinstalling copy of the viewer program. Average time for recording and labeling images for each examination on MO was 125 + 30 sec. Average time for retrieval, display of all sequences, thorough review of the study for final diagnosis, on CD or MO for each study were calculated and compared to VHS:

	CD or MO	VHS
Retrieval (sec)	19 + 4	145 + 65
Display (sec)	155 + 47	187 + 72
Review (sec)	181 + 52	424 + 98

In conclusion, this new technique of storage make the management and consultation of the obtained archives more rapid, resulting in substantial saving of time. Furthermore, our digital archives allow all physicians in the ward to substitute conventional static photographs with the direct view of the echo sequences on the PC, with improved perception of patient's condition and a positive cultural impact.

P1674 Computer-aided quality control, documentation, result, and report generation and education in echocardiography

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The growing number of echocardiographic examinations called for the development of a system generating Documentation and Reports (Transthoracal, Transoesophageal, and Stress Echo). The program we developed eventually contained additional features allowing Quality Control and Training.

Methods: The development is based on the following publications in echocardiography:

- ACC/AHA Guidelines for the Clinical Application of Echocardiography
- German Quality Guidelines (Deutsche Gesellschaft für Kardiologie)
- A number of standard textbooks.

The program contains the following characteristic features:

- Graphic User Interface with anatomical objects for fast and easy data aquisition.
- Automatic generation of reports and results based on standardised expressions in Echocardiography without the need for dictation
- Plausibility Checks of data entered
- (d) On-line access to a knowledge base of more than 500 examples, clinical, images, tables, and cine loops.
- Important echocardiographic websites (off-line mirrored on a server)
- Export of HTML-stylesheets for presentation of statistics on the web
- Part of the medical and economical documention system of the "Oldenburg Heart Centre".

The software was developed using ORACLE®'s developer 2000 and runs under Windows NT 4.0 and Windows 9x. It is based on a Client-Server architecture with an ORACLE® 8 database and can be used in networks of any size.

Conclusion: The practical application of the program led to an increase in time saved and a more accurate interpretation and documentation of echocardiographic examinations. As a further development storage and retrieval of DICOM images were tested.

P1675 Quality control using automated validation tools can improve interoperability of DICOM implementations

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Background: The overwhelming success of the acceptance of the DICOM standard by industry and the cardiology users has brought to the market many devices that are sold as being DICOM conformant. In practice interoperability between different DICOM devices is not always accomplished easily and/or completely.

Methods: Implementations of cardiac X-ray Angio DICOM data-sets on CD-R from 10 vendors were tested by 2 DICOM validation applications: (a) a checker that checks the conformance taking into account conditional rules and value domains to which data elements are restricted; (b) an application profiler to define Application Profiles and to check conformance to the defined Application Profiles. 5 DICOM CD-R viewers were used to see whether interoperability for viewing purposes did correlate with the results of the validation programs.

Results: Only 2 out of 10 tested implementations turned out to deliver data-sets on CD-R that were fully in conformance with the DICOM standard. The other 8 implementations contained errors that ranged from minor to major disrespect of the DICOM rules. The viewer interoperability test showed a high correlation with our validation results: For the 3 CD-R's that contained most serious errors most viewers were not able to show the images the way they should be shown.

Conclusion: Vendors' claims to be fully DICOM compliant could not all be sustained when the CD-R data sets were checked thoroughly. This undesirable situation may be improved significantly if proper DICOM validation tools will be used during DICOM application development. DICOM's chances for reaching device interoperability will be greatly increased if this approach is strictly adhered to.

P1676 Analysis of reproducibility of measurements of regional and global left ventricular function using quantitative digital contrast ventriculography

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The aim of this study was to determine the variability (interstudy, intra- and interobserver) of measuring LV volume and function from contrast ventriculograms recorded on DICOM compact discs (CD).

Methods: 16 patients with stable ischemic heart disease and a history of an old myocardial infarction underwent two ventriculography performed using the same catheterization and imaging procedures. The images were recorded on the CD and analysed twice by two independent observers using commercial software (Sanders Data System. End diastolic (EDV), end systolic (ESV) and stroke (SV) volumes and ejection fraction (EF) were determined by the area length method. The severity of hypokinesis (HypoK) in the territory of culprit artery and of hyperkinesis in the opposite region (HyperK), and the percentage of chords with motion < -2 SD (%HypoK), and with akinesis and dyskinesis (%AK) were calculated using the centerline method.

Results: the intra and interobserver variability for all parameters was very small with correlation coefficient $r > 0.87$ ($p < 0.0001$) excepted HyperK with $r = 0.73$ ($p = 0.002$). Inter study variability are as follow:

	EDV	ESV	SV	EF	HypoK	HyperK	%HypoK	%Ak
r	0.82	0.78	0.86	0.83	0.90	0.53	0.82	0.84
r^2	0.67	0.61	0.74	0.68	0.81	0.28	0.67	0.71
SEE	1.95	2.77	0.81	1.19	0.12	0.16	1.85	1.06
Cut-off	16.8	18.6	12.3	8.94	0.75	1.35	11.7	5.71

In conclusion: The cut-off values found in this study are larger than those reported for 35 mm cinefilm and should be considered when evaluating serial studies of left ventricular function from DICOM formatted CD's.

COMPUTERS IN CARDIOLOGY: OTHER ASPECTS

P1677 External cardiac modulation: evidence of wedensky phenomenon in healthy subjects and ventricular tachycardia patients

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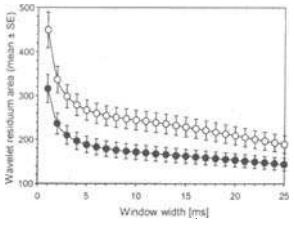
Subthreshold stimulation without capture reduces the stimulation threshold and changes the action potential of a subsequent suprathreshold stimulation (Wedensky Phenomenon). To investigate this phenomenon after transthoracic subthreshold stimulation (2 ms pulse of 5–40 mA between surface precordial and subscapular patches delivered synchronous with R wave detection), 60 to 200 subthreshold stimulated QRS complexes were signal averaged and compared with the same number of averaged non-stimulated complexes recorded during the same experimental session. The electrocardiographic recordings were obtained with standard orthogonal leads. In order to detect even minor changes within the QRS complex, each lead of both stimulated and unstimulated averaged complexes were wavelet decomposed (53 scales of the Morlet wavelet with central frequencies of 40–250 Hz). The wavelet residuum corresponding to the Wedensky phenomenon was obtained by subtracting the vector magnitude wavelet decomposition of the unstimulated QRS from that of the subthreshold stimulated QRS. The surface area of the residuum was investigated in windows of 1–25 ms following the stimulation. The test was performed in 47 pts with EP inducible ventricular tachycardia (mean age 63 ± 13 years, 83% male) and in 30 healthy controls (mean age 44 ± 16 years, 60% male).



20 mA stimulation (filled circles = VT patients, unfilled circles = control).

The residuum showed an increase in the spectral power of the stimulated complex that was significantly more marked in healthy volunteers ($p < 0.01$) than in VT patients (figure). Thus, Wedensky phenomenon induced by an external subthreshold stimulation can be documented in man and differentiates VT patients from controls.

P1678 Predicting survival in coronary disease: machine-learning computer models versus expert clinicians

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Background: To be useful, computer-based algorithms must enhance the experience of human experts. We compared the prognostic ability of artificial neural network, regression tree, and Cox proportional hazards models with that of a panel of 49 cardiologists.

Methods: A series of 2,099 symptomatic, medically treated patients with significant coronary artery disease (75% stenosis of at least one vessel) were identified from the Duke cardiovascular database. Patients were divided into training (n = 1823) and testing (n = 276) subsets. A five-layer, back-propagation neural network and a cross-validated regression tree were fitted against the training set. Predicted probabilities for 3-year survival and 3-year infarct-free survival were collected from 49 cardiologists for patients in the test set. The computer models generated similar predicted probabilities for the test set patients. The C-index (equivalent to the area under a receiver operating characteristic curve) and Spearman rank correlations evaluated each predictor's ability to distinguish patients who had events from those who did not.

Results: For infarction-free survival, each of the computer models had a higher C-index than the cardiologists.

	Survival		Infarction-free Survival	
	C-index	Spearman	C-index	Spearman
Cardiologists	0.76	0.42	0.67	0.28
Regression tree	0.75	0.40	0.72	0.38
Neural network	0.80	0.48	0.73	0.39
Cox model	0.81	0.49	0.73	0.38

Conclusions: Machine learning methods, including neural networks and regression trees, may augment human clinical experience. These methods form the groundwork for future helpful clinical tools.

P1679 Neural networks versus multiple regression models to predict costs of acute myocardial infarction: GUSTO-I

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Background: Data-mining techniques, including artificial neural networks (NN), offer new tools for understanding hospital costs. This study assessed the ability of NN and multiple linear regression (MR) models to describe hospital costs for patients with acute MI.

Methods: A total of 20,873 U.S. patients from the GUSTO-I study were randomly divided into a training set (n = 15,654) and a test set (n = 5219). Univariate analyses identified 77 candidate variables for use in NN and MR models of log (cost). Back-propagation NN and MR models were fitted against training set subgroups of increasing size, and validated against the test set.

Results: All correlation coefficients were highly significant ($p < 0.001$). Pearson correlation coefficients were similar for the overall models (NN 0.90, MR 0.89). Mean absolute residuals for the NN on the largest training set were comparable to the MR residuals on the smallest training set. Spearman coefficients showed that MR correctly ranked costs better than NN. The overall models results did not differ, by Wilcoxon rank-sum tests ($p = 0.52$).

Training	Mean Absolute Residual		Spearman r_S		Pearson r	
Set (n)	NN	MR	NN	MR	NN	MR
250	0.390	0.209	0.672	0.954	0.694	0.187
500	0.343	0.150	0.793	0.964	0.769	0.890
1000	0.329	0.146	0.794	0.968	0.777	0.833
5000	0.228	0.140	0.910	0.977	0.888	0.653
15,624	0.207	0.131	0.917	0.982	0.904	0.894

Conclusions: Nonparametric methods, such as r_S, may better reflect the performance of log (cost) models. MR techniques may be more parsimonious and efficient for small datasets. With a training set of sufficient size, NN can generate accurate descriptive cost models. This deserves further study.

P1680 Three dimensional echocardiographic data sets registered with a virtual heart model in augmented reality applications

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Augmented reality applications combine real image data with virtual objects. The necessary spatial and temporal synchrony is achieved by a registration procedure. We evaluated the accuracy of the match of three-dimensional echocardiographic (3DE) data sets registered to a virtual surface model of the heart. The model was designed based on expert knowledge. Its ideal representation of the heart is currently not adapted to individual patient morphology. The augmented reality scenario is used in an echocardiographic training simulator and for orientation in 3D data sets.

Methods: Three dimensional echocardiographic data sets were acquired and postprocessed with a TomTech 3D workstation and a Vingmed System V scanner with integrated 3D capability using a 2.5 MHz transthoracic probe. A rotational stepper motor was used to acquire 3DE data sets with 60–90 scan planes. We categorized the scanned hearts in four groups: normal hearts, volume loaded left ventricles (LV), pressure loaded LV and congenital malformations. A total of 50 data sets with high image quality were analyzed. Registration was performed manually based on anatomical landmarks using the apex of the LV and the centres of the valves. A set of echocardiographic standard views were used for the evaluation. Each view shows the ultrasound image and the analogous model slice superimposed. Accuracy was evaluated measuring the overlap of the mitral-, aortic- and tricuspid valve and the areas of the left and right ventricle in the model and in the echocardiographic images respectively.

Results: The accuracy of registration was dependent on the underlying pathology of the scanned heart, yielding the best results in normal hearts and hearts with minor geometric alterations and worst in hearts with congenital heart diseases. In the latter group a registration was sometimes impossible. Registration was better using widely distributed anatomical landmarks including the left ventricular apex. Thus, data sets acquired by apical scans were more useful than those acquired by parasternal scans.

Conclusion: The result of the registration depends on the underlying pathology of the heart and the possibility to identify widely distributed landmarks in the data set. Currently the augmented reality application is used for navigation and orientation without deriving any diagnostic information from the model itself. The degree of match between the echocardiographic images and the model for this purpose is sufficient.

P1681 Neural network based approach for localization of the origin of ventricular tachycardia from body surface potential mapping

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Introduction: Body surface potential mapping (BSPM) data obtained during endocardial stimulation at multiple ventricular pacing sites show a broad spectrum of potential distributions. In this demonstration, BSPM sequences are analysed using a neural network approach based on self-organisation that provides a noninvasive estimation of the site of origin of stimulated ventricular activation. The localisation results are visualized on a realistic model of the endocardial surfaces of the right and left ventricles.

Methods: The Self-Organizing Map (SOM) network used in this study is arranged as a two-dimensional lattice of neurons, each of them representing a particular distribution of body surface potentials. In the initialization phase, a random potential pattern is assigned to each neuron of the SOM. For the training of the SOM network, 123-channel BSPM recordings were obtained from 86 endocardial pacing locations in 19 patients with a previous myocardial infarction. Potential distributions on the body surface from 3 paced ventricular beats for each pacing location were sampled at 5 ms intervals from the beginning to the end of the ventricular activation. Based on this procedure, altogether 8346 instantaneous potential distributions were obtained and subsequently presented to the SOM. During the training phase, the SOM network automatically extracts and organises the most prominent features of the recorded BSPM sequences until a global ordering of the network nodes has been achieved.

Ventricular activation patterns from different pacing sites are visualized as time traces on the trained SOM. Classification of the activation patterns with respect to the endocardial pacing location was performed by Learning Vector Quantization. The output of the classification yields a probability distribution for the localisation of the origin of ventricular activation.

Demonstration: During the demonstration, BSPM data are presented to SOM networks trained with different learning parameters. The organisation of the SOM in the learning process is visualised using animation tools. Time traces of the ventricular activation during endocardial stimulation are displayed. Finally, the localisation results are visualised on a realistic 3-dimensional model of the endocardial surfaces.

COMPUTERS IN CARDIOLOGY: ARRHYTHMIA AND SIGNAL PROCESSING

P1682 Artificial intelligence techniques of 12-lead holter monitoring in cyberspace

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The ECG-Based-Cardiology System (www.bion.hu) includes: hypertext-based ECG Tutorial with 420 ECG demo recordings, Database server for conventional and 12-lead Holter ECG recordings. The hypertext ECG encyclopedia contains 512 articles from the literature related to the conventional and Holter ECG. The subparts of these articles were linked together and structured using fuzzy logic. An interactive on-site 12-lead Holter recorder was developed using DSP technique with an automated arrhythmia detection, ST-segment monitoring, measuring the ventricular repolarisation (QT, Qtc, Qtd). The automated measurement and interpretation of these parameters was developed by a neural network model. The interactive on-site Holter equipment could connect automatically to the PC via infra-red communication route or alarms the patient to connect to the PC. The cardiologist in the core laboratory site could communicate with the patient via the Internet. The present study compares the on-site, automated measurements of the above mentioned parameters with core laboratory results, where the manual measurements were taken place. The study population consists of the 48 h Holter recordings of 266 patients with coronary artery disease. Agreement (agr.) between categorial (yes/no)assessments were described by kappa (k) statistics, where k = (actual agr.- agr. by chance)/(1.00(maximal agr.)-agr. by chance), comparisons between groups were performed by the Mann-Whitney rank-sum test. The agreement between the local, automated ECG interpretation module of the Holter equipment and the analysis of the core ECG laboratory of 1024 episodes of automated alarming: atrial fibrillation (N = 221, kappa = 0.89, p = n.s.), ventricular run > 5 beats (28, 0.81, n.s.), II/III-AV-block (9, 0.77, n.s.), bundle branch block (17, 0.92, n.s.), pathological Q (97, 0.74, $p < 0.05$) ST-elevation (343, 0.69, $p < 0.05$) ST-depression (511, 0.63, $p < 0.02$), T-wave inversion (302, 0.71, $p < 0.02$). The results show a good overall agreement between the two sites, but the automated measurement cannot be applied blindly, without confirmation of the cardiologists via the Internet.

P1683 Interobserver agreement on measurement of signal-averaged P-wave electrocardiogram: comparison to signal-averaged QRST in normal subjects

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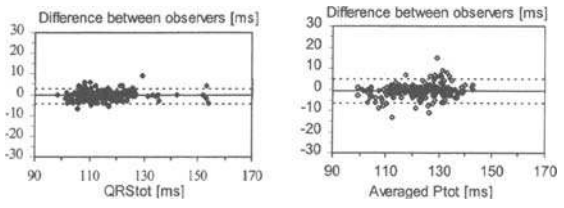
The interobserver agreement on measurement of signal averaged P wave was assessed in 306 ECG obtained from normal subjects (age 32 ± 8 years) using PHiRES and HiRES software (Marquette Medical Systems). The onset and offset of SA P wave were automatically detected and then manually corrected by two independent observers, and the averaged values of total filtered P wave duration (P_{tot}), RMS of the terminal 40, 30, and 20 ms (P_{40}, P_{30}, P_{20}), RMS voltage of the P wave, and P wave integral were taken for the analysis. The agreement between observers was assessed by Bland-Altman method and by the regression analysis.

Results: The interobserver agreement on QRS_{tot} was only slightly higher compared to that on P_{tot}. Figure presents Bland-Altman plots for interobverver agreement on QRS_{tot} (left) and P_{tot} measurement (right; bold line = mean of difference between measurements, dashed lines = mean ± 2 SD). Correlation coefficients were 0.98 and 0.95, respectively. For the voltage criteria, the best agreement was found for P40 followed by P30 (correlation coefficients 0.92 and 0.84, respectively; for RMS40 of signal averaged QRST r = 0.90.



Conclusion: The interobserver agreement on signal averaged Pwave did not differ from that of QRST. The best agreement was achieved for P_{tot}.

P1684 Phasic aspects of the oscillation of heart rate and blood pressure in man: cross-spectral analysis

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Purpose: Cross-spectral analysis is frequently used for the analysis of non-random oscillations of cardiac cycles (RR) and arterial blood pressure (BP), mainly for the estimation of the baroreflex sensitivity. Phase lag between RR and BP oscillation has been studied to a lesser extent.

Methods: A population of 103 patients (73 males, 30 females) of mean age 50 ± 35 years, with coronary artery disease and/or hypertension has been studied. ECG and non-invasive continuous finger arterial pressure (Finapres) were digitized during 5 min period at rest in supine position and two 3 min periods of controlled breathing at frequencies of 6 and 20 cycles per minute. Cross-spectral indices have been assessed for the fluctuation of systolic (SBP), diastolic (DBP), pulse pressure (PP) and RR in low frequency (0.033–0.133 Hz) band (LF).

Results: Baroreflex gain was 6.8 ± 5.1, 10.1 ± 7.9 and 6.0 ± 4.8 ms/mmHg during spontaneous (SB), slow (SCB) and fast (FCB) controlled breathing, respectively. Phase lags (PL) in degrees and seconds between different modalities of BP and RR, as well as frequency (F) of the peak coherence in the LF band were as follows [means (SD)]:

Breathing:		Spontaneous	Slow (100 mHz)	Fast (333 mHz)
PP-RR	PL (degr)	−63.0 (53.5)	−70.8 (52.4)	−86.7 (72.4)
	PL (sec)	−3.2 (4.0)	−2.0 (1.6)	−4.0 (4.1)
	F (mHz)	73.8 (29.8)	100.8 (9.5)	72.7 (22.4)
SBP-RR	PL (degr)	−98.4 (43.4)	−79.1 (46.5)	−109.4 (57.8)
	PL (sec)	−4.7 (3.9)	−2.4 (1.7)	−5.1 (4.6)
	F (mHz)	73.5 (26.3)	97.6 (13.7)	72.9 (22.8)
DBP-RR	PL (degr)	−119.3 (39.3)	−94.3 (56.9)	−125.6 (51.9)
	PL (sec)	−5.3 (3.5)	−2.8 (1.9)	−5.5 (4.2)
	F (mHz)	74.9 (24.9)	97.1 (14.1)	75.6 (24.1)

Conclusion: The differences of phase lags for PP, SBP and DBP were in accordance with DeBoer's model. However, absolute values of phase lags in LF band during SB and FCB were strikingly higher (due to significantly longer period of oscillation compared to SCB) than those previously reported.

P1685 Automated analysis of distributions of atrial premature beat coupling intervals preceding onset of atrial fibrillation to detect focal atrial fibrillation

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Previous studies suggest that atrial premature beats (APB) trigger episodes of atrial fibrillation (AF). Unifocal APB's as the presumed cause of some cases of paroxysmal AF, as recently described. We report an automated method to investigate this phenomenon.

Method: A library of 177 beat interval files from 24-hr Holter recordings of paroxysmal AF pts was examined. AF episodes were identified by a validated technique, and 2 min of sinus rhythm (SR) preceding each AF episode and SR sections remote from AF were studied (SR after AF, AF itself, and noisy segments were excluded). The prematurity index (PI) of all beats was calculated as the ratio between the preceding RR interval duration and the median duration of the 10 preceding beats. APBs were defined as supraventricular beats with PI < 0.8. For each recording, separate histograms of the PI of APB's prior to and remote from AF were constructed. APB's of the same PI are visualised by a narrow significant peak (spike) in the distribution. Visually there was either a spike seen only prior to AF (pattern A), spikes seen in both remote and prior to AF (pattern B), or (3) no spikes present (C). To remove observer bias the presence of spikes was assessed by: (1) the width of the spike (>15 ms), (2) the proportion of all APB's which were within the spike, (3) the kurtosis of the spike (reflects the sharpness of the spike), (4) whether the spike is present at a coupling interval < 600 ms, and finally (5) the distance between the spikes in the histograms remote from and prior to AF (to define pattern B).

Results: Of 74 tapes, 8 demonstrated pattern A, 19 pattern B, and 53 pattern C. Only on 2 of 74 recordings automated and manual classification (performed by 2 independent observers) disagreed.

Conclusion: The automated analysis of histograms of PI of APB's might study the mechanism triggering AF onset.

P1686 Superconducting quantum interference devices (squids) in magnetocardiography: findings on normals in trinidad and tobago

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The objective of this study was to measure the magnetic fields of the heart of a normal volunteer using a newly accquired Superconducting Quantum Interference Device (SQUID)magnetometer. This instrument is the first of its kind to ever be introduced to the Caribbean region.The database obtained by using this instrument will be used as a reference for studies on cardiac patients.

This study involved 16 normal volunteers: 7 females, 9 males of mean age 27.4 years. Magnetic fields at 36 points on a 6x6 grid on their anterior chest wall were recorded with the detector 1 cm above the grid.Using specialized software, the data were processed to yield the Magnetocardiogram (MCG).From this the MCG P-wave, QRS complex and T wave intervals were computed. A map of the magnetic field variation over the entire grid area was also constucted for one heart cycle.

The results show that the magnetic equivalents of the P,QRS and T components of the electrocardiogram are present in all cases. The values of the P., QRS and T time intervals in the MCG were found to be 57.2 ± 8.5 ms, 51.9 ± 8.2 ms and 96.3 ± 7.6 ms respectively. Isomagnetic contour maps constructed show that there are variations in the magnetic fields of the heart for this group of healthy subjects. Further investigations will address factors contributing to these differences.

The database that is being established will serve as an invaluable tool for further research.

STUNNING, HIBERNATION AND PRECONDITIONING

P1687 Prior exposure to lipopolysaccharides and ischaemic preconditioning increase the TNFα-inhibitory serum activity in rabbits

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Prior exposure to lipopolysaccharides (LPS) and ischemic preconditioning (IP) reduce the infarct size resulting from ischemia/reperfusion (I/R) in rabbits. Furthermore, both LPS and IP reduce the TNFα-concentration during I/R. One potential explanation for such decline in the TNFα-concentration relates to an increased TNFα-inhibitory serum activity (TNFα-ISA). We therefore analyzed the serum TNFα-concentration and its TNFα-ISA during 30 min coronary occlusion and 180 min R in anesthetized rabbits either not exposed (controls, G1, n = 7) or exposed to LPS 72 h prior to I (G2, n = 9) or preconditioned by a single cycle of 5 min I and 10 min R (G3, n = 9). TNFα-ISA was assessed by co-incubating LPS-stimulated fresh rabbit blood with serum obtained from individual rabbits of G1–G3 and measuring TNFα-production using the WEHI assay. Heart rate and peak aortic pressure were comparable among all groups throughout the protocol. Also, regional myocardial blood flow (microspheres) was similar during control and I. With a comparable area at risk, infarct size in G1 averaged 36.9 ± 11.1 (SD)% and was reduced to 17.3 ± 11.3% ($p < 0.05$) and 13.1 ± 11.6% ($p < 0.05$) in G2 and G3, respectively. The serum TNFα-concentration was similar under control in G1 (793 ± 82 U/ml) and G3 (863 ± 244 U/ml), but was reduced in G2 (454 ± 120 U/ml, $p < 0.05$). While the TNFα-concentration increased during I/R in G1 (1119 ± 224 U/ml, $p < 0.05$), it remained unchanged in G2 and G3. The TNFα-ISA during I/R was significantly increased in G2 and G3, resulting in less TNFα-production by LPS-stimulated blood.

	Control	IP	Ischemia	Reperfusion
G1	2578 ± 240		2592 ± 542	2505 ± 358
G2	1262 ± 303$^{\#a}$		1395 ± 164$^{\#}$	1359 ± 138$^{\#}$
G3	2640 ± 380	2537 ± 320	1913 ± 400$^{*\#}$	1610 ± 148$^{*\#}$

TNFα-concentration of LPS-stimulated fresh rabbit blood (U/ml) co-incubated with serum, mean ± SD. *: $p < 0.05$ vs. Control; $^{\#}$: $p < 0.05$ vs. G1; ^{a}: $p < 0.05$ vs G3; 2-way ANOVA

Thus, cardioprotection by LPS and IP is associated with a reduced serum TNFα-concentration and increased TNFα-ISA.

P1688 Importance of proton gradient during transient ischaemia for the effect of ischaemic preconditioning on norepinephrine release and arrhythmias in rat hearts

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Transient ischemia (TI) reduces norepinephrine (NE) release during sustained global ischemia in rat hearts indicating a neural preconditioning which may affect the incidence of ventricular arrhythmias during myocardial ischemia. We tested how neural preconditioning and ventricular arrythmias are affected by changes of transmembranal proton gradient during TI and reperfusion. NE release during sustained ischemia (30 min ligation of LAD artery) was determined by HPLC and the incidence of ventricular fibrillation (VF) was analyzed by ECG in isolated perfused rat hearts. Both, NE release and the incidence of VF were reduced during sustained ischemia by preceding TI (3 × 5 min) from 83 ± 11 to 47 ± 5 pmol/g (NE) and from 65 to 43% (VF) (each $P < 0.01$). When hearts were reperfused after each TI with an acidic medium (pH 6.2) to attenuate the reperfusion-induced transmembranal proton gradient, both, the suppression of NE release and the incidence of VF was completely abolished (NE: 85 ± 14 pmol/g; VF: 73%). Furthermore, hearts reperfused after each TI with an alkalic medium (pH 8.8) showed an increased effect of TI on NE release (31 ± 5 pmol/g) and incidence of VF (25%). Additionally, induction only of intermittent intracellular acidosis by NH4+ prepulse (3 × 10 mM) instead of TI was sufficient to suppress both NE release and the incidence of VF during sustained ischemia.

Conclusion: Ischemia-induced NE release and VF in rat hearts are suppressed both by transient ischemia. The induction of a transmembranal proton gradient either by transient ischemia and reperfusion or by transient intracellular acidosis contributes to this effect and may support data suggesting an activation of pH-regulating transporter during ischemic preconditioning.

P1689 Canine myocardial stunning is attenuated by the cardioselective synthetic glycolipid RC-552

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Monophosphoryl lipid A (MLA), a glycolipid produced as a derivitized purified fermentation product of *S. minnesota* R595 has been demonstrated to reduce regional myocardial stunning associated with cyclical transient ischemia in dogs when administered 24 hours prior to ischemia. A second generation synthetic glycolipid (RC-552) devoid of the residual immunostimulatory activity observed with MLA, was evaluated in a canine model of regional myocardial stunning for an acute and prolonged protective effect.

Methods: Dogs were randomized to receive IV: 1) RC-552 (35 μg/kg, 10 minute pre-ischemia); 2) RC-552 (35 μg/kg, 24 hour pre-ischemia); or 3) vehicle (equivalent volume, 24 hours pre-ischemia). Anesthetized dogs were subjected to five transient cycles of 5 minute LAD occlusion (Occ_T) and 10 minute reperfusion (Rep_T). Regional segment shortening was measured in the subendocardium by sonomicrometry using two piezoelectric crystals placed 10–15 mm apart. Radioactive microspheres were used at 5 minute occlusion (Occ) and 2 hours prolonged reperfusion (Rep) to assess transmural blood flow.

Results: Following either a 10 minute or 24 hour pretreatment with RC-552 a significant and equivalent improvement in systolic segment shortening was observed both during cyclical reperfusion and prolonged reperfusion. No drug associated effects on myocardial blood flow, mean blood pressure, heart rate, or rate-pressure product were observed.

Treatment/ Time Pre-Occ	N	% of Baseline Segment Shortening					
		Occ_T	Rep_T	Prolonged Rep			
		#1	#1	15″	30″	60″	120″
RC-552/10 min.	8	−37 ± 9	59* ± 5	44* ± 4	47* ± 4	51* ± 7	45* ± 7
RC-552/24 hrs.	7	−37 ± 9	59* ± 5	44* ± 4	47* ± 4	46* ± 6	48* ± 7
Vehicle/24 hrs.	6	−40 ± 5	34 ± 8	15 ± 5	10 ± 9	14 ± 8	11 ± 5

* $p = <0.05$ vs vehicle, ANOVA; Data from Occ_T and Rep_T cycle 2–5 not shown

Conclusion: IV administration of RC-552 (35 μg/kg) either 10 minute or 24 hour pre-occlusion resulted in improved recovery of contractility both during cyclical periods of reperfusion and throughout 2 hours prolonged reperfusion without the potential immunostimulation effect of MLA and without effect on peripheral hemodynamics.

P1690 The protein kinase inhibitor-α gene: another key to postischaemic myocardial dysfunction?

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This study was performed to identify differential expressed genes involved in myocardia stress rexponse. Several different mechanisms such as formation of oxygen radicals, calcium overload, sarcoplasmic reticulum dysfunction and proteolysis of troponin are thought to cause myocardial stunning, long-lasting reversible myocardial dysfunction following short coronary occlusions. However, none of the proposed mechanisms completely explains the phenomenon of myocardial stunning.

Methods: To overcome the above-mentioned problem we tried to clone differentially expressed genes, probably involved in the genesis of myocardial stunning. Therefore, differential display reverse transcribed polymerase chain reaction (= DDRT-PCR) was used to study RNA from postischemic pig myocardium. To clone full-length cDNAs, one of the cloned fragments (RKCU13.4.2) was used to screen a cDNA library. We identified this clone as a part of the protein kinase inhibitor alpha (= PKIαa) cDNA. By uses of a recombinant PKIα peptide (amino-acids 14–22) and a rat "working heart" model, its cardiac function was assessed.

In summary, we cloned with 4000 bp in length the porcine PKIα cDNA and showed it's inducibility by ischemia. It encodes a 76-amino-acids open reading frame with 100% homology in its active center to known sequences from different species. We show a concentration-dependent (up to 2 μMol), reversible negative inotropic effect. This may be due to the inhibition of phosphorylations via protein kinase A, especially the inhibition of the sarcoplasmic reticulum ATPase via nonphosphorylated phospholamban or the inhibition of the phosphorylation of troponin I.

In conclusion: The PKIα gene is a new stress-induced factor. We describe the full length porcine cDNA of about 4 kb and present a sophisticated new hypothesis whereby the PKIα plays a pivotal role in pathophysiological regulation leading to postischemic myocardial dysfunction.

P1691 Densities of the sarcoplasmic reticulum calcium release channel and L-type calcium channel are decreased in postischaemic ("stunned") myocardium

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Background: In stunned myocardium the intracellular calcium metabolism shows an imbalance. The intracellular concentration of calcium is increased and responsible for the contractile dysfunction. In this study we investigated the densities of the sarcoplasmic reticulum release channel (CRC) and L- type calcium channel (L-type) and further the calcium sensitivity of the CRC in postischemic myocardium.

Methods: In homogenates from porcine hearts after 10 minutes occlusion of the LAD and 90 minutes reperfusion, the density of the CRC and L-type were determined using ^{3}H-ryanodine and ^{3}H-PN 200 110 as radioligands. Non-ischemic porcine myocardium of the same animals served as control. For determination of the calcium sensitvity, the homogenates were incubated with 12 nM ^{3}H-ryanodine in the presence of different [Ca^{2+}].

Results: Densities of the CRC and L-type were significantly decreased ($p < 0.05$). The calcium senstivity of the CRC was unchanged. Table: Values are means ± SEM postischemic (n = 14) vs control (n = 14). EC_{50} = [Ca^{2+}] at half maximal ^{3}H-ryanodine binding with 95% confidence intervals. Bmax = maximal specific ^{3}H-ryanodine- or ^{3}H-PN 200 110-binding, $^*p < 0.05$ vs control.

	CRC Bmax	EC_{50}	L-type Bmax
postischemic	71.5 ± 7.6*	1.9 (1.81–1.96)	18.6 ± 4.18*
control	107.4 ± 6.5	1.85 (1.7–1.88)	38.1 ± 9.3

Conclusion: The decreased densites of the CRC and L- type in postischemic myocardium could be a contribute of the altered intracellular calcium metabolism.

P1692 On-line assessment of myocardial viability using electromechanical mapping

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Assessment of myocardial viability immediately after diagnostic coronary angiography allows prompt decision-making with regard to therapeutic intervention. The NOGA™ system is a novel catheter-based, nonfluoroscopic endocardial mapping system which allows simultaneous acquisition of both local electrical activity and myocardial contractility. To validate its potential for assessment of viability, 51 pts (41 m, 10 f; 61.4 ± 8.2 years) with coronary artery disease underwent NOGA mapping and perfusion (SPECT, Tc-99m) and metabolism imaging (PET). Analyzed parameters: Amplitude (UV, mV), fragmentation index (FI) of the local unipolar potential, local shortening (LS, %) as a parameter for contractility. The left ventricle was divided into 9 segments.

Results:

SPECT	N	UV/meanSD	FI	LS
Normal	282	11.2 ± 4.9	1.1 ± 0.2	8.2 ± 5.0
Reversible defects/deficits	50	11.6 ± 4.8	1.2 ± 0.2	7.7 ± 7.0
Fixed defects	74	6.4 ± 3.0	1.3 ± 0.2	3.6 ± 4.5
Normal vs reversible		NS	NS	NS
Normal vs fixed		p < 0.001	P < 0.001	P < 0.001

A threshold of 4.5 mV (UV) and a FI > 1.5 identified nonviable tissue (diagnosed by PET) with a specificity of 90% and a sensitivity of 65%.

Conclusion: Electromechanical mapping allows the assessment of myocardial viability in one catheterization procedure. Patients with hibernating myocardium could be immediately revascularized without any time delay.

P1693 Structural and metabolic outcome of prolonged moderate ischaemia in pigs

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It is still a matter of debate whether the chronic contractile dysfunction seen in hibernating myocardium is the result of persistent ischemia (I) or of repetitive episodes of I/reperfusion. Detailed analyses of regional flow and function during controlled I over more than 5 h are lacking. Therefore, in 16 enflurane-anesthetized swine the LAD was cannulated and hypoperfused at constant flow for 24 h and then reperfused for 2 h. Coronary inflow was reduced to decrease regional myocardial systolic wall thickening (WT, sonomicrometry) at 5 min I to 60%. Eight out of 16 swine survived the 24 h I. In 4 survivors (G 1), 14.3 ± 5.5 (SD)% of the myocardium at risk was infarcted (TTC, histology), while in other 4 survivors (G2) the myocardium remained completely viable.

	Control	5 min I	24 h I
CP G1	8.6 ± 1.6	3.1 ± 1.8*	5.7 ± 4.1*
G2	9.0 ± 1.0	3.8 ± 0.8*	8.0 ± 4.8
ATP G1	3.5 ± 0.5	2.6 ± 0.6*	1.9 ± 1.2*
G2	3.8 ± 0.8	2.5 ± 1.2*	3.3 ± 0.7#

*p ≤ 0.05 vs. Control, #p < 0.05 vs G1, 2-way ANOVA

Transmural myocardial blood flow (microspheres) was decreased to the same extent at 5 min I (0.40 ± 0.10 vs. 0.48 ± 0.10 ml/min/g) and 24 h I (0.46 ± 0.14 vs. 0.42 ± 0.10 ml/min/g) in G1 and G2, respectively. Also, the decline of WT at 5 min I (23.9 ± 6.1 vs. 23.6 ± 4.0%) and 24 h I (7.6 ± 5.2 vs. 9.5 ± 3.4%) was similar in G1 and G2. In both groups, myocardial creatine phosphate content (CP, biopsies, μmol/g wet weight) and ATP content were decreased at 5 min I. In G1, CP partially recovered, but ATP content decreased further during 24 h I. In contrast, both CP and ATP contents recovered to almost baseline at 24 h I in G2.

Conclusion: In a subset of swine, the myocardium can adapt to a 24 h I period; i.e. it remains viable and its energy metabolism recovers.

P1694 Uncoupling of mitochondrial oxidative phosphorylation preconditions the isolated rat heart

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Background: Recent studies have implicated the opening of the K-ATP channel, located on the inner mitochondrial membrane, as the final effector in myocardial preconditioning (PC). To further elucidate the role of the mitochondrion in PC we applied the uncoupling agent 2,4 dinitrophenol (2,4-DNP, 50 micromolar, 5 min, 5 min reperfusion) in a model of regional ischaemia (35 min index ischaemia, 120 min reperfusion) in the isolated perfused rat heart. Risk volume and infarct size were delineated using fluorescent microspheres and triphenyltetrazolium staining respectively. Computerised planimetry was used to quantitate volumes and the% infarct within the risk zone was calculated.

Results: Base line heart rate, coronary flow, and left ventricular developed pressure were comparable in controls, PC, and DNP-treated hearts. After 5 min of DNP treatment and 5 min of reperfusion, hearts had a reduced heart rate (215 ± 66 vs. 345 ± 50, $p < 0.001$) which persisted throughout the experiment. Coronary flow and left ventricular developed pressure were similar in the three groups. Measurement of infarct size demonstrated a significant reduction of the infarct/area at risk ratio (I/R ratio: 9.0 ± 5.9 vs. 27.4 ± 6.1% in controls, $p < 0.001$) similar to the effect seen with PC (8.1 ± 3.2%, $p < 0.004$). The mitochondrial K-ATP channel blocker 5-HD (100 micromolar) given for 15 min during DNP exposure elicited irreversible contracture in all hearts tested (n = 4).

Conclusion: Transient uncoupling of the mitochondrial oxidative chain from ATP generation reduces infarct size to a similar extent as PC. This effect might not to be mediated by the mitochondrial K-ATP channel.

P1695 Mismatch of regional perfusion and local electrical activity: a new indicator for viability in chronic ischaemic myocardium?

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A mismatch of regional myocardial function and perfusion has been used to identify viable myocardium. To assess the relationship of local electrogram characteristics and regional perfusion, 21 patients with coronary artery disease and regional LV dysfunction were investigated. Regional perfusion was assessed by Tc-99m-MIBI-SPECT prior to elective coronary artery bypass grafting. During surgery, 102 bipolar epicardial electrograms were simultaneously recorded from the epicardium using a ventricular sock electrode and a commercial mapping system. The electrograms were matched to the findings of Tc-99m-MIBI-SPECT. According to the epicardial grid of the mapping electrode, a 3D-data matrix was computed. A total of 1302 regions (reg.) were analysed.

Tc-99m-MIBI	100–75%	75–50%	50–25%	25–0%
Number of reg.	633	550	98	21
AMP [mV]	8.6 ± 6.6	8.3 ± 7.2	9.3 ± 8.1	$4.1 \pm 4.4^{*\#}$
DUR [ms]	26.4 ± 18.0	29.2 ± 19.3	29.7 ± 20.0	$44.2 \pm 26.1^{*\#}$
A–/Dyskinesia [% reg.]	9	12	23	76

[Mean ± SD, $^{*}p < 0.001$ compared to 100–75% Tc-99m-MIBI uptake, $^{\#}p < 0.01$ compared to 75–50% and 50-25% uptake]

Only regions with severely reduced perfusion (0–25% of max. 99mTc-MIBI uptake) were characterized by low amplitudes and prolonged signal duration of electrograms. However, regions with moderately reduced perfusion (25–75%) did not show any difference in amplitude and duration of local epicardial electrograms compared to regions with normal perfusion.

Conclusion: A mismatch of mild to moderately reduced myocardial perfusion and normal epicardial electrogram characteristics was found in areas of chronic myocardial ischaemia. This mismatch of regional perfusion and electrical activity may reflect myocardial viability and may be helpful to predict recovery of regional myocardial dysfunction after revascularization in patients with chronic ischaemic myocardium.

P1696 A new porcine stent model of hibernation and assessment of myocardial viability

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Aim: A non-surgical porcine stent model of coronary stenosis was developed in order to investigate the relationship between chronic left ventricle (LV) dysfunction and myocardial viability.

Methods: A progressive stent stenosis in proximal LAD was produced by implantation of an oversized polymer coated stent in 21 pigs. Quantitative coronary angiography (QCA) was performed at baseline and at sacrifice. Weekly LV function was evaluated by echo and at the time of developed anterior wall motion abnormality (VMA), dobutamine stress echocardiography (DSE) and PET examination was performed. At sacrifice biopsies were taken for histology and the stented coronary artery segment was dissected for morphometriy.

Results: Based on the results the pigs were divided into three groups: In group I (n = 4), myocardial infarction was found with severe stenosis, severe VMA without improvement with DSE, "matched necrosis" pattern with PET and necrotic cells with histology. In group II and III, animals had viable myocardium in the setting of coronary stenosis, moderate to severe VMA, which exhibited normalization at low dose and sustained improvement or biphasic reaction at high dose with DSE, "matched normal" (group II; n = 9) and "mismatch" (group III; n = 8) pattern with PET. In these groups histologic evaluation showed normal morphology and in a few cells sarcomere loss and glycogen storage was observed. (see table):

PET, Morphometry and ECHO results

	PET: NH3	PET: FDG	Area stenosis	ECHO: FS	ECHO: AWT
I. Matched necrosis	57	72	96	35	21
II. Matched normal	89+	90	65*	56	52+
III. Mismatch	86+	105++	74*	47	41+

+p = 0.005 group I vs II and III, ++p < 0.005 group II vs III, *p < 0.01 group I vs II and III; ECHO values:% of baseline; Abbreviations: FS = fractional shortening, AWT = anterior wall thickening

Conclusion: In group II and III we developed a pig model of myocardial hibernation in the setting of progressive coronary stenosis, with chronic LV dysfunction, with residual inotropic reserve and viable PET patterns. Animals with "matched normal" PET pattern may correspond to repetitive stunning and with "mismatch" to chronic hibernation.

IMAGING OF LEFT VENTRICULAR DYSFUNCTION AND HIBERNATION: NUCLEAR, POSITRON EMISSION TOMOGRAPHY, ECHOCARDIOGRAPHY AND MAGNETIC RESONANCE IMAGING

P1697 Assessment of myocardial viability with dobutamine magnetic resonance imaging and pet in a porcine model of chronic left ventricular dysfunction

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Aim: Different techniques have been applied in a non-sugical porcine stent model of coronary stenosis with chronic left ventricle (LV) dysfunction to identify viable myocardium (VM) and distinguish it from myocardial necrosis.

Methods: A progressive stenosis in LAD was produced by implantation of an oversized polymer coated stent in 14 pigs. Weekly LV function was evaluated by echo. At the time of developed anterior wall motion abnormality (WMA), dobutamine magnetic resonance imaging (DMRI) (at rest and during low dose (LD) and high dose (HD); n = 14) and PET examination (n = 5) were performed. To determine the coronary stenosis quantitative coronary angiography and morphometry were done. At sacrifice biopsies were taken for histology. Additional 6 animals without stent implantation served as normal controls and underwent the same follow-up.

Results: According to the results, the stented pigs were divided into two groups. In group I (n = 5), myocardial infarction was found which was characterized by severe stenosis, akinesia with echo, severely reduced end-diastolic wall thickness, absence of contractile reserve with DMRI and necrotic cells with histology. One animal had PET examination which showed "matched necrosis" pattern.

In group II (n = 9) animals had VM in the setting of coronary stenosis, WMA with echo, decreased wall thickening at rest that exhibited improvement at LD and deterioration at HD (biphasic reaction) with DMRI. The animals that had PET showed viable patterns: "match normal" (n = 1) and "mismatch" (n = 3) patterns. Histology showed normal morphology and in a few cells sarcomere loss and glycogen storage was observed.

Morphometry, Echo and DMRI results (%)

	Morphometry	EHCO			DMRI		
	AS	FS	AWT	IPW	EF at Rest	EF at LD	EF at HD
Gr I.	90*+	9*+	2*+	46	48*	53*	51*
Gr II.	74*	16*	22*	45	52*	55*	45*
Controls	0	34*	46	47	66	70	75

*p < 0.001 vs controls, +p < 0.001 Gr I vs Gr II; Abbreviations: AS = area stenosis, FS = fractional shortening, AWT = anterior wall thickening, IPWT = infero-posterior wall thickening, EF = ejection fraction, LD = low dose, HD = high dose

Conclusions: In our animal model with severe coronary stenosis and chronic LV dysfunction, DMRI accurately detected ischemia and distinguished VM from myocardial necrosis, which was confirmed by PET and histology.

P1698 Myocardial viability assessment by endocardial electroanatomical mapping: validation of a new method by metabolic imaging using F-18 fluorodeoxyglucose positron emission tomography

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Data from animal experiments and first clinical studies suggest that a recently developed catheter-based endocardial mapping system may identify the presence and absence of myocardial viability. To validate the method a comparison with metabolic imaging using PET and Fluorine-18 deoxyglucose (FDG) was performed.

Methods. Twenty-nine patients with prior (≥2 weeks) myocardial infarction were studied. All patients underwent FDG PET and Tc-99m sestamibi SPECT prior to invasive viability assessment. For quantitative nuclear analysis the left ventricle was divided into 25 regions (R) in both PET and SPECT data sets. Regional definition of myocardial viability by SPECT/PET studies was based on previous follow-up studies. The left ventricle was mapped and divided into 12 R, which were assigned to corresponding nuclear R.

Results. Regional unipolar electrogram amplitude (UA) was 12.1 ± 5.1 mV in R with normal perfusion, 9.3 ± 3.8 mV in R with reduced perfusion but preserved FDG-uptake (mismatch, p < 0.001 vs. normal), 9.2 ± 3.7 mV in R with intermediate viability (ns vs. mismatch) and 5.9 ± 2.6 mV in scar R (p < 0.001 vs. normal, p < 0.01 vs. mismatch and intermediate). Eighty-nine percent of the R with a UA of >9.3 mV were viable and 89% of the R with a UA of <6.0 mV were scar. By visual analysis, using 6 mV amplitude as threshold, mapping identified 16/20 (80%) scar areas and 20/21 (95%) areas with preserved FDG uptake.

Conclusion. These data suggest that electroanatomical mapping of the regional unipolar electrogram amplitude can be used for viability assessment in the catheterization laboratory.

P1699 Mild fixed defects on Tl-201 stress-reinjection SPECT do not improve in function post-revascularization

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Thallium-201 stress-reinjection (Tl-201 SR) imaging has a high sensitivity to predict improvement of function post-revascularization, while specificity remains suboptimal. The lower specificity can be related to the definition of viability on Tl-201 SR: both reversible defects and mild fixed defects are considered as indicators of viable myocardium. While both groups may represent viable tissue, their predictive accuracy may not be comparable. Hence, the predictive accuracy of these different viability criteria was evaluated.

Methods: 68 patients (LVEF 34 ± 9%) were studied with Tl-201 SR pre-revascularization. Regional function was studied by resting echo-cardiography (16-segment model) pre- and 3 months post-revascularization. The SPECT data were analyzed semi-quantitatively (polar maps, 16 segments). Dysfunctional segments were classified into 5 groups: 1) normal Tl-201 uptake, 2) mild-moderate (≥50% activity) fixed defects, 3) mild-moderate reversible defects, 4) severe (<50%) fixed defects, 5) severe reversible defects. Group 1, 23, 5 segments were considered viable.

Results: 1088 segments were evaluated; 545 (50%) were dysfunctional, 421 were viable and 124 nonviable on Tl-201 SR. Recovery of function occurred in 11 (9%) nonviable segments and in 170 (40%) viable segments. While incidence of recovery was 44%, 54% and 76% in groups 1, 3, 5, the incidence of recovery was only 15% in group 2 (P < 0.05).

Conclusion: Nonviable segments (group 5) do not recover function. In the viable segments, recovery occurs mainly in segments with normal Tl-201 uptake or reversible defects, while midl-moderate fixed defects do not recover. Mild-moderate fixed defect may represent nontransmural scars.

P1700 Use of ultrasonic integrated backscatter to predict recovery of function following myocardial infarction

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Cyclic variation in ultrasonic integrated backscatter (Cyclic IBS) is reduced in regions of myocardium supplied by the infarct related artery (IRA) following myocardial infarction (MI). This is thought to be due to reduced microvascular pulsatile flow in these regions. Once patency of the IRA has been restored either with thrombolysis or by coronary angioplasty (PTCA), cyclic IBS should return to normal levels provided that microvascular perfusion is re-established. Thirty patients were studied following acute MI. Cyclic IBS was measured in regions of myocardium supplied by the IRA pre thrombolysis (where possible), post thrombolysis, pre discharge and at 1 and 3 months. In addition a wall motion score index (WMSI) was determined by dividing the total wall motion score by the number of segments scored. A scoring system of 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic was used. Following thrombolysis, coronary angiography was performed. If the IRA was occluded PTCA was performed to restore TIMI 3 flow. 28/30 patients had TIMI 3 flow in their IRA pre discharge. An increase in cyclic IBS of >30% pre discharge compared with the initial value was used to predict recovery of wall motion.

Results: All patients had a similar WMSI initially and pre discharge. Patients whose cyclic IBS had improved significantly pre discharge had the greatest improvement in their WMSI at 1 and 3 months. See table below.

Results

No. Patients	Change in cyclic IBS (dB)	Initial WMSI	Pre discharge WMSI	1 and 3 month WMSI
12	0.18 (6%)	1.9	1.9	1.9
18	2.4 (38%)	1.7	1.7	1.17
	p<0.0001	NS	NS	p<0.0001

Conclusions: Cyclic IBS can be used to predict those patients who have restoration of perfusion at a microvascular level post MI and who will have recovery of myocardial function.

P1701 Low-dose versus high-dose dobutamine echocardiography in the assessment of myocardium viability: comparison with pet

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Low-dose (LD) (up to 10 mcg/kg/min) dobutamine echocardiography (DE) is commonly employed to search for viability (VIA). However the higher doses (HD) (up to 40 mcg/kg/min) can give important informations for the presence of VIA. Aim of this study was to compare the accuracy of LDDE alone and LD+HD DE in searching for VIA, using fluorine-18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) as gold-standard.

Methods: twenty-five consecutive pts, with prior myocardial infarction, were studied by DE up to 40 mcg/kg/min (plus atropine, if necessary to reach target heart rate); every pt was also submitted to a 18-FDG-PET within 15 days of the DE. The left ventricle was divided in 16 segments (seg), both in DE and PET examination. VIA was considered present in seg with severe dysfunction at rest plus either of the following signs: 1) improvement at LD, 2) improvement at LD and worsening at HD (biphasic response), 3) improvement only at HD, 4) worsening at HD of a severe basal hypokinesia, excluding akinesia becoming diskinesia that was considered a mechanical phenomenon (ischemic response). The gold standard for VIA was considered a FDG uptake ≥ 50% at PET study.

Results: The sensitivity, specificity and diagnostic accuracy (%) of LDDE alone (sign 1) and LD + HD DE (signs 1 to 4) in searching for VIA are reported in the table.

	Sensitivity	Specificity	Accuracy
LDDE	62	88	72
LD + HD DE	87	77	84

Conclusions: Our study suggest that, in searching for VIA, DE is more accurate if is continued up to the HD, and not stopped at LD.

P1702 A head-to-head comparison of serial dual-isotope Tc-99m-tetrofosmin and 18-FDG SPECT and dobutamine stress echo for the prediction of improvement of ejection fraction in patients with left ventricular dysfunction after revascularization

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Objective: To compare head-to-head the predictive value of dual-isotope simultaneous acquisition [DISA] SPECT with Tc-99m-Tetrofosmin/18-FDG and dobutamine stress echocardiography [DSE] for improvement of left ventricular [LV] ejection fraction after revascularization [CABG] in patients with ischemic LV dysfunction using radionuclide ventriculography [RNV] as a reference.

Methods: 55 patients [46 male], ejection fraction of 32 ± 9% [mean ± SD], were studied with RNV, DISA-SPECT and DSE. Both DSE and DISA-SPECT were scored using a 16-segment model. Viability by DISA-SPECT/DSE was noted if segments with severe dyssynergy at rest showed normal perfusion and FDG uptake, mildly reduced matched perfusion and FDG uptake or mismatches respectively a biphasic, sustained improvement or worsening response during DSE. Non-viability by DISA-SPECT/DSE was scored if severely reduced or absent perfusion/FDG uptake respectively a scar response was present. RNV was repeated 9 months after CABG, improvement was present if RNV increased >5%. Data are presented as odds ratio's [OR] with 95% CI.

Results: 15/55 patients showed an improved EF > 5%. By ROC analysis the optimal number of viable segments per patient related with functional recovery > 5% by DISA-SPECT and DSE was respectively 4 and 3, with a corresponding area under the curve of 69 and 81%. The OR for functional improvement of DISA-SPECT and DSE were respectively 4.1 [1–19] and 9.8 [2–73] [p = 0.03].

Conclusion: These data suggest a higher predictive accuracy of DSE compared to DISA-SPECT for functional improvement after CABG in patients with LV dysfunction.

P1703 Increased detection of viable myocardium using myocardial perfusion analysis in patients with resting wall motion abnormalities

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Assessment of viability in patients with resting wall motion abnormalities during Dobutamine Stress Echocardiography (DSE) may not always be accurate in identifying all viable segments. However, Improvement in myocardial perfusion during DSE detected by quantitative color coded myocardial perfusion analysis (MPA) may identify viable myocardial segments. Therefore, we studied 68 patients who underwent DSE with Optison and Tc99m sestimibi. All patients had also coronary angiograms. The patients were divided into two groups, based on presence or absence of viability using nuclear imaging as gold standard. Wall thickening (WT) and MPA were performed off-line by using custom software. Using regional wall thickening, ratio of normal myocardial wall thickness to the infarcted wall was compared at baseline (WTRb) and peak Dobutamine (WTRp). Similarly, ratio of quantitative myocardial perfusion in the normal and infarct regions was calculated both for baseline (MPAb) and peak Dobutamine (MPAp)

	WTRb	WTRp	MPAb	MPAp
Viable	2.9	2.46	3.4	2.3
Non viable	2.7	2.72	3.7	3.5
p	NS	0.06	NS	0.0001

Accuracy of assessment of viability increased from 62% to 87% when quantitative perfusion analysis is added to visual interpretation of Dobutamine Stress Echocardiography.

Conclusion: Increased perfusion ratio derived from quantitative analysis is very sensitive marker for detecting myocardial viability during contrast DSE compared to wall thickening

P1704 Comparison of intermittent power harmonic contrast imaging and low-dose dobutamine stress echocardiography in predicting recovery of left ventricular function in chronic ischaemic heart disease

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The purpose of this study was to compare MCE using i.v. LevovistTM and DSE in the prediction of functional recovery in patients affected by CAD.

Methods: MCE following i.v. continuous infusion of Levovist (400 mg/ml) at a rate of 300 ml/h associated with triggered end-systolic Power Harmonic Imaging and DSE were performed in 19 patients affected by CAD. Apical 4 and 2 chambers views were recorded. Each segment was evaluated for Contractile Reserve (CR) by DSE and perfusion by MCE. Regional wall motion and perfusion were scored as follows: 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic for systolic wall thickening and 0 = non opacified or patchy opacification, 1 = homogeneous opacification, for perfusion. CR was defined as the presence of improved thickening in at least one abnormal segment during DSE or during a follow-up echocardiogram three months later.

Results: 69 dysfunctional myocardial segments were observed: 35 hypokinetic, 31 akinetic, and 3 dyskinetic. Hypokinetic segments were more likely to exhibit perfusion by MCE (15/35; 43%) and CR by DSE (16/35; 46%) than akinetic segments (perfusion was present only in 1 akinetic segment, whereas CR was seen in 6/31; 19%).

Of the 69 dysfunctional segments, 17 (25%) showed myocardial perfusion by MCE and 22 (32%) had CR by DSE. 28 segments improved at follow-up. Functional recovery occurred in 10 of 17 perfused segments (59%) and did not occur in 34 of 52 segments (65%) that did not show perfusion by MCE. Functional recovery took place in 15 of 22 dysfunctional segments with CR(68%) and in 13 of 47 segments (28%) that did not have CR. The sensitivities, specificities, positive and negative predictive values of MCE and DSE in predicting recovery of LV function are expressed in the table 1.

Table 1

	MCE (%)	DSE (%)
Sensitivity	36	54
Specificity	83	83
Positive predictive value	59	68
Negative predictive value	65	72

Conclusions: MCE with Power Harmonic Imaging and DSE had similar specificities and negative predictive values in predicting LV functional recovery.

P1705 Improved detection of viable myocardium early after myocardial infarction by delayed intermittent myocardial contrast echocardiography

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Detection of viable myocardium in the infarcted zone has both therapeutic and prognostic implications. Myocardial contrast echocardiography (MCE) is a new technique for the detection of microvascular integrity which is a surrogate marker of viable myocardium (VM). We have hypothesised that due to low MBF in the infarcted zone (because of residual stenosis or low cardiac output state following AMI), the rate of destruction of contrast will exceed its replenishment in this zone during shorter intermittent imaging, thereby underestimating VM. Nitrate enhanced MIBI has been shown to reliably detect VM. Accordingly, 30 consecutive patients underwent nitrate enhanced MIBI SPECT and MCE on separate days, early after AMI following thrombolysis. MCE was performed during slow IV bolus (0.5 ml) of Optison and intermittent pulse-inversion imaging was performed at intervals of 1 (early), 5 and 10 (delayed) cardiac cycles. VM was defined as presence of more than 50% MIBI uptake qualitatively in a dysynergic segment (16 segment model). A dysynergic segment was considered viable by MCE when the contrast score was 1 (1 = normal, 2 = reduced, 3 = absent) at any of the triggering intervals. Of a total of 156 dysynergic segments MIBI considered 76 segments as VM of which early MCE detected only 17 (22%) while delayed MCE detected 48 (64%) ($p < 0.001$ vs early MCE). Of the 80 non VM segments by MIBI, early MCE correctly detected 68 (85%) while delayed MCE detected 54 (70%) as non-VM (p = NS). Thus delayed intermittent MCE improved detection of viable myocardium early after AMI.

P1706 Feasibility of intracoronary contrast echocardiography for the evaluation of myocardial viability: correlation with dobutamine stress echocardiography

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Background: Decision-making for revascularization after myocardial infarction is frequently difficult and based on the presence of myocardial viability (MV). Viable myocardium has an intact microvasculature allowing myocardial perfusion. The purpose of this preliminary study was to evaluate intracoronary contrast echocardiography (ICE) as a modality for detecting viable myocardium.

Methods: A coronary stent with a pro-thrombotic surface was implanted in 10 juvenile domestic pigs to cause severe narrowings or occlusions. All animals underwent DSE and angiography at baseline and at 28 days. ICE was performed prior to sacrifice at 28 days. For ICE, 1 ml of Optison® contrast was injected into each coronary artery during continuous 2-dimensional echocardiographic imaging. The echocardiographer was blinded to the angiograms. Videotape images underwent wall thickening (WT) scoring offline. MV was defined on DSE as decreased WT at rest, which improved at low dose dobutamine, or on ICE, as the presence of intramyocardial contrast either from ipsi- or contralateral contrast injection. The hearts were harvested and histology performed.

Results: Myocardial infarctions occurred in 5 pigs histologically and this was associated with a total coronary occlusion in the relevant territory.

Stenosis	100	100	100	100	100	90	40	40	35	20
DSE	N	–	–	+	+	+	+	+	N	N
ICE	N	–	–	+	+	+	+	N	N	N

N = Normal, +,– = presence or absence of myocardial viability.

There was 100% correlation between DSE and ICE in hearts with infarcted areas, whereas there was an 80% correlation in hearts without an infarct. In one heart, DSE was positive but ICE was normal in keeping with the angiographic finding.

Conclusions: ICE correlated well with DSE in the detecting MV in this series and may provide clinical information on MV in the catheterization laboratory during interventional procedures. Studies are ongoing to extend this data.

P1707 Determinants of left ventricular remodelling in remote stage of recanalized myocardial infarction using myocardial contrast echocardiography

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The aim of present study is to elucidate major determinants of left ventricular (LV) remodeling in the remote stage of recanalized anterior myocardial infarction (MI).

Methods: Seventy two patients who underwent left ventriculography both in the acute stage (day 0) and remote stage (3 to 15 months) with recanalized anterior MI were studied. Serial myocardial contrast echocardiography using selective coronary infusion of sonicated contrast material was performed on day 0 (d0), day 1 (d1), and in the chronic stage (c) (3 to 4 week after reperfusion (R)). Relative size of initial risk area (RA ratio) and microvascular integrity (peak gray scale ratio (PGSR)) within the initial risk area were determined using computed analysis. Age, Elapsed time of recanalization (ET), Collateral grade before R (Coll) (grade 0 to 3), TIMI grade flow after R on d0, Left ventricular regional wall motion (SD/chord) on d0 (RWM), re-elevation of ST segment (ST re-ele) immediately after R, % diameter stenosis using QCA analysis on d0 (%DS), RA ratio, and PGSR (d0), or PGSR (d1), or PGSR (c) were determined as independent variables. Further, LV remodeling (i.e., LV end-systolic volume on remote stage/LV end-systolic volume on d0 is grater than 1.2) was determined as dependent variable, and multiple logistic regression analysis was performed.

Results: Results were shown on the following table.

Factor	χ^2	P value	χ^2	P value	χ^2	P value
Age	0.39	0.53	1.73	0.18	0.49	0.48
ET	0.48	0.48	0.05	0.82	0.28	0.59
Coll	2.59	0.11	2.28	0.13	0.39	0.53
TIMI	0.84	0.36	0.84	0.36	1.38	0.24
RWM	4.83	0.03	4.28	0.04	3.80	0.05
ST re-ele	0.44	0.50	2.88	0.09	0.002	0.96
% DS	2.86	0.09	2.88	0.09	0.63	0.43
RA ratio	4.64	0.03	4.02	0.05	2.53	0.11
PGSR (d0)	3.97	0.04	–	–	–	–
PGSR (d1)	–	–	4.86	0.03	–	–
PGSR (c)	–	–	–	–	3.48	0.06

Conclusions: Both relative size of the initial risk area and microvascular integrity within the initial risk area in the acute stage of MI are more important predictors of left ventricular remodeling in the remote stage of MI than those in the chronic stage of MI.

P1708 Serial assessment of cardiac remodelling after myocardial infarction in rats by MRI

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Changes in cardiac geometry and function after myocardial infarction (MI) are subject of intense research. In the present study we investigated the serial morphologic and functional changes after left coronary artery ligation in the intact rat using Magnetic Resonance Imaging (MRI).

MRI-scans were done 4, 8, 12 and 16 weeks after MI on a 7 T-scanner using an ECG-triggered Cine-FLASH-sequence: 16 contiguous short axis slices, slice thickness 1 mm, echo-time 1.2 ms, in plane resolution 230 μm. In 11 Wistar rats MI-size, left ventricular (LV) mass, LV volumes, cardiac output (CO), ejection fraction (EF), enddiastolic remote wall- (ed wth) and scar thickness (scar) and systolic myocardial wall thickening (SWT) were compared to 4 sham operated rats.

Results for 4 and 16 weeks are shown in the table. Mean MI-size was 30.2 ± 3.1%. EDV of infarcted rats at 16 weeks was correlated to MI-size ($r = 0.85$, $p = 0.001$).

	4 weeks		16 weeks	
	control	MI	control	MI
LV mass (mg)	500.6 ± 5.9	531.8 ± 19.3	511.9 ± 5.8	863.3 ± 34.4$^{*\$}$
EDV (μl)	329.8 ± 10.6	591.3 ± 40.8$^{\$}$	339.7 ± 16.4	711.3 ± 65.7$^{*\$}$
ed wth (mm)	1.44 ± 0.02	1.28 ± 0.06	1.46 ± 0.03	1.9 ± 0.05$^{*\$}$
SWT (%)	65.1 ± 5.8	53.6 ± 6.2	64.3 ± 12.3	31.7 ± 3.8$^{*\$}$
Scar (mm)		0.97 ± 0.05		0.47 ± 0.05*
EF (%)	69.0 ± 1.6	36.5 ± 2.8$^{\$}$	68.0 ± 1.9	34.2 ± 2.2$^{\$}$
CI (ml/kg*min)	256.7 ± 18.2	225 ± 7.9$^{\$}$	280.2 ± 16.12	227.9 ± 16.3$^{\$}$

Data is given in mean ± SEM. $^{*}p < 0.01$ vs. 4 weeks of the same group, $^{\$}p < 0.05$ vs control at the same time, EDV: enddiastolic volume. CI: cardiac index (CO/bodyweight).

The data are in good accordance to previous invasive and post- mortem studies. MRI is well suited for non-invasive sequential studies of LV remodeling post MI.

EXPERIMENTAL HEART FAILURE AND NEUROHORMONAL CONTROL OF HEART FAILURE

P1709 A novel closed chest in vivo assay system of post-infarction remodelling in the rabbit

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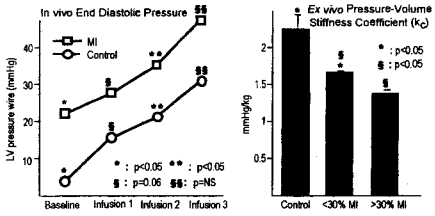
An intact pericardium plays a crucial role during ventricular remodelling. We present a novel closed chest model of rabbit myocardial infarction (MI) and characterise the subsequent changes in left ventricular (LV) geometry and function.

Methods: The right carotid artery of adult NZW rabbits was canulated and coronary angiography performed prior to positioning of a 0.014′ thrombogenic coil in the proximal circumflex artery. 40% of rabbits (n = 8) survived the infarct and were recanulated at 100 days. A 0.014′ pressure tipped wire measured LVEDP following 3 × 100 mls infusion of colloid. A pressure sensitive balloon was secured in the LV of excised hearts into which saline was infused at 3 mls/min. Chamber stiffness (k_c) was derived from the pressure-volume relationship. Cardiac weight, dimensions and infarct size were recorded. Controls (n = 7) did not undergo coil deployment.

Results: Mean LV mass, length, and diameter significantly increased in infarcted rabbits compared to control (7.03 v 6.06 g, 32.55 v 27.19 mm, 13.36 v 8.10 mm; all $p < 0.05$). Rabbits with MI > 30% showed a trend towards increased LV mass and diameter compared to those with MI < 30% (7.69 v 6.53 g, 15.76 v 11.56 mm), and a significant increase in LV length (35.98 v 29.97 mm; $p < 0.05$).



Conclusions: We have developed a rodent model of MI that obviates the need for pericardial excision. This assay system displays fidelity to key end points that can be related to the failing human heart and may provide a powerful tool in the investigation of experimental heart failure.

P1710 Effect of β-blockers on free radical induced cardiac contractile dysfunction

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Objective: Effects of hydroxyl radicals (OH•) on human myocardial contractility and on sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) activity as well as effects of the β-receptor antagonists metoprolol, carvedilol and its metabolite BM-910228 were examined.

Methods: Isometric force of contraction was determined in electrically stimulated (1 Hz, 37°C) isolated human myocardial preparations. SERCA activity was determined in isolated myocardial membrane preparations.

Results: H_2O_2 (1 mmol/l) and Fe^{3+}-nitrilotriacetic acid (Fe^{3+}-NTA, 0.1 mmol/l) used for generation of OH• induced a decrease in basal force of contraction and an increase in diastolic tension in atrial and left ventricular myocardial preparations. After challenge with OH•, the maximum positive inotropic response to Ca^{2+} (1.8–15 mmol/l) was decreased by 60% and by 39%, respectively. Effects of OH• could be blocked by catalase. Both, carvedilol and its metabolite BM-910228 significantly attenuated the OH• induced impairment of the inotropic response to Ca^{2+} in atrial myocardial preparations. Metoprolol had no significant effect. The stimulation frequency (0.5–3.0 Hz) dependent increase in force of contraction and decrease in diastolic tension was abolished after exposure of atrial trabeculae to OH•. In parallel, SERCA activity was decreased by OH• concentration-dependently as determined in myocardial membrane preparations. BM-910228 partially restored the force-frequency relationship and preserved SERCA activity.

Conclusions: OH• radicals induce an impairment of contraction and relaxation and an attenuation of the force-frequency-relationship in human myocardium, which could be due to an inhibition of SERCA. Carvedilol and BM-910228 partly prevented OH• induced contractile dysfunction. These observations could explain the improvement of ejection fraction in heart failure trials with carvedilol without a restoration of β-adrenoceptor density.

P1711 Increased xanthine oxidoreductase activity in hypertrophic and failing heart

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Objective: The molecular basis for heart failure is unknown, but oxygen free radicals have been implied in the genesis of this disease. Xanthine oxidase as a source of free radicals in human heart is controversial. However, recent evidence indicates that explanted human heart contains desulfo xanthine oxidoreductase, which uses NADH as substrate and generates superoxide. We tested therefore the hypothesis that xanthine oxidoreductase activity increases in hypertrophic and failing heart.

Methods: We used two rat models for our study: Group 1) Animals were treated with a bolus injection of monocrotaline, which induces right ventricular hypertrophy in some and dilated right ventricular failure in other animals; Group 2) Animals underwent coronary ligation to induce myocardial infarction. This leads to compensated heart failure at three weeks and decompensated heart failure at eight weeks post-infarction. In both models, also animals were studied in the pre-failing stage, i.e., during the development of cardiac hypertrophy. Xanthine oxidoreductase activity was measured at 30°C in myocardial extracts with 0.1 mM xanthine; xanthine disappearance and urate formation were detected at 280 nm after high performance liquid chromatography. Data analysis took place by ANOVA. Data are presented as means ± SEM.

Results: In Group 1, the hypertrophic hearts showed a non-significant 36% higher enzymatic activity in right than in left ventricles. The hearts showed also a larger xanthine oxidoreductase activity in failing right ventricle than in the unaffected left (65 ± 5 vs. 47 ± 3 mU/gram wet weight; n = 6–7, $P < 0.05$). In Group 2, activities after three and eight weeks were similar and therefore combined for statistics. The activity in the left ventricle increased from 29.4 ± 1.4 mU/g (n = 6) in sham-operated rats, to 48 ± 3 and 80 ± 6 mU/g (n = 8, $P < 0.05$ vs. sham) in the vital and infarcted left ventricular part of failing hearts, respectively. Even right ventricular activity was 30% higher (NS) in failing hearts than in sham-operated ones. In failing hearts, enzymatic activity in left ventricle increased by 46% ($P < 0.05$) compared with that in right ventricle.

Conclusion: In two rat models of heart failure, xanthine oxidoreductase activity increased in failing ventricle compared to internal (unaffected ventricle) and external controls (sham). This could indicate that oxygen free radicals, generated by (the desulfo form of) this enzyme, play a role in the etiology of the disease.

P1712 Endothelium-dependent and -independent vasoreactivity of cerebral arteries in experimental heart failure

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Endothelial dysfunction of peripheral arteries in patients with heart failure and in experimental models has been described for the aorta, coronary arteries and skeletal muscle vascular bed. However, it has not yet been elucidated whether endothelial dysfunction is also present in cerebral vessels, which might contribute to the increased number of cerebrovascular events associated with heart failure.

Methods: We investigated in vitro the reactivity of the aorta and the basilar artery from rats with heart failure due to large myocardial infarction (≥45% of left ventricle) 12 weeks following ligation of left coronary artery (MI) or sham-operation (SO).

Results: In the aorta, the concentration-response curve of the endothelium-dependent, acetylcholine-induced relaxation (following precontraction with phenylephrine) was significantly shifted to the right and the maximum relaxation was attenuated (ED_{50} (−log) 6.58 ± 0.07, R_{max} 86 ± 3%) as compared to SO (7.12 ± 0.05, 97 ± 1%). In contrast, in the basilar artery (following precontraction with serotonin) there was no difference neither in acetylcholine (10 nM–100 μM)-induced relaxation (MI: ED_{50} (−log) 6.7 ± 0.1, R_{max} 59.5 ± 5.5%, SO: ED_{50} 6.7 ± 0.1, R_{max} 61.3 ± 4.3%) nor receptor-independent relaxation induced by the calcium ionophore A 23187 (10 nM–100 μM; MI: ED_{50} 5.8 ± 0.1, R_{max} 58.7 ± 5.4%, SO: ED_{50} 5.8 ± 0.2, R_{max} 61.8 ± 7.6. In addition, endothelium-independent relaxation induced by sodium nitroprusside was not affected in basilar artery following infarction. Moreover, contraction elicited by KCl (124 mM), serotonin (1 μM) or endothelin (1 pM–10 nM) was not altered in MI.

Conclusion: These data show that rats with chronic heart failure following myocardial infarction do not develop changes in basilar artery reactivity despite endothelial dysfunction in other vascular beds.

P1713 In vivo magnetic resonance micro-imaging in two murine models of cardiac failure

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Purpose of our study was to assess the changes of left ventricular (LV) geometry, myocardial function and mass in two mouse models of cardiac failure: myocardial infarction and aortic banding.

Methods: We investigated C57bl/6 mice two weeks after surgical ligature of LAD (n = 5) or aortic banding (n = 5) by *in vivo* ECG-gated magnetic resonance imaging (MRI). Each group was compared to an age matched reference group by MRI studies 2 weeks after sham operation. (n = 5 each).

Results: MR measurements in mice with *myocardial infarction* revealed a significant increase in end-diastolic volume (EDV, 145.3 ± 12.3 μl vs. sham 64.6 ± 5.3 μl, mean ± SEM, $p < 0.001$) and end-systolic volume (ESV, 111.5 ± 15.6 μl vs. sham 27.1 ± 2.6 μl, $p < 0.001$). There was a significant decrease of ejection fraction (EF, 25 ± 5% vs. sham 58 ± 3%, $p < 0.001$), whereas stroke volume (SV, 33.8 ± 4.2 μl vs. 37.5 ± 4.0 μl, $p = 0.54$) and cardiac output (CO, 17.3 ± 3.5 ml vs. sham 18.6 ± 1.1 ml) were not significant different from sham operated mice. The end-diastolic LV anterior wall was significantly thinned (EDAW, 0.48 ± 0.04 mm vs. sham 0.93 ± 0.03 mm, $p < 0.001$), the MRI determined infarct size was 53 ± 5%. Comparison of LV mass (LVM) showed no significant differences between infarcted and sham operated mice.

MR measurements in mice 2 weeks after *aortic banding* showed an 59% increase of LVM (121.9 ± 9.1 mg vs. sham 76.8 ± 8.0 mg, $p < 0.01$) and a 53% increase of LV ED wall thickness (1.13 ± 0.07 mm vs sham 0.74 ± 0.06 mm, $p < 0.01$). However, LV SV (28.6 ± 2.4 μl vs. sham 35.1 ± 4.0 μl, $p = 0.04$) and EF (47 ± 4% vs. sham 70 ± 5%, $p < 0.01$) were significantly decreased in aortic banded mice.

Conclusions: MRI revealed significant geometric and functional changes in two murine models of cardiac failure 2 weeks after the surgical procedure. The exact time course of LV remodeling and hypertrophy in these models remains to be evaluated in detail.

P1714 Interleukin-1b and TNF-a in skeletal muscle biopsies of patients with chronic heart failure: relation to the expression of inducible nitric oxide synthase

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Recently, an inverse correlation between the expression of inducible nitric oxide synthase (iNOS) and functional work capacity was described in skeletal muscle (SM) of patients (pts) with chronic heart failure (CHF). According to in vitro studies the expression of iNOS is induced by cytokines, especially TNF-a and IL-1b. The present study was designed to examine if also in vivo in the SM of CHF pts cytokines may be responsible for the induction of iNOS expression.

Method: SM biopsies and serum was obtained from forty-four pts with CHF (EF < 40%, NYHA II–III). The expression of iNOS, IL-1b and TNF-a in SM was visualized by immunohistochemistry and quantified by videodensitometry. The serum concentration of IL-1b and TNF-a was evaluated by Elisa. For in vitro experiments L6 rat skeletal myoblast or myocytes were incubated with IL-1b and/or TNF-a and iNOS induction was evaluated by quantitative RT-PCR and Western-blot.

Results: Immunohistochemical analysis of SM biopsies revealed a linear correlation between iNOS and IL-1b expression ($r = 0.66$; $p < 0.0001$) but not between iNOS and TNF-a. Measuring serum concentrations of cytokines no correlation was found between iNOS expression and IL-1b or TNF-a. The necessity of IL-1b for the induction of iNOS expression in SM was confirmed by cell culture experiments.

Conclusion: Cytokines, in particular IL-1b, regulate at least partially the expression of iNOS in SM of pts with CHF. However, serum concentrations of cytokines fail to predict the level of iNOS expression in SM.

P1715 Postischaemic heart failure in tumor necrosis factor alpha deficient mice

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There is indirect evidence that tumor necrosis factor alpha (TNF) is involved in the development of heart failure. To directly investigate this issue, we assessed postischemic LV dysfunction in TNF deficient mice. In sixty-four mice (30 controls, 16 TNF-deficient (TNF−/−), 12 sham control, 6 TNF−/−sham), myocardial infaction was produced by 90 minutes of coronary artery occlusion followed by 2 weeks of reperfusion. At day 14, regional (anterior and posterior wall thickening, AWT, PWT) and global (LV systolic fraction) LV function was assessed by echocardiography (Acuson Sequioa system). Acute myocardial infarction resulted in regional and global contractile dysfunction (table, *$p < 0.05$ vs PWT, **$p < 0.05$ vs sham).

Table

	AWT (%)	PWT (%)	LVSF (%)
Control (n = 30)	36 ± 6*	52 ± 7	28 ± 2**
TNF−/− (n = 16)	32 ± 5*	47 ± 7	26 ± 2**
Sham control (n = 12)	50 ± 4	57 ± 3	44 ± 3
Sham TNF−/−(n = 6)	55 ± 6	52 ± 8	40 ± 5

Yet, TNF deficient mice failed to develop reduced regional and global systolic dysfunction when compared to controls. This suggests that TNF alpha is not a major determinant of the development of heart failure in this model.

P1716 Cardiac troponin T as a marker of experimentally induced cardiomyopathy

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The cardiac effects of antineoplastic drugs were investigated in rabbits *in vivo* from the viewpoint of release of cardiac troponin T (cTnT) measured using Elecsys Troponin T STAT Immunoassay – Boehringer Mannheim (Germany).

During development of daunorubicin-induced cardiomyopathy (daunorubicin 3 mg/kg i.v., once a week, 10 weeks, n = 13), cTnT was within physiological range (i.e. cTnT < 0.1 μg/l) at the beginning of experiment, but after the 8*th* administration cTnT was significantly higher (0.31 ± 0.11 μg/l) in 46% animals with premature deaths compared with the rest of group (0.04 ± 0.03 μg/l). In the control group, the levels of cTnT were always lower than 0.1 μg/l during the experiment. Following administration of a new drug Oracin (6-[2-(2-hydroxyethyl)aminoethyl] dioxo-5,6-dihydro-11H-indeno[1,2-c]-isoquinoline hydrochloride, 10 mg/kg i.v., once weekly, 10 administrations, n = 7), no increase in cTnT levels was present. These findings correlated with the fact that only mild changes in the PEP:LVET index were found and no premature death of animals occurred in the Oracin group. Histological examination of the myocardium revealed only a very slight damage in the Oracin group in comparison with a very marked, diffuse damage in the daunorubicin group. The combination of daunorubicin and Oracin (n = 7) did not caused significant deterioration of the examined parameters which is very important from the clinical point of view.

It is possible to conclude that cTnT is a useful marker for the prediction of experimentally induced anthracycline cardiomyopathy and for the evaluation of cardiotoxic (and, possibly, cardioprotective) effects of new drugs.

P1717 Beneficial renal effects of adrenomedullin infusion in experimental heart failure

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Introduction: Adrenomedullin (AM) is a peptide hormone with vasodilating and diuretic properties. While the actions of natriuretic peptides as atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are blunted in heart failure, the hemodynamic and renal effects of adrenomedullin are imperfectly defined.

Methods: We used the aortocaval shunt in male Wistar rats as a model of experimental heart failure and infused cumulative doses of human adrenomedullin (0.05, 0.1, 0.5 and 1 $\mu g/kg \times min^{-1}$) over 20-minute periods.

Results: In controls, AM induced a dose-depending decrease in arterial blood pressure by 6.0 ± 0.9 to 21.6 ± 3.2 mmHg. In shunt-operated rats, the hypotensive response was blunted ($p < 0.01$ vs controls). The urine flow rate, which was diminished in rats with aortocaval shunt, was raised and normalized by AM administration. Similarly, sodium excretion increased from 14.4 ± 2.8 to 23.6 ± 5.0 mmol/20 min after AM. In contrast to the blunted hypotensive effect, the renal blood flow increased in both groups (controls: 8.4 ± 1.0 to 13.1 ± 1.0 ml/min, $p < 0.001$; shunts: 5.1 ± 0.6 to 8.7 ± 1.4 ml/min, $p < 0.01$) and was paralleled by a significant increase in glomerular filtration rate in either group (controls: 2.4 ± 0.2 to 3.5 ± 0.3 ml/min, $p < 0.01$; shunts: 1.8 ± 0.3 to 3.0 ± 0.6 ml/min, $p < 0.01$).

Conclusion: Our data indicate a beneficial renal action of adrenomedullin in parallel with a mild hypotensive effect in heart failure. Thus, the infusion of adrenomedullin might have potential therapeutic value in the management of heart failure.

P1718 Soluble adhesion molecules as unique molecular markers for atherosclerosis and coronary heart disease

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Background: Binding and recuritment of circulating leukocytes to the vascular endothelium and further migration into the subendothelial spaces are the major processes in the development of atherosclerosis and are mediated through a diverse family of cellular adhesion molecules that are expressed on the surface of vascular endothelial cells. This study was designed to determine the ability to use circulating cellular adhesion molecules as a molecular of atherosclerosis and coronary heart disease (CHD).

Methods: plasma levels of vascular cell adhesion molecule-1 (sVCAM-1), endothelial-leukocyte adhesion molecules-1 (sE-selectin) and intercellular adhesion molecule-1 (sICAM) was evaluated in 31 patients with CHD, 35 patients with carotid atherosclerosis (CAA) and 20 control subjects.

Results: Higher levels of sE-selectin and sICAM-1 were observed in patients with CHD compared to control subjects (sE-selectin 39.3 Vs 32.8 ng/ml; sICAM-1 293.0 Vs 240.3 ng/ml). In CAA patients significant increase in sE-selectin (43.0 Vs 32.8 ng/ml) and in sICAM-1 (288.2 Vs 240.3 ng/ml) compared to control group. Levels of sVCAM-1 were not significantly different among all studied groups. Logistic regression analysis results showed that sICAM-1 and sE-selectin in patients with CHD and CAA were independent of other known CHD risk factors.

Conclusion: we defined significant relationship of sICAM-1 and sE-selectin levels with the burden of atherosclerosis as measured by carotid B-model ultrasound, and CHD indicating that, they might serve as a molecular markers of atherosclerosis and CHD development.

P1719 Relationship between angiotensin converting enzyme inhibitor dosages and the suppression of the renin angiotensin pathway in chronically treated patients with congestive heart failure

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An incomplete blockade of the renin angiotenin (RA) axis by long term angiotensin converting enzyme (ACE) inhibition in congestive heart failure (CHF) has been reported. However, recent studies have emphasized the efficacy of high-versus low-doses of ACE inhibitors (ACEI) in CHF.

We studied the relationship between the suppression of the RA axis and the ACEI dosages in 198 patients with CHF, chronically treated by ACEI. For each patient, ACEI dosage was standardized as percent of maximal recommended dosage for each compound. Plasma renin activity (PRA), plasma angiotensin II (AII), and plasma aldosterone (Ald) were measured in all the patients. NYHA functional class, furosemide dosages, plasma sodium, plasma norepinephrine (NE), plasma atrial natriuretic peptide and plasma endothelin-1 were also analysed.

No correlation was observed between PRA, plasma AII and plasma Ald, and ACEI dosage. Multiple regression analysis showed that (1) PRA depended on plasma sodium ($\beta = -0.19$, $p = 0.008$) and on plasma NE ($\beta = 0.19$, $p = 0.011$), (2) plasma AII depended only on PRA ($\beta = 0.28$, $p = 0.0004$) and (3) plasma Ald depended on PRA ($\beta = 0.2$, $p = 0.006$) and on plasma NE ($\beta = 0.24$, $p = 0.002$).

Thus, in chronically treated patients with CHF, there is no relationship between ACEI dosage and the degree of suppression of the RA axis. Persistent activation of this axis seems partly modulated by sympathetic activation. This finding argues for the use of combined neurohormonal blockade in addition to ACEI in the treatment of heart failure.

P1720 The effects of chronic, sustained-release moxonidine therapy on clinical and neurohumoral status in patients with heart failure

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CHF is characterized by neurohumorally mediated vasoconstriction and tachycardia, and plasma norepinephrine (PNE) is an important predictor of mortality and morbidity. Moxonidine selectively stimulates imidazoline receptors which centrally inhibit sympathetic outflow and potently suppress levels of circulating PNE.

Methods: This study evaluated 25 CHF patients (age = 69 ± 7 years, 20 males) in NYHA class II or III, stabilized on chronic therapy with diuretics and ACE inhibitors. Mean EF was 28 ± 7% and mean PNE concentration was 343 ± 132 pg/ml at baseline. Patients were randomized and titrated in a double-blind fashion to 12 weeks of oral placebo (n = 9) or sustained-release moxonidine 0.9 mg bid (n = 16). Patients' clinical status was monitored and blood was sampled weekly and twice for 12 hours at baseline and on chronic therapy, and daily following abrupt withdrawal for PNE, plasma renin activity and serum moxonidine. Heart rate and systemic arterial BP were recorded by ambulatory BP and Holter monitoring at baseline, on chronic therapy, and for 60 hours following withdrawal. Heart rate variability was assessed using standard, time-domain variables.

Results: All patients reached the target dose without drug-related serious adverse events. Apart from dry mouth, the side-effect profile (including orthostatic hypotension) of moxonidine was not significantly different from placebo. PNE was substantially reduced at the maximum dose (0.9 mg BID) by 50% ($p = 0.0005$) as compared to placebo. A significant reduction in heart rate ($p = 0.01$) was observed. Systolic pulmonary arterial pressures, as assessed by Doppler, were reduced ($p < 0.05$). A trend towards a reduction in ventricular arrhythmia during chronic therapy was seen. A 39% increase in the standard deviation of normal-to-normal intervals (SDNN) was observed during chronic moxonidine therapy ($p < 0.001$) with a significant correlation between this improvement and the reduction in PNE ($r = -0.69$, $p < 0.05$). Abrupt withdrawal of chronic therapy resulted in rapid increases in PNE, BP and heart rate to or above baseline.

Conclusions: Twelve-week therapy with sustained-release moxonidine in CHF was well-tolerated with substantial and sustained reductions in PNE and attenuation of tachyarrythmias. Due to the observed effects of moxonidine discontinuation, tapering of therapy is recommended. Trials appropriately designed to evaluate the efficacy of long-term moxonidine therapy on morbidity and mortality in CHF are warranted.

P1721 Noradrenaline stimulates cardiomyocytes to produce interleukin-6, indicative of a proinflammatory action, which is suppressed by carvedilol

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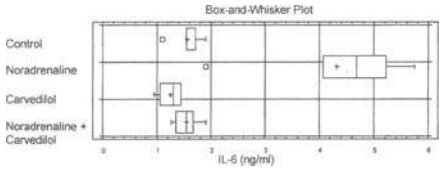
It is a matter of debate, how cytokine release is triggered in severe heart failure. Potential players include a neurohumoral dysbalance with an enhanced sympathetic tone or an overspill of cytokines from the failing heart itself. Here we report that noradrenaline *in vitro* stimulates the release of interleukin-6 (IL-6) from cardiomyocytes (CM), in line with a previously unrecognized direct proinflammatory effect of noradrenaline on CM.

Methods: Spontaneously beating neonatal rat CM were incubated for 8–24 h in serum-free medium supplemented with or without noradrenaline (0.1–1 μM), in the absence or presence of carvedilol (10 μM). In some experiments, an inhibitor of phosphodiesterase (3-isobutyl-1-methylxanthine, IBMX, 0.5 mM) or TNF-α (20 ng/ml) was simultaneously added. The adrenergic response was documented by monitoring the beating rate. Inflammation was assessed by the IL-6 (bioassay) content of culture supernatants.

Results: In numerous experiments, noradrenaline significantly enhanced IL-6 content of CM supernatants (figure). The IL-6 release was more pronounced in the presence of IBMX or TNF-α, but suppressed by carvedilol.



Conclusion: The release of proinflammatory cytokines in heart failure may be directly linked to the enhanced sympathetic tone.

P1722 Evidence for a positive inotropic effect of bradykinin in human atrial muscle preparations

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One essential difference between a therapy with angiotensin converting enzyme (ACE) inhibitors and angiotensin-antagonists is the increase in bradykinin concentrations by ACE-inhibitors. Whereas the vasodilating effect of bradykinin is well known, its myocardial effect is unknown or controversial. We investigated the effect of bradykinin on maximum developed force of isometrically contracting right atrial human muscle preparations (60 beats/min; 37° C).

Bradykinin without pretreatment (n = 18) had no inotropic effect at all. Assuming that the myocardial ACE may inactivate bradykinin, preparations (n = 14) were pretreated with enalaprilate (10^{-6} M). In 8 preparations a positive inotropic effect was observed: Maximum developed tension increased by 34 ± 6% ($p < 0.05$) at 10^{-5} M bradykinin. This effect was blocked by propranolol (10^{-5} M).

Conclusions: Bradykinin has a positive inotropic effect in the majority of human atrial preparations, which can be explained by the release of endogenous catecholamines. This finding may be of great importance regarding the clinical efficacy of ACE-inhibitors and AT-receptor antagonists.

P1723 Plasma brain natriuretic peptide as a biochemical marker for physiological pacing

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Cardiac natriuretic peptides are reported to reflect various hemodynamic changes. Plasma brain natriuretic peptide(BNP) has been found to be more sensitive than ANP for predicting hemodynamic abnormalities. We investigated whether or not plasma BNP is influenced by different pacing modes or electrical stimulation.

Methods: Subjects consisted of 223 permanent pacemakers patients with sick sinus syndrome or a high degree of atrioventricular block. The patients with atrial fibrillation or spontaneous beats were excluded from the study. The implanted pacemakers were 52 VVI, 30 AAI and 82 DDD types. We selected 20 age-matched normal subjects who demonstrated atypical chest pain with normal coronary angiograms. Plasma BNP and ANP were measured at a rate of 70 beats/min after 45 minutes in the supine position. Under ECG monitoring, the pacing mode was switched from DDD to VVI in 12 patients and from DDD to AAI in 4 patients with a dual-chamber pacemaker. Plasma ANP and BNP levels were also measured 30, 60 min and 1 week after mode switching. Plasma ANP and BNP levels were both significantly higher in the non-physiological pacing group than in the physiological pacing group(ANP: 66.8 ± 6.93 vs 30.88 ± 1.45 pg/ml, $p < 0.0001$, BNP: 74.6 ± 8.38 vs 22.5 ± 1.93 pg/ml, $p < 0.0001$, respectively). Both ANP and BNP levels were similar in the DDD and AAI pacing groups. One week after switching from DDD to VVI, plasma ANP and BNP levels increased significantly, however no significant changes were observed after switching to AAI. Based on univariate regression analysis of 13 non-invasive clinical parameters, ejection fraction, pressure gradient of tricuspid regurgitation and plasma ANP and BNP correlated significantly with physiological pacing($p = 0.0056$, $p < 0.05$, $p < 0.0001$, $p < 0.0001$, respectively).Based on the final stepwise multivariate regression analysis, only low plasma BNP correlated significantly with physiological pacing.

In conclusion, plasma BNP, similar to ANP, is influenced by the pacing mode, but is not influenced by electrical stimulation. In addition, low plasma BNP is important in relation to physiological pacing.

P1724 Prognostic value of endothelin peptides in patients with heart failure

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In addition to endothelial cells, endothelin-1 (ET-1) is also synthesized by epithelial cells in the kidney and is excreted in urine. Renal ET-1 is involved in fluid handling. An increased plasma concentration of ET-1 in congestive heart failure has been found to be associated with a poor prognosis. The aim of this study was to investigate urinary excretion of ET-1 in patients with heart failure, in the different functional NYHA classes, and its prognostic value.

We prospectively studied, for a mean follow-up period of 3.8 years, 158 patients with heart failure classified at enrollment according to NYHA criteria (class I, n = 12; class II, n = 44; class III, n = 68; and class IV, n = 34). Blood and urine samples were collected for measurement of daily urinary ET-1 and big ET-1 excretion and for plasma ET-1, big ET-1, ANP, AVP, and PRA assays. All collections were performed at least 48 h after ACE-inhibitors and diuretics withdrawal. Twenty healthy controls of equivalent age were also investigated.

Plasma concentration and urinary excretion of ET-1 in NYHA class I patients were not significantly different from those found in controls. In NYHA class II patients urinary ET-1 excretion, but not plasma ET-1 concentration, was significantly increased vs controls (9.6 ± 4.1 vs 1.7 ± 0.8 ng/gUC, $p < 0.001$, for urine; 0.77 ± 0.26 vs 0.72 ± 0.22 pg/ml, ns, for plasma). ANP plasma concentration was also enhanced in class II patients ($p < 0.01$), whereas in those patients PRA and AVP were not significantly higher than in controls. Plasma concentration of ET-1 was increased in patients in III NYHA class ($p < 0.01$) and urinary ET-1 remained elevated. During the follow-up period 76 patients died from a cardiac cause. At stepwise multivariate Cox proportional hazards regression analysis only urinary ET-1 excretion was significant independent predictor of functional class worsening ($p < 0.0001$). Conversely, plasma big ET-1 and ET-1 ($p < 0.0001$ for both), but not urinary ET-1, PRA, ANP and AVP resulted significantly independent predictors of mortality.

In conclusion 1) urinary ET-1 excretion increased in the early phase of heart failure, and 2) was an independent predictor of clinical worsening, whereas 3) high plasma levels of ET-1 and big ET-1 were independent predictors of mortality.

P1725 Elevated plasma norepinephrine levels in endstage heart failure are significantly correlated to upregulation of Na^+/Ca^{2+} exchanger protein levels

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Recent studies reported upregulation of sarcolemmal Na^+/Ca^{2+} exchanger (NCX) and downregulation of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) gene expression in terminal cardiac failure. Alterations in gene expression could derive from neurohumoral activation.

Plasma levels of norepinephrine (NE), epinephrine (E), atrial natriuretic peptide (ANP), plasma renin activity (PRA), aldosterone (ALD), tumor necrosis factor (TNF)-alpha, and TNF-receptors 1 and 2 (TNF-R1, TNF-R2) were determined in 26 patients suffering from endstage heart failure in the hours preceding heart transplantation. Protein abundance of NCX and SERCA was determined after cardiectomy by western blot analysis of myocardial samples. There was a significant positive correlation between NE and NCX protein levels ($r = 0.58$, $p < 0.004$). Moreover, NE plasma levels were significantly correlated to cardiac index ($r = -0.54$, $p < 0.01$). Patients with plasma NE > 900 pg/ml which has previously been shown to be an independent indicator for increased mortality in heart failure had significantly elevated NCX protein levels ($p < 0.01$). Sudden death is a major cause of mortality in endstage cardiac failure. In a subgroup of patients with a history of sustained ventricular tachycardia or ventricular fibrillation (n = 6) NE levels were significantly higher than in patients without sustained arrythmic events ($p < 0.01$). There was no significant correlation of SERCA protein levels with neither NE, nor E, ANP, PRA, ALD, TNF-alpha, TNF-R1 or TNF-R2. Furthermore, we found significant correlations of the stage of heart failure (according to Soufer Am J Cardiol 55: 1032–36) and TNF-R1 ($r = 0.56$, $p < 0.05$) and TNF-R2 ($r = 0.63$, $p < 0.01$). E and ANP significantly correlated with cardiac index ($r = -0.55$, $p < 0.01$ and $r = -0.51$, $p < 0.05$, respectively).

In conclusion, in endstage cardiac failure NCX protein levels significantly correlated with plasma NE. Significantly elevated plasma NE levels occurred in patients with a history of sustained ventricular arrythmia. Downregulation of SERCA could not be related to neurohumoral activation.

P1726 Treatment with Carvedilol improves arterial baroreflex control of heart rate in chronic heart failure. Comparison of spectral and phenylephrine techniques

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Since beta-adrenergic blockade (BB) in chronic heart failure (CHF) has been shown to improve signs and symptoms of ventricular dysfunction, we have investigated whether this effect is also accompanied by a restoration of vagal reflexes as assessed by the phenylephrine method (PHE) and by a spectral technique (Robbe method, SPE). Twenty consecutive CHF patients with moderate and stable CHF (age 51 ± 9 yr., NYHA CL. II-III, LVEF 24+8%, optimised therapy), underwent PHE and SPE analysis at baseline and after randomisation to receive (n = 10) or not (n = 10) BB therapy (carvedilol) for a mean period of 9 ± 3 months. At baseline PHE was computable in all patients while SPE only in 9/20 patients due to a low coherence (<0.5) in the RR and systolic pressure spectral bands. In the 9 patients with both tests measurable, mean SPE and PHE were similar (6.3 ± 4.5 and 6.8 ± 2.6 ms/mmHg, ns), but with a correlation coefficient of r = 0.51, ns. In the patients who underwent BB there was a significant improvement in NYHA CL, LVEF, Echo deceleration time and peak VO_2 (all $p < 0.05$), and PHE increased significantly from 3.7 ± 4.3 to 9.3 ± 5.9 mmHg, $p = 0.03$. After BB therapy, SPE was computable in all patients with a mean value of 9.5 ± 3.5 ms/mmHg (ns vs PHE, correlation coefficient with PHE = 0.67, $p < 0.05$). In the 4 patients with SPE measured at baseline, it increased significantly after BB (from 8.6 ± 3.1 to 12.4 ± 1.6 ms/mmHg, $p = 0.02$). No significant differences were observed in not treated patients in both hemodynamic and BRS data.

Conclusions: In CHF, treatment with Carvedilol, besides the well known effects on ventricular function, restores the capability to reflexly increase vagal activity. The PHE method seems the technique of choice in the assessment of BRS, since SPE is computable only in a limited number of patients. However, both methods, when measurable, are effective in revealing the improvement of BRS function by BB treatment.

P1727 A- and B-type natriuretic peptides respond differently to rapid reduction in cardiac preload

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Natriuretic peptides ANP and BNP with propeptides Nt-proANP and Nt-proBNP may serve as biochemical markers of cardiac preload. The purpose of this study was to detect differences between these peptides in their response to rapid reduction in cardiac preload subsequent to nitrate infusion. Sixteen men and 4 women aged 63.0 ± 10.4 years (mean ± SD) with congestive heart failure (NYHA III) and pulmonary capillary wedge pressure (PCWP) ≥ 18 mmHg, were given a 24-hour infusion of nitroglycerin (N = 8) or nicorandil (N = 12). Doses were titrated to obtain a reduction of PCWP of at least 30% and then maintained. Natriuretic peptides were measured by radioimmunoassay at baseline, 1, 3, 12 and 24 hours:

	Baseline	3 hours	12 hours	24 hours
PCWP	25.5 ± 5.7	15.3 ± 3.6*	15.5 ± 4.7*	16.7 ± 5.7*
RAP	10.6 ± 4.4	8.1 ± 2.6*	7.7 ± 3.1*	8.8 ± 4.4*
ANP	84.8 ± 50.8	49.7 ± 30.1*	52.9 ± 31.4*	64.5 ± 44.4*
Nt-proANP	1998 ± 922	1663 ± 797*	1612 ± 835*	1819 ± 928*
BNP	100.6 ± 57.7	90.0 ± 49.3	68.2 ± 36.9*	53.9 ± 31.8*
Nt-proBNP	258.2 ± 136.0	255.5 ± 128.5	205.1 ± 90.4*	156.7 ± 67.6*

RAP: Right atrial pressure; Units: mmHg; pmol/l; Mean ± SD, *p < 0.01 versus baseline.

PCWP and RAP fell rapidly within 3 hours, and then increased slightly. ANP and Nt-proANP followed the same pattern. In contrast BNP and Nt-proBNP fell steadily throughout the observation period, reaching minimum levels at 24 hours. Peptide responses were independent of type of nitrate given.

Conclusion: The A-type peptides reflect rapid changes in preload while the B-type peptides seem to respond much slower. This difference is of relevance to the interpretation of peptide measurements in the clinical setting.

P1728 Sympathetic and reflex alterations in hypertensive heart failure patients

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Heart failure (HF) is characterized by sympathetic activation, which is also common of hypertensive patients (H) with normal cardiac function. It is unknown, however, whether the concomitant presence of H and HF further enhances the neural abnormalities characterizing the above mentioned cardiovascular diseases.

Methods: In 8 normotensive control subjects (C, age: 54.9 ± 4.8 yrs, mean ± SEM), 7 untreated H, 10 normotensive untreated HF patients (NYHA class II–III, LVEF 39.8 ± 3.1%) and 9 untreated HF patients with H (HFH, NYHA class II–III, LVEF 39.3 ± 3.0%), all age-matched with C, we measured mean arterial pressure (MAP, Finapres), heart rate (HR, EKG) and postganglionic muscle sympathetic nerve traffic (MSNA, microneurography) at rest and during baroreceptor stimulation and deactivation induced by stepwise i.v. infusions of phenylephrine (PHE) and nitroprusside (NTP) respectively.

Results: MAP was higher in H and in HFH (108.7 ± 3.7 and 104.4 ± 4.3 mmHg respectively, $p < 0.01$ for both) than in C and in HF (88.7 ± 3.5 and 81.6 ± 3.1 mmHg), while HR was significantly increased only in HFH. MSNA values were significantly higher in H and in HF than in C (42.0 ± 2.2 and 45.5 ± 2.7 vs. 30.8 ± 2.5 bs/min respectively, $p < 0.01$ for both), a further increase being detected in HFH (59.9 ± 4.7 bs/min, $p < 0.05$). In C the mean BP increase induced by PHE caused a reflex reduction in HR (−12.3 ± 1.5 b/min) and in MSNA (−71 ± 9% i.a.), while the mean BP fall induced by NTP caused opposite effects (HR: +20.5 ± 2.3 b/min; MSNA: +115 ± 18% i.a.). While in H only baroreflex modulation of HR was impaired (−42 ± 7%, $p < 0.01$ vs C), in HF both HR and MSNA changes were attenuated (−59 ± 6 and −61 ± 7% respectively, $p < 0.01$ for both), a further attenuation being observed in HFH (−69.3 ± 8 and −68.4 ± 6% for HR and MSNA).

Conclusions: Thus the concomitant presence of HF and H triggers a sympathetic activation greater for magnitude than that found in these pathological conditions. This is accompanied by a marked impairment in baroreflex control of both vagal and sympathetic components, which is greater for magnitude than that observed in HF and in H.

P1729 Inhibitory sympathetic norepinephrine release in volume overloaded cardiac hypertrophy

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It has been known that angiotensin II (AII) accelerate norepinephrine (NE) release from sympathetic nerve terminal during sympathetic activation in the normal heart. Therefore, cardiac NE release might be much enhanced in the process from cardiac hypertrophy to failure due to increased tissue AII and cardiac sympathetic nervous activity, while it has not been directly examined. We investigated how AII modulates cardiac NE release during sympathetic activation in volume overloaded cardiac hypertrophy in the rat.

Methods: Four weeks after operation of abdominal aortocaval shunt (group A, n = 20) or sham oepration (group B, n = 20), rats were anesthetized and pithed. The heart was perfused retrogradely in Langendorff's manner, and a balloon was inserted into the left ventricle for measurement of left ventricular (LV) pressure. Heart rate, coronary perfusion pressure and LV end-diastolic pressure were kept constant. Electrical field stimulation of sympathetic nerve (SNS) was performed from the spinal canal for 45 sec after atropine administration. SNS were repeated under constant infusion of AII (1 nM, n = 10 in each group) or AII type 1 receptor blocker, losartan (10 μM, n = 10 in each group). Coronary effluent was collected from the right atrium. Total ammount of NE released during SNS was calculated from coronary flow and NE concentration, and normalized by heart weight.

Results: In control SNS without drug administraion, NE release was significantly greater in group B than group A (21 ± 3 pmol/g vs 63 ± 13 pmol/g, $p < 0.01$). In group B, AII infusion during SNS increased NE release by 113 ± 36% compared with control SNS, however, losartan did not affect NE release. On the contrary, in group A, AII infusion during SNS decreased NE release by 31 ± 7% compared with control SNS, and losartan significantly increased NE release by 100 ± 48%. These changes of NE release by AII or losartan altered isovolumic LV pressure in a similar fasion.

Conclusions: Against our expectation, AII produced inhibitory effect on cardiac sympathetic neuron NE release in volume loaded LV hypertrophy. It would indicate a protective effect of AII to activation of cardiac sympathetic nervous system at least in the early stage of volume overloaded hypertrophy.

P1730 Isolated hearts from α_{2a}-adrenoreceptor-deficient mice show altered left ventricular function but unchanged catecholamine responsiveness

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α_2-adrenergic receptors (AR) play a central role in the regulation of the sympathetic nervous system. To date, three subtypes of α_2-AR have been identified (termed α_{2A}, α_{2B}, α_{2C}). To determine the physiological significance of these α_2-AR subtypes, the gene for the α_{2A}-AR was deleted in mice by gene targeting. Mean aortic pressure in vivo did not differ between α_{2A}-AR deficient ($\alpha_{2A}^{-/-}$) and wild type (WT) mice, but basal heart rate (HR) was increased by 45% in $\alpha_{2A}^{-/-}$ mice. Tissue catecholamine levels and myocardial β-receptor density were decreased in $\alpha_{2A}^{-/-}$ mice. To determine the effect of α_{2A}-AR disruption on the heart without the influence of the adjacent vasculature and central nervous system, we studied isovolumic isolated hearts at baseline, during increased HR and during isoproterenol stimulation.

Heart weight and heart weight/body weight ratios of 20–25 week old mice were identical for both groups. Spontaneous HR was similar for $\alpha_{2A}^{-/-}$ and wild type, but left ventricular developed pressure (DevP) was 24% lower in $\alpha_{2A}^{-/-}$ hearts (85 ± 2 vs 65 ± 4 mmHg). Furthermore, $\alpha_{2A}^{-/-}$ hearts showed significantly higher rate of pressure rise (+dP/dt/DevP) and shorter time to peak pressure (55.5 ± 2.3 vs 61.0 ± 1.4 ms) compared to WT. These differences were preserved when hearts were paced at 420 or 600 min-1. Isoproterenol dose response (10^{-10} to 10^{-7} M) for DevP, HR, +dP/dt/DevP and time to peak pressure was similar in both groups.

We conclude that chronic increase in sympathetic tone in mice lacking α_{2A}-AR leads to unique changes of left ventricular function in isolated hearts: Decreased DevP and, simultaneously, increased rate of pressure development. These transgenic mice represent a novel model to determine the impact of neurohumoral activation (as occurs in heart failure) on myocardial contractility.

P1731 Sympathetic and vascular responses to a high carbohydrate load in severe heart failure: evidence for imbalance between insulin's vasopressor and vasodilatory actions?

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It is established that patients with heart failure (HF) are insulin resistant. Insulin has opposing vasodilatory and sympathoactivatory actions and the balance between the two appears to be altered in the context of insulin resistance. This preliminary study sought to explore the vascular and sympathetic effects of endogenous insulin, produced in response to a carbohydrate load, in patients with severe HF.

Methods: Six patients with severe HF (ejection fraction < 20%; NYHA class 3–4) on conventional therapy and six healthy controls (HC) matched for age (50 ± 6; 50 ± 6 yrs respectively) and body mass index (28 ± 1; 28 ± 1 kg/m^2 respectively) were studied. Following an overnight fast, steady state calf vascular resistance (CVR) and right peroneal muscle sympathetic nerve activity (MSNA) data were obtained over 2 min periods before, and every 10 min for 2 hours after, a 2.5 MJ carbohydrate load.

Results: Plasma insulin increased significantly ($p < 0.05$. Paired *t* test) in both groups to reach a peak of 954 ± 244 pmol/l in HF, and 1290 ± 405 pmol/l in HC. There was no significant difference in insulin profile between groups. Following the insulin peak, CVR (arbitrary units) fell significantly in HC from 54 ± 6 to 28 ± 2 ($p < 0.05$), but not in HF, and there was a significant increase in MSNA (bursts/100 beats) in HF from 59 ± 5 to 86 ± 11 ($p < 0.05$) but not in HC. Results expressed as mean ± SEM.

Conclusion: In severe heart failure the vasodilatation occurring during post-prandial hyperinsulinaemia is impaired and this may be due to a concomitant increase in sympathetic vasoconstrictor output.

P1732 Brain natriuretic peptide does not exhibit diurnal variation in patients with ischaemic heart disease or heart failure

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Brain natriuretic peptide (BNP) may be a useful test for the detection of LV systolic dysfunction (LVSD) and heart failure in the community and following acute myocardial infarction (MI). BNP is stable in whole blood for up to 72 hours and modern assays have excellent reproducibility. The diurnal and day-to-day variation of BNP has not been previously assessed. This is clearly an important clinical consideration and the aim of this study was to establish this.

Methods: 8 patients (7 with LVSD and 1 with normal LV function; 5 with prior MI) were enrolled in the study. They remained in the research unit for 24 hours. Blood was taken for BNP at 3 hourly intervals from 0900 hours. The patients also had blood taken in the morning on 5 non-consecutive days over the subsequent 2 weeks. Food, fluid and medications were taken as per normal. BNP was measured using the 'direct' Shionoria IRMA assay.

Analysis: The BNP data was log transformed and significance tested by paired t-test analysis. Each BNP was compared with the 0900 hr BNP sample. Each 'day' BNP sample was compared with the day 1 BNP in the same way.

Results: There was no significant difference between the BNP at time 0900 hrs and 1200, 1500, 1800, 2100, 0000, 0300, 0600 or 0900 hrs (next day). The respective p values were 0.98, 0.97, 0.82, 0.82, 0.70, 0.65, 0.59 and 0.64. Comparing day 1 BNP with days 2, 3, 4 and 5, the p values were 0.75, 0.97, 0.95 and 0.89 respectively.

Conclusion: BNP exhibits no diurnal variation, nor any day-to-day variation, in this patient group. This fact, along with its known stability in whole blood, suggests that BNP is suitable for use in clinical practice, perhaps in the diagnosis of LVSD and heart failure.

P1733 Influence of heart rate on neurohumoral parameters in patients with left ventricular dysfunction

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Question: Is there an association between heart rate (HR) and neurohumoral humoral parameters in left ventricular dysfunction (LVD) and is an elevated heart rate at admission of prognostic relevance?

Methods: 428 consecutive nonselected patients with ejection fraction (EF) ≤ 45% were registrated. Follow-up time was 498 ± 287 (median 454) days. Patients: 78% male, age 64 ± 11 years, EF 29 ± 9%.

Etiology: 60% coronary heart disease, 29% dilated cardiomyopathy, 11% other.

Results: Mean heart rate at admission was 81 ± 21 bpm.

n = 428	Nor (pg/ml)	Vaso (pg/ml)	ANP (pg/ml)	Aldosteron (pg/ml)	Renin (μU/ml)	Endo (pg/ml)
HR > 81	452 ± 336	3.7 ± 5.3	464 ± 302	92.2 ± 98.9	126 ± 325	9.4 ± 5.7
HR ≤ 81	336 ± 315	3.2 ± 3.2	344 ± 237	83.7 ± 101	163 ± 875	9.4 ± 9.3
p (t-Test)	0.0005	n.s.	<0.0001	n.s.	n.s.	n.s.

nor = norepinephrine, vaso = vasopressin, endo = endothelin

21.5% of all patients died during follow-up-time. Mortality at HR > 81 bpm was 31.7%, while 15.8% of the patients with HR ≤ 81 bpm deceased.

Conclusion:

(1) In patients with LVD and HR > 81 bpm the mortality is twice higher than in patients with heart rate ≤ 81 bpm.
(2) In comparison to lower heart rates, HR > 81 bpm is associated with elevated norepinephrine and ANP. There is no association between HR and vasopressin, aldosteron, renin and endothelin.

P1734 Permanent left ventricular-based pacing decreases atrial natriuretic peptide and norepinephrine levels in patients with advanced heart failure

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In pts with severe congestive heart failure (CHF) plasmatic levels of atrial natriuretic peptide (ANP) and norepinephrine (NE) increase in proportion to the severity of the disease. The aim of the present study was to evaluate the effect of permanent left ventricular (LV) based pacing on these indirect markers of the severity of CHF.

Methods: we included 19 pts (68.2 ± 6 years; 17 males) in stable NYHA class III (6 pts) or IV (13 pts) in spite of "optimal" medical therapy with permanent left bundle branch block. ANP and NE level determinations (ANP: high performance liquid chromatography; NE: radioimmunologic technique) were obtained just before implantation, at 1 month, 6 months, 12 months and every year thereafter.

Results: The level of ANP was 68.2 ± 45 pg/ml at baseline and 25.2 ± 12.6 pg/ml after a mean follow-up of 6.1 ± 7 months ($p = 0.001$); for NE the values were respectively 2.6 ± 1.5 pmol/ml and 1.97 ± 0.9 pmol/ml ($p = 0.11$; NS).

Conclusion: long-term left ventricular-based pacing decreases the levels of ANP and NE but significantly only for ANP. These results are arguments to consider that LV-based pacing improves 0the prognosis of severe CHF.

P1735 Haemodynamic optimization in decompensated congestive heart failure decreases circulating big endothelin-1 and endothelin-1 without affection of pulmonary or coronary concentration gradients

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In congestive heart failure (CHF), plasma levels of endothelin-1 (ET-1) and, in particular, big ET-1 closely correlate with the severity of disease. However, the consequences for the peptide levels of acute cardiac decompensation and recompensation are unknown. It is, furthermore, of particular interest whether acute haemodynamic changes induce any imbalances of endothelin peptides across pulmonary or coronary circulation, which both show chronically increased expression of ET-1 in CHF. We investigated, in the course of intensive care treatment of CHF patients for acute left heart decompensation (ALHD), venous concentrations of big ET-1 and ET-1 as well as concentration gradients of both peptides across pulmonary vasculature (difference between aorta/radial artery [A] and pulmonary artery [PA]) and coronary circulation (difference between coronary sinus [CS] and A) (time points: V, A, PA, 0 min, 30 min, 1, 2, 6, 12, 18, 24 h; CS, 0–2 h). Compared to patients with compensated CHF (group II, NYHA II, n = 7) and healthy individuals (III, n = 10), CHF patients with ALHD (I, NYHA III-IV, n = 7) showed significantly ($p < 0.05$) impaired haemodynamics (pulmonary capillary wedge pressure [PCWP], cardiac index [CI]) and significantly elevated plasma levels (V, A, PA, CS) of big ET-1 and ET-1. In I, application of sodium nitroprusside over 24 h significantly improved haemodynamics (PCWP, −41 ± 4%; CI +98 ± 7%)and decreased plasma levels (V, A, PA) of big ET-1 (−45 ± 7%, mean of V, A, and PA) and ET-1 (−39 ± 5%). In contrast, no significant changes were documented in II. Both in I and II, pulmonary and coronary gradients of endothelin peptides did not differ from nil at any time point investigated. We conclude that in CHF patients with ALHD acute haemodynamic optimization decreases elevated circulating big ET-1 and ET-1. Despite remarkable alterations of peptide concentrations in the course of decompensation and recompensation, pulmonary and coronary gradients for big ET-1 and ET-1 remain balanced.

P1736 Cardiovascular effects of low-dose adrenomedullin in humans

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Adrenomedullin (ADM) was found to be increased in heart failure, chronic renal failure and severe hypertension.

We evaluated the cardiovascular effects of ADM incremental infusion (at 1, 2 and 3 pmol/kg ·min for 30 minutes each) in 6 healthy volunteers (mean age 29 ± 2 years) in a double blind, placebo controlled, random order, cross-over study. Doppler echocardiography was used to determine cardiac volumes, filling and emptying parameters and systemic haemodynamics in baseline conditions, during and after the infusion of ADM and placebo. High resolution ultrasound scan of the carotid artery was used to evaluate changes in vessel properties.

At the highest infusion dosage, ADM reached plasma levels comparable with those observed in disease states, and induced significant decrements in left ventricular (LV) systolic diameter ($F = 9.2$, $p < 0.0001$), mean arterial pressure ($F = 2.70$, $p = 0.03$) and systemic vascular resistance ($F = 4.20$, $p = 0.003$), and increases in the percent thickening of LV posterior wall ($F = 2.40$, $p = 0.05$), LV ejection fraction ($F = 7.50$, $p < 0.0001$) and cardiac index ($F = 2.70$, $p = 0.03$), without affecting heart rate and LV diastolic function (mitral E/A ratio, mitral E wave deceleration, pulmonary vein systolic fraction and A wave amplitude). The time-to-peak of the pulmonary flow shortened ($F = 5.60$, $p < 0.0001$). Right ($F = 2.50$, $p = 0.04$) and left ($F = 3.3$, $p = 0.01$) atrial emptying fraction increased. Distension of the carotid artery increased ($F = 2.65$, $p < 0.04$).

These results suggest that ADM contributes to the overall regulation of circulatory homeostasis mainly because of its vasodilating activity.

SOPHISTICATED MAPPING METHODS

P1737 Endocardial activation patterns in patients with atrial arrhythmias: computer-assisted animation of electrical signals recorded with a 64-electrode basket catheter

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The three-dimensional activation patterns of cardiac arrhythmias are not completely understood due to limitations of the conventional mapping techniques. The aim of this study was to assess the value of a new mapping technique based on computer-assisted animation of multielectrode basket catheter recordings in patients with atrial arrhythmias.

The study included 33 patients (59 ± 10 years) with atrial tachycardia (AT) and 38 patients (61 ± 11 years) with atrial flutter (AFl). A software program was developed to analyze the activation patterns based on 56 bipolar electrograms recorded with a 64-electrode basket catheter deployed in right atrium (RA).

Results: In 23 patients with right AT, the animated maps revealed that arrhythmia was unifocal in 15 patients, multifocal in 4 patients, pleomorphic in 2 patients and macroreentrant in 2 patient. In 10 patients with left AT, breakthroughs on the right side of septum (1 in 8 patients and 2 in 2 patients) and a left-to-right activation of RA were demonstrated in animated maps. In patients with typical AFl, the reentry circuit was a broad activation front with preferential propagation around the tricuspidal annulus. Double potentials were recorded in the presumed positions of crista terminalis and eustachian ridge in 100% and 88%, respectively. The intercaval block was complete in 88% of patients; in 4 out of 31 episodes, there were breakthroughs posterior to vena cava superior. In 8 patients with atypical AFl, the reentry circuit involved one of the vena cava (around inferior vena vava 5 patients, around superior vena cava 2 patients) and a line of block located in posterior wall. A figure-eight reentry, with common pathway located in posterior RA, was documented in one patient.

Conclusions: The computer-assisted animation of multiple electrograms recorded with a basket catheter is a valuable mapping tool that enables the three-dimensional activation patterns of various atrial arrhythmias. The technique is appropriate for complex, short-lived or unstable arrhythmias.

P1738 Validation of the unipolar recordings to locate the site of origin of the atrial activation

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Unipolar recordings have been demonstrated predictive of the eventual ventricular ablation site in WPW syndrome. Similarly, there are some reports suggesting a similar predictive value to localise the origin of ectopic atrial tachycardia. However, to date no systematic study has been performed to validate unipolar recordings to localise the origin of the atrial activation.

Methods: We studied 19 patients without structural heart disease after successful ablation of supraventricular tachycardia. Unipolar recordings of all 4 poles and bipolar recordings of the distal pair of a steerable quadripolar catheter (2–4–2 mm interelectrode spacing) were obtained. This catheter was introduced into the right atrium and placed, first over the lateral wall, and, later, over the septal wall. The catheter was manipulated causing the tip to mechanically induce ectopy while recording. The morphology of the recorded unipolar electrograms were analysed along with the unipolar and bipolar activation times, the unipolar electrogram duration and voltage, and the dV/dt of the downstroke of the negative deflection of the unipolar electrograms. Ectopy which was superimposed over the preceding T wave, or having less than 2 mV amplitude – suggesting poor electrode-myocardium contact- in the unipolar electrogram recorded from electrode number 4, were discarded from the analysis.

Results: There was a significative association between a unipolar QS morphology and the distal electrode recording (33 out of 34). However, 54 out of 105 electrograms recorded from the proximal electrodes also showed QS patterns. A QS pattern showed 97% sensitivity and 49% specificity for the distal electrode. There were no differences between lateral or septal origins of the mechanically induced ectopy. The unipolar electrogram recorded from the most distal electrode exhibited a faster slope but there was a high overlap of values with those recorded from the proximal electrodes (Electrode#1 0.3 ± 0.3, electrode#2 0.1 ± 0.1, electrode#3 0.05 ± 0.04, and electrode#4 0.04 ± 0.03 mV/ms)

Conclusions: In isolation none of the unipolar analysed variables allow the origin of the atrial activation to be predicted. This predictive value may be even lower in the clinical setting, where ventricular repolarisation often merges with the atrial unipolar electrogram.

P1739 Non-contact mapping of complex and/or non-sustained supraventricular and ventricular tachycardia: feasibility and implications for radiofrequency catheter ablation

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Non-contact mapping with the Ensite 3000 System (Endocardial Solutions Inc.) was performed in 13 patients (pts.) with supraventricular (n = 9) or ventricular tachycardia (n = 4). Six of 13 pts. had complex or non-sustained tachycardia, difficult to approach or even not approachable with conventional mapping: Non-sustained ectopic atrial tachycardia (EAT; inducible for 2–6 seconds): n = 2; Accessory pathway (AP) associated with severe Ebstein anomaly: n = 1; Permanent junctional reciprocating tachycardia (PJRT): n = 1; Non-sustained ventricular tachycardia (VT, inducible for 6–21 seconds): n = 2. Prior to the mapping procedure, the geometry of the target heart chamber was established carefully to achieve a high degree of anatomical accuracy.

Results: Reconstruction of the chamber geometry was completed within 13–23 minutes. In pts. with EAT the focus could be reliably identified within the high right atrium. Analysis of maps obtained during successive runs of non-sustained EAT showed an identical origin and activation pattern. Ablation was successful in both cases. In the pt. with Ebstein anomaly the AP was localised during pre-excited sinus rhythm and successfully ablated with a single radiofrequency application. In the pt. with PJRT the atrial insertion of the pathway was localised just outside the coronary sinus and successfully ablated. In pts. with non-sustained VT both, the exit site as well as the area of slow conduction could be identified. In one pt. single radiofrequency applications proved successful while in one pt. multiple applications forming a lesions line rendered the VT non-inducible.

Conclusions: Mapping with the Ensite System is feasible to reliably identify successful target sites for catheter ablation in pts. with complex or non-sustained tachycardia. Careful establishment of the geometry of the assessed heart chamber seems to be crucial to achieve the high degree of electrical and anatomical congruence necessary for successful ablation.

P1740 Online visualization and ablation of common type atrial flutter guided by non-contact mapping: initial experiences

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A non-contact multielectrode catheter in the right atrium (RA) enables a high resolution mapping of atrial flutter (AFl) activation. A non-contact mapping (NCM) guided radiofrequency ablation (RFA) is performed by visualizing the electroanatomical isthmus of common type atrial flutter and by documenting the catheter positioning with corresponding ablation sites.

Methods: The mathematical reconstruction of 3,300 endocardial electrograms (ECG) is achieved via a 64 electrode wire braid around a saline filled 8 ml balloon. The ECG generates an isopotential map on a 3D anatomical computer model of the endocardium where also a 5 kHz signal emitted from the ablation catheter's tip is displayed. NCM guided RFA was performed in 11 patients (pt; male n = 8, age 68 ± 5 y.) during hypothesized atrial flutter. The wavefront velocities (WV) were measured at the RA lateral wall (LW), between coronary sinus and His (Cs-His), V. cava inferior and Cs (VCI-Cs), between VCI and tricuspid valve (VCI-TCV) and in an assumed electrical isthmus (Ist) of the circuit.

Results: In contrast to the surface ECG indicating a common type atrial flutter, NCM showed only in 7/11 pt the activation pattern of a counterclockwise reentry circuit. The comparison of the cycle lengths of the atrial flutter (mean 234 ± 23 msec) with the WVshowed a positiv correlation to VCI-TCV (R = 0.95) and to Ist (R = 0.63). Using an 8 mm tip ablation catheter AFl could be ablated by applying 19 ± 11 RF applications around the isthmus region or VCI-TCV. In two pt NCM displayed an activation gap that could be closed by targeted RF applications. The 4 pt showing modified patterns of AFl were also ablated successfully by RFA around the earliest activtion exit sites.

Conclusion: NCM enables an online visualization and characterization of atrial flutter activations. It is helpful to target critical zones of atrial conduction circuits.

P1741 Three-dimensional non-fluoroscopic electroanatomical mapping and modification of the sinus node for inappropriate sinus tachycardia using a novel 3D non-fluoroscopic system

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We present our result with mapping and modification of the sinus node in patients with inappropriate sinus tachycardia using a three-dimensional non-fluoroscopic mapping system (CARTO). Thirteen wormen underwent mapping and modification of the sinus node using this system. The age ranged between 18 and 47 years. All patients failed at least one anti-arrhythmic drug before the procedure. The mean heart rate (HR) at rest was 96 ± 15 beats per minute (bpm). In each patient, 3-D maps of the right atruim (RA) were created in sinus rhythm and during isoproterenol (ISO) infusion. Ablation was performed during ISO infusion starting at the site of the earliest activation. Map of the RA was recreated if a decrease in HR was observed or after ablation in the region of the earliest activation was performed without significant HR change. In each patient the earliest sites of activation were correlated to the crista terminalis location identified by the presence of split potentials during coronary sinus pacing at 500 ms. In all 13 patients the sinus rate increased with ISO infusion at 2 mg per minute between 170 to 187 bpm. Administration of ISO resulted in cranial shift of the early site of activation. Radiofrequency ablation was performed starting at the site of earliest activation and extending around for about 5 mm. In all 13 patients a decreasing HR to 105–120 bpm was associated with a caudal shift of the earliest activation which ranged from the mid postero-lateral region of the right atrium to the infero-lateral region near the inferior vena cava. The shift of the earliest site of activation ranged from 2.5 cm to 4 cm. In all 13 patients successful sinus node modification was achieved without need for permanent pacemaker. The total fluoroscopy time for sinus node modification did not exceed 13 minutes. At follow-up one patient experienced recurrence of sinus tachycardia and was successfully re-ablated.

In conclusion, this 3-D non-fluoroscopic mapping appeared to be a useful tool to achieve successful sinus node modification limiting the fluoroscopy exposure and possibly the risk of inadvertent excessive damage to the sinus node. Successful modification was consistently associated with a caudal shift of the earliest point of activation.

P1742 Electroanatomic catheter mapping and ablation of the inferior isthmus in atrial flutter: contemporary ablation without fluoroscopy?

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The induction of contiguous and transmural lesion lines within the isthmus between the tricuspid annulus (TA) and the inferior caval vein (ICV) for ablation of atrial flutter (AFL) may be time consuming and requires a substantial resort to fluoroscopy. The increase in the lifetime risk of fatal malignancy from prolonged radiation after catheter ablation for supraventricular tachycardia is currently under intensive discussion.

In 30 patients (pts) with typical AFL, 3-dimensional (3-D) maps of the TA-ICV isthmus were constructed with an electro-anatomical non-fluoroscopic mapping system (Carto) for precise reconstruction of the individual isthmus geometry. After definition of the distal isthmus at the TA and the proximal isthmus at the ICV by means of fluoroscopy, the induction of a contiguous lesion line was performed non-fluoroscopically. After dislocation of the ablation catheter, the electromagnetic navigation system allowed precise re-navigation to predetermined sites. In all pts, complete conduction block within the isthmus could be achieved (7.3 ± 4.7 pulses, 4-mm tip electrode), in 14 pts with the first lesion line. The overall fluoroscopy time inclusive diagnostic studies and ablation measured 8.7 ± 3.7 min. (in the last 15 pts, 6.8 ± 2.3 min). The radiation time during isthmus ablation measured 1.6 ± 1.9 min (in the last 15 pts, 0.8 ± 1.6 min), and isthmus ablation was done completely non-fluoroscopically in 6 pts.

High-density 3-D electromagnetic catheter mapping within the TA-ICV isthmus allows precise induction of contiguous and transmural lesion lines for ablation of AFL. By using electromagnetic mapping during induction of linear lesions, it proved possible to reduce the period of fluoroscopy during ablation of AFL to that of diagnostic electrophysiologic studies. This approach may have a significant impact on the long-term safety of this procedure.

P1743 Mapping of human right atrial fibrillation using a non-contact system

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Mapping atrial fibrillation (AF) has been limited by complexities in the arrhythmia and anatomy. Non-contact mapping has the potential to overcome this by generating global simultaneous maps. The non-contact multielectrode array (MEA), which allows reconstruction of 3,360 unipolar electrograms which are superimposed onto a computer model of the endocardium thus creating isopotential maps, was used to create high resolution maps of the entire right atrium (RA) of 11 patients (pts) with AF. Pts had either sustained AF (3) for >6 months or developed AF during the study (n = 8). AF initiated in 1 pt from 2 successive atrial ectopic beats from the site of a roving contact catheter which resulted in a single reentry wavefront circuit rotating around the right atrium which rapidly degenerated to disorganised activity with 3 or 4 wavefronts being present at any time. During established AF, 4 patients predominantly had a single RA wave front, 2 had 2 wave fronts and 5 patients had 3–5 wave fronts for most of the time. The number of wavefronts present correlated with the coarseness of atrial activity seen on the EKG baseline. Periods of RA electrical silence were seen in 8 pts, after which activity emerged from consistent septal sites, either superior alone (3), superior and inferior septum (2) or superior, mid and inferior septum (3). With intravenous flecainide, 2 pts organised to AFl which terminated with isthmus block in 1 and required pace termination in the other. In the remaining pt, progressively fewer wavefronts and longer periods of electrical silence were followed by atrial tachycardia with a focus moving superiorly in the lateral RA before terminating.

Conclusion: Non-contact mapping of the RA demonstrated AF initiation and termination. It also showed different RA activation patterns in AF and that the left atrium may sustain AF in many pts.

P1744 Three-dimensional electroanatomical mapping-guided radiofrequency catheter ablation of complex atrial tachyarrhythmias following cardiac surgery

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The mechanism of atrial tachycardia (AT) following cardiac surgery is so complicated that the clinical outcome of radiofrequency catheter ablation (CA) has not yet become well accepted. We performed catheter-based intracardiac mapping in conjunction with the conventional method and a new three-dimensional electroanatomical mapping (CARTO; Biosense Inc.) in 22 patients (pts) presenting with post-operative atrial tachyarrhythmia. The existing structural heart disease and history of previous cardiac surgery consisted of valvular disease after replacement in 2 pts, tricuspid atresia after the Fontan procedure in 3 pts, tetralogy of Fallot after repair in 6 pts, ASD after patch closure in 8 pts, VSD after patch closure in 2 pts and ischemic heart disease after CABG in 1 pt. Twenty-seven atrial tachyarrhythmias were reproducibly induced in the 22 pts. Endocardial mapping by electroanatomical mapping system exhibited focal AT in 2 pts, incisional macro-reentrant AT in 18 pts and counterclockwise typical atrial flutter in 7 pts. Two focal ATs and 16 macro-reentrant ATs with area of slow conduction (A-SC) in the reentrant circuit were terminated by single-site facal CA (not linear) and were no longer inducible. The ablation site was the earliest excitation in focal ATs and the A-SC demonstrating concealed entrainment in macro-reentrant ATs. Linear CA between two different anatomical barriers was required to cure 2 macro-reentrant ATs without apparent A-SC and 7 typical atrial flutters. All CA procedures were successful and no complications were observed.

Conclusion: The electroanatomical mapping system is useful to understand the mechanisms of arrhythmia in patients with complicated anatomical substrate created by the previous surgery. Interestingly, linear CA is not always required to cure the incisional macro-reentrant AT which is the most common arrhythmia after open heart surgery.

P1745 Virtual RF ablation in a three-dimensional anatomical computer model of the atrium

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A realistic 3D anatomical model of human atria has been designed which simulates the cellular and tissue electrophysiology of atria. Since atria are constituted of thin walls, the propagation of electrical activity in atria is a problem that we can simulate with today computer power.

Methods: Based on a 2D heterogeneous and anisotropic model of conduction in the cardiac tissue that has proved to be realistic in previous experiments, we have developed a 3D anatomic model of human atria which uses a modeling of the cellular membrane ion kinetics given by Beeler-Reuter or Luo-Rudy. The simulated size of both atria is 3 cm × 3 cm × 7 cm with about 250'000 cardiac cells. Holes have been placed on the surface to simulate the veins and the valves. Normal sinus beat is initiated from the sino-atrial node (SA node) and the propagation speed-in basic conditions is 50 cm/s.

Results: Virtual electrophysiologic experiments have been performed, using an S_1–S_2 protocol. S_1 has been initiated from the SA node and several locations, sizes, intensities and timings have been tested for the ectopic beat S_2. Most of the attempts have led to nonsustained arrhythmias. However, for a given size, intensity and timing, we have identified that some locations are more likely to generate a sustained atrial flutter: the region between the inferior vena cava and the tricuspid valve and the region of the pulmonary veins. This observation correlates with the observations made in humans. After having initiated sustained atrial flutter, we have tested some antiarrhythmic interventions like RF ablation of the isthmus of Cosio. The ablation had the effect of stopping the arrhythmia and the reinitiation of the flutter after ablation was unsuccessful, showing the effectiveness of the treatment.

Conclusion: Our virtual atria can reproduce observations made on humans but with the advantage of showing details difficult to study in nature and of being reproducible. Furthermore, it allows us to study the impact of pacing and pharmacological interventions. Computer simulations are therefore a new tool for the study of arrhythmias and their treatment.

P1746 Sequence of ventricular repolarization and its correlation to that of the activation: monophasic action potential mapping in humans using an electro-anatomical mapping system

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Disturbances in myocardial repolarization are associated with the genesis of arrhythmias. However, the global sequence of repolarization and its correlation to that of the activation are little known.

Methods: Endocardial monophasic action potentials (MAPs) were recorded from 44 ± 16 left or right ventricular sites in 8 patients using an electro-anatomical mapping system (CARTO). The onset of the MAP upstroke was defined as the local activation time (AT) and the intersection between the baseline and the tangent to the steepest slope on phase 3 as the end-of-repolarization (EOR). The AT, MAP duration and EOR at each site were calculated and 10 sets of activation, EOR and MAP duration maps were constructed, 5 left and 5 right ventricular maps.

Results: (1) The EOR sequence was clearly depicted in all the 10 maps. In 8 maps, the EOR followed the same sequence as the activation, regardless during sinus rhythm, premature beats or ventricular tachycardia and the presence of normal QRS and concordant T waves, preexcitation or bundle branch blocks with secondary ST-T changes. (2) In 9 maps, the longest MAPs were recorded in the earliest activation area, while in 8 of them the shortest MAPs in the latest activation area. (3) A statistically significant negative correlation between the MAP duration and the AT was found in all the 10 maps ($r = -0.63 \pm 0.18$), but a positive correlation between the EOR and the AT in 9 maps ($r = 0.66 \pm 0.28$), the linear regression slope being less negative than −1 (-0.58 ± 0.40) for the former and less positive than +1 (0.53 ± 0.19) for the latter.

Conclusions: (1) A clearly recognizable sequence of EOR is commonly seen over the human ventricular endocardium, which verifies the existence of transventricular gradients of repolarization. (2) The ventricular endocardial repolarization frequently follows the activation sequence, regardless the activation sequence is normal or not, which suggests that the activation sequence is an important determinant for the repolarization sequence. (3) Progressively later activation associated with progressively shorter MAP duration is a general electrophysiologic feature. The magnitude of this MAP shortening relative to that of the local AT is a critical factor governing the direction of the EOR.

ECG MARKERS OF SUDDEN DEATH

P1747 High incidence of sudden death in myocardial disease due to a lamin A/C gene mutation

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We have studied fifty-four members of a large French family in which 17 members presented a cardiomyopathy, transmitted as an autosomal dominant mode. In the affected members, the mean age of onset for cardiac symptoms was 33 years (ranging from 15 to 47 years) and the first symptoms were related to a severe auriculoventricular conduction defect and sinus dysfunction, requiring the implantation of permanent pace-maker in seven cases. Myocardial dysfunction occurred rapidly in the course of the disease associated to ventricular dysrhythmias and resulted in a severe dilated cardiomyopathy requiring heart transplantation in 3 cases.

Eight members of this family died suddenly and in two cases, it was the first and unique manifestation of the disease. The six remaining cases had prior history of rhythmic and left ventricular dysfunctions before sudden death and two of them died despite the implantation of a permanent pace-maker.

Genetic analysis of this new form of autosomal dominant dilated cardiomyopathy demonstrated a nonsense mutation in LMNA gene located on chromosome 1q11–q23. This gene encodes lamins A and C which are proteins of the nuclear lamina located at the inner face of the nuclear envelope.

In conclusion, the genetic modification of a component of the nuclear envelope associated with high incidence of life threatening dysrhythmias opens new insights in the molecular mechanisms exposing to sudden death.

P1748 Blockade of the human ether-a-go-go-related gene (HERG) potassium channel by amitriptyline: another mechanism for cardiotoxicity

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Amitriptyline, a frequently prescribed tricyclic antidepressant, impairs cardiac conduction, prolongs QT interval and produces life-threatening arrhythmias including torsades de pointes during overdoses. Most reports have focussed on sodium channel blockade by amitriptyline as a mechanism for its cardiotoxicity. The cardiac repolarizing potassium channel, IKr, is a primary target of drugs causing QT prolongation and is encoded by HERG. The effect of amitriptyline on HERG channels has not been previously reported.

Aim and methods: We examined the effect of amitriptyline on HERG stably transfected into Chinese hamster ovary (CHO-K1) cells using the whole cell configuration of the patch-clamp technique.

Results: HERG tail currents were elicited at −60 mV after a 3.9 sec depolarizing step from −80 mV to +30 mV. Amitriptyline blocked these currents in a concentration-dependent manner, with an IC50 of 10 ± 1.1 μM and a Hill slope of 1.38. Block by amitriptyline 10 μM and 30 μM displayed no voltage-dependence between −20 mV and +30 mV. Amitriptyline did not enhance the rate of current decay during prolonged (15 sec) depolarizing pulses. Channel inhibition by amitriptyline 10 μM was independent of the depolarizing pulse duration using an envelope of tails protocol.

Conclusion: In addition to blockade of cardiac sodium channels, amitriptyline also blocks the HERG potassium channel at concentrations relevant in clinical overdosage (toxic serum concentrations ~5 μM to 10 μM). This blockade likely underlies the prolongation of QT interval and torsades de pointes observed during poisoning with this drug. Our data suggests that amitriptyline preferentially binds HERG in a closed state, although a fast open-state block cannot be ruled out.

P1749 Effects of dronedarone on calcium handling in cardiac ventricular myocytes

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Dronedarone (D), an amiodarone-like non-iodinated antiarrhythmic compound, is currently undergoing clinical trials. As well as amiodarone, D has been described as Na, Ca and K currents blocker. The present experiments investigate the effects of D at 37°C on action potential, shortening, Ca^{2+} transient and L-type calcium current (iCaL) of isolated guinea pig myocytes.

Action potential in isolated cells was studied in current-clamp by perforated patch technique. At 10 μM, D decreased the plateau of the action potential which suggests an inhibition of calcium current. Thus, intracellular calcium was measured using the fluorescent calcium probe indo-1 simultaneously with contraction measured using video edge-detector system. D decreased both amplitude of contraction and intracellulrar calcium with IC50 of 1.1 ± 0.4 μM and 4.4 ± 0.6 μM, respectively.

iCaL was measured by patch-clamp technique. Current-potential curves were measured between −40 and +50 mV, stepped from prepulse of −40 mV and holding potential at −80 mV. D failed to modify activation potential of iCaL. In contrast, peak current measured at 0 mV was totally blocked at 3 μM and the IC50 was 92 ± 6 nM. D-induced use-dependent block was studied using a train of 30 pulses with interpulse intervals of 0.5 s and a test pulse at 0 mV. The onset of use-dependent block was exponential yielding time constants of 1.7 s in control condition and 0.4 s in the presence of 10 nM D. The voltage dependence of iCaL inactivation was evaluated using 1 s prepulses ranging from −80 to +20 mV. After exposure to D, the inactivation curve was shifted from −23.8 ± 1.2 to −31.6 ± 0.8 mV.

These results show that D blocks iCaL in a concentration- and use-dependent relationship and induces a decrease in Ca transients and consequently in shortening.

P1750 Native versus cloned Kv1.5 channels: effects of tedisamil on human cardiac rectifier K+ channels

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Human atrial myocytes exhibit a rapidly activated, sustained outward current Iso that corresponds to the cloned K^+ channel Kv1.5. Whilst availability of human tissue for the study of native channels is limited, there is an almost unlimited access to cloned Kv1.5 channels that are stably expressed in mouse fibroblasts. Hence new drugs with a therapeutical potential are preferentially studied in cloned channels. Here we provide a systematic comparison of the effects of the class III antiarrhythmic agent tedisamil (TED) in these two systems. The aim of our study was to validate the use of Kv1.5 in pharmacological experiments. Whole-cell voltage clamp experiments were carried out in human atrial myocytes or cultured mouse fibroblasts at room temperature. In both types of cells, TED concentration-dependently reduced the time constant of current inactivation with little influence on maximum current amplitude. The EC_{50} values for end-of-pulse current reduction were 2.0 μM for Iso and 2.8 μM for Kv1.5 The apparent acceleration of inactivation is compatible with open channel block. With 10 μM TED fractional block of Iso in atrial cells and Kv1.5 in fibroblasts developed with a time constant of 11 ± 4 ms and 31 ± 2 ms, respectively. Recovery from block was biphasic in Kv1.5 of fibroblasts, a fraction of 0.51 recovered with an ultrarapid time constant of 60 ± 21 ms, the remainder with a slow time constant of 691 ± 74 ms. We therefore conclude, that TED had similar qualitative effects in native and cloned K^+ channels. From the dissociation kinetics (recovery from block) TED is expected to be particularly effective at high frequencies.

P1751 Signal averaged electrocardiography in patients with chronic ischaemic heart diasese

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Background: The signal averaged electrocardiography (Sa-ECG) has been widely utilised to early identify the subgroup of post-myocardial infarction patients (pts) at high risk of serious arrhythmic events.

Objectives: The aim of the present study was to define the incidence of late potentials (LPs) in a large population of pts with chronic ischemic heart disease and angiographically documented coronary artery disease (CAD).

Methods and patients: Our study population included 971 consecutive pts (787 M, 184 F, mean age 58.2 ± 8.5 yrs) who underwent ergometric stress test (EST) for clinical reasons. History of myocardial infarction (>6 months) was present in 546 (56.2%) pts; 526 (55%) pts referred angina pectoris.

The Sa-ECG was acquired in all pts immediately before EST. The LPs were considered present if two of the following three criteria were satisfied: QRS complex duration >110 msec after 25 Hz and >114 msec after 40 Hz filtering; root mean square voltage of terminal 40 msec (RMS40) <25 mV after 25 Hz and <20 mV after 40 Hz filtering; duration of low amplitude signals <40 mV greater than 38 msec at both filters of 25 and 40 Hz.

Results: LPs were detected in 185/971 (19%) pts. The clinical features, the prevalence of the most common cardiovascular risk factors, the distribution of CAD, the incidence of exercise-induced myocardial ischemia and of effort-induced ventricular arrhythmias were similar between pts with and those without Lps. The prevalence of LPs was 20.5% in pts with myocardial infarction (MI) and 17.2% in those without previous MI. Among pts with MI, Lps were present in 22% of pts with Q-MI and in 15% of those with nonQ-MI. A significant relation between Lps and an inferior myocardial infarction was documented ($p = 0.03$).

Conclusion: In a large population of pts with ischemic heart disease the prevalence of Lps was low. The clinical characteristics, the severity of CAD and the incidence of exercise-induced ischemia and ventricular arrhythmias were similar between pts with and without Lps. Among pts with MI, a significant relation between Lps and the inferior MI was documented.

P1752 Evaluation of wavelet decomposition of the signal-averaged electrocardiogram in idiopathic dilated cardiomyopathy: association with clinical and prognostic features

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This study evaluated the potential usefulness of wavelet decomposition (WD) analysis of the signal averaged ECG (SAECG) in patients (pts) with idiopathic dilated cardiomyopathy (IDC). SAECGs recorded at presentation were available in 82 pts (mean age 43 ± 14 years, 60 men) with IDC (WHO criteria), and in 72 normal controls (mean age 44 ± 15, 48 men). During 24 ± 18 months of follow-up, 23 pts developed progressive heart failure, 5 suffered from sudden cardiac death and the others remained clinically stable. Four parameters of WD analysis, QRS length, maximum count, surface area, and relative length, were derived from each recording using an in-house program.

Results 1) There were significant differences in all measurements of WD between IDC pts and controls ($p < 0.0001$). 2) Significant differences in WD measurements (except for relative length) were found between pts who developed progressive heart failure and pts who remained clinically stable ($p \leq 0.001$). 3) Although numeric values of WD in sudden death pts were similar to those in stable pts, 3 of 5 sudden death pts had 3 'abnormal' measurements (defined as exceeding the mean values ± 2 standard deviation in normal controls). 4) No relationship between ventricular arrhythmias and abnormal WD analysis results was detectable. 5) The predictive accuracy of WD (≥2 abnormal measurements) for prediction of progressive heart failure is: sensitivity 74%, specificity 61%, positive predictive accuracy 45% and negative predictive accuracy 85% respectively ($p = 0.005$). 6) All WD measurements significantly correlated with left ventricular end-diastolic dimension ($r = -0.33$ to 0.35, $p \leq 0.01$).

Conclusions WD analysis of the SAECG can identify pts at increased risk of clinical deterioration, but not at high risk of arrhythmic events, in IDC.

P1753 The puzzle of paradoxical post-operative P wave shortening : the role of autonomic tone

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Background: Prolonged P wave duration on the pre-operative signal averaged ECG (SAECG) indicates slow intra-atrial conduction and is a marker of post-coronary artery bypass (CABG) atrial fibrillation. Since cardiac surgery may result in transient atrial damage, we postulated that the post-CABG P wave SAECG would show further P wave prolongation.

Methods: 40 patients without prior AF or valve disease were studied. SAECG was performed 1 day preoperatively and on day 1 or 2 after surgery.

Results: Adequate paired (pre- and post-operative) tracings were obtained in 26 pts. CABG resulted in an unexpected and highly significant shortening of P wave duration which was associated with a significant increase in heart rate.

	Pre-operative	Post-operative	
P wave duration (msec)	118 ± 13	107 ± 11*	
Heart rate	(HR: bpm)	64 ± 7	77 ± 9*

*$p < 0.01$ compared to pre-operative value.

Regression analysis indicated a strong correlation ($r = 0.71$; $p < 0.01$) between the percentage change in pre- to post-operative HR and the change in P wave duration.

Conclusions: Following CABG, P wave duration decreases as HR increases. This most probably reflects changes in autonomic tone and points to the importance of considering HR when interpreting the P wave SAECG.

P1754 Reproducibility of the signal-averaged P wave: comparison to conventional QRST signal-averaged electrocardiogram in healthy subjects

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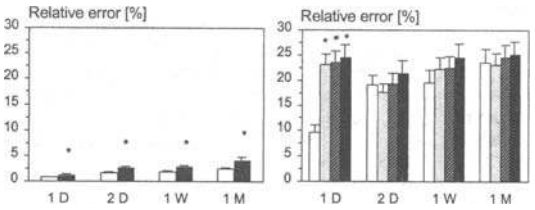
Abnormal signal averaged P wave electrocardiogram has been recognized as a marker of a substrate for atrial tachyarrhythmias. However, reproducibility of measurement yet has not been established.

Methods: The reproducibility of the total filtered P wave duration (P_{tot}), total filtered QRS duration (QRS_{tot}) root mean square (RMS) voltage of the terminal 40 ms of the P wave (P_{40}), RMS voltage of the terminal 40 ms of the QRS (RMS_{40}) was compared in 51 healthy volunteers (30 men; age 32 ± 8). Serial SAECG was recorded twice with 5-minute interval on day 1, then once on day 2, and then 1 week and month apart. SAECG parameters were automatically recalculated after manual correction of the onset and offset of the P wave (PHiRES, HiRES software, Marquette Medical Systems). A relative error was used to assess the variability of the results.

Results: The reproducibility of QRS_{tot} and was significantly higher compared to P_{tot} in all the recordings ($p < 0.001$; left figure; open bars = QRS_{tot}; solid bars = P_{tot}; data presented as mean ± SE). The reproducibility of RMS_{40} was significantly higher compared to P_{40}, P_{30}, and P_{20} only in the 'immediate' recordings ($p < 0.008$), whereas no difference was observed on day 2, in 1 week and 1 month (right figure; open bars = RMS_{40}; dotted bars = P_{40}; hatched bars = P_{30}, solid bars = P_{20}).



Conclusion: In healthy subjects, the 'immediate' reproducibility of the P wave SAECG is significantly lower than that of the QRS SAECG. The short-and long-term reproducibility of P_{tot} remains significantly lower compared to QRS_{tot}, whereas no difference is observed between voltage parameters of both the P wave and QRS SAECG.

P1755 Laplacian cardiac electrograms: a new surface mapping system for the detection of the sequence of heart activation

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Background: The non-invasive detection of the cardiac sequence of activation is very useful for the rapid diagnosis of arrhythmias. At this purpose, a multi-channel, experimental system provided with tripolar concentric sensors for the detection of local electric activity was tested. The signal recorded is the second spatial derivative of the surface ECG at the site where the sensor is placed and it is defined Laplacian Electrogram (LECG). We refer to the zero crossing of the signal as to the Moment of Activation (MoA), representing the instant of cardiac depolarization near the center of the sensor. The processing of MoA allows the generation of isochronal and isopotential maps of heart activation.

Methods: Real time LECGs were recorded from 70 subjects (8 healthy volunteers and 62 patients with various heart pathologies, such as recent and old myocardial infarcts, left and right bundle branch block, atrial fibrillation and flutter). After a first experimental phase, LECGs from seven chest sites and standard ECG Lead II (used as time reference lead) were simultaneously recorded by means of an 8 channels A/D converter connected to a laptop computer for data collection and analysis. Automatic recognition of the MoA allows the delays of activation to be determinated between sites and on a beat by beat basis. Using these delays, isochronal maps were constructed.

Results: Conduction delays were recorded in bundle branch blocks. Comparing the MoAs at sites above the right and left ventricles, the delays could be quantited non invasively. The isochronal maps from 20 frontal and subaxillary sites showed different sequences of activation in healthy subjects and in patients with previous infarct, as the isochrones gradually converged toward the presumed centre of the infarct. Finally, the feasibility of LECGs recordings during cycloergometer exercise was explored with a discrete success.

Conclusions: The portable LECG mapping system provides a new tool for understanding the propagation sequence of the heart non-invasively, in quasi-real time. The system has the potential to become a helpful tool for rapid arrhythmia diagnosis. Clinical applications are also pursued for EEG and EMG.

P1756 Wavelet decomposition of QRS complex alternans: differences between patients with ventricular tachycardia and normal healthy volunteers

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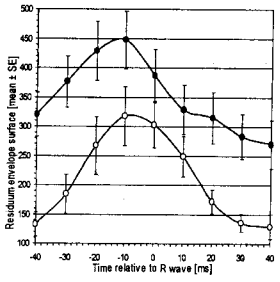
While the electrical alternans of the ST segment and T wave has been extensively researched, the alternans of the QRS complex has not been thoroughly investigated mainly because of difficulties in detecting it. In 47 patients with EP inducible ventricular tachycardia (mean age 63 ± 13 years, 83% male) and in 30 healthy volunteers (44 ± 16 years, 60% male), 120 to 400 QRS complexes were digitally recorded using orthogonal leads. The complexes with even and with odd order numbers were separately aligned and averaged. The resulting high gain signals were processed with wavelet decomposition (53 scales of Morlet wavelets with central frequencies of 40–250 Hz) and the differences between the resulting 3D spectral envelopes were computed. These created alternans related 3D spectral envelopes and were characterised by surface areas in subsequent 10 ms windows.

The surfaces of the alternans 3D spectral envelopes were substantially larger (Figure) in VT patients (filled circles) compared to controls (unfilled circles).



The differences between the groups were particularly marked within the initial and terminal portions of the QRS complex ($p < 0.00005$). Hence, (a) wavelet decomposition of alternating signal averaged ECG is capable of detecting electrical alternans within the QRS complex, (b) the QRS complex alternans is significantly more expressed in VT patients compared to healthy controls, and (c) the QRS complex alternans differs between VT patients and controls mainly at the beginning and at the end of the QRS complex.

P1757 Late potential analysis in digital Holter-ECG recordings – influence of tilt, exercise, heart rate, different lead positions and noise on the signal-averaged QRS-complex

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Digital recorders have enabled late potential analysis even in Holter-ECG-recordings. However, varying conditions such as tilt, exercise, heart rate, different lead positions and noise could nonspecifically affect the results.

In 30 healthy subjects standard time-domain analysis (Simson method, 40–250 Hz) was compared to analysis during different tilt (0°, 90°, 180°, 270°), bicycle-exercise (25 W), low heart rate 40–60 bpm (provoked by β-blockers), high heart rate > 90 bpm (provoked by isoproterenol), different lead positions (X,Y,Z-lead versus standard Holter lead positions), different noise (0.7 mcV versus <0.2 mcV and 0.8–1.0 mcV) using an Oxford-Medilog-FD3 recorder.

In standard time domain analysis fQRS was 91 ± 11 ms, RMS 41 ± 18 mcV and LAS 20 ± 11 ms. No healthy subject showed late potentials. Tilt 270° significantly increased fQRS (111 ± 21 ms, $p < 0.05$) and LAS (32 ± 19 ms, $p < 0.05$) but also RMS (68 ± 20 mcV, $p < 0.05$), whereas tilt 90°, 180° had no significant influences. Bicycle exercise 25 W did not significantly change time domain parameters (noise < 0.7 mcV achieved in all persons). Heart rate 40–60bpm increased fQRS (113 ± 22 ms, $p < 0.01$) and decreased RMS (20 ± 16 mcV, $p < 0.05$) (2 subjects fulfilled late potential criteria), whereas heart rate > 90 bpm (maximum 141bpm) had no significant influences. Holter-lead positions did not reveal altered time domain parameters. Signal averaging in order to decrease the noise level < 0.2 mcV increased fQRS (110 ± 17 ms, $p < 0.05$) and decreased RMS (29 ± 11 mcV, $p < 0.05$), (1 person developed late potential criteria), noise levels 0.8–1.0 mcV led to increased fQRS (109 ± 21 ms, $p < 0.05$)and increased RMS (62 ± 31 mcV, $p < 0.05$) (2 persons fulfilled late potential criteria).

Thus, time domain late potential analysis in digital Holter-ECG-recordings is only affected by extreme tilt, very low heart rate, noise < 0.2 mcV or noise > 0.8 mcV. However, if late potential analysis is performed in Holter-ECGs, information about tilt, noise and heart rate should be available.

P1758 Value of the P wave signal-averaged ECG for predicting of atrial fibrillation recurrence in patients with paroxysmal atrial fibrillation

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P wave signal averaged electrocardiography (SAECG) has been reported to be useful to identify the patients at risk for paroxysmal atrial fibrillation (PAF) during sinus rhythm. However there have been no definite methods to predict the recurrence of PAF, so the purpose of this study was to determine prospectively whether the recurrence of atrial fibrillation could be predicted by the use of P wave SAECG.

Methods: In 79 patients (57 Male, 49 ± 10 y) with at least one documented episode of PAF, P wave duration on SAECG, the left atrial diameter and the patient age were collected after 24 hours from the last PAF episodes. A bimonthly follow up was performed (6 months/pts) for identifying patients with (Group A, 21 patients) and without (Group B, 58 patients) PAF recurrence, in order to define the arrhythmic risk predictor value of P wave duration on SAECG.

Results: All results are below.

	Group A	Group B	P value
Age (year)	48.6 ± 12	50.5 ± 11	0.545
Left atrial diameter (cm)	3.6 ± 5.7	3.6 ± 5.4	0.977
SAECG P wave duration (ms)	134 ± 13	125 ± 10	0.005

In the discrimination of two groups a filtered P wave duration > 128 ms showed 71% sensitivity, 75% specificity, 51% positive and 88% negative predictive value.

Conclusion: These results indicate that P wave SAECG could be useful to identify patients at risk for the recurrence of atrial fibrillation.

P1759 QT-dispersion during life is closely related to collagen volume fraction at autopsy

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Background: QT-dispersion is a marker of sudden cardiac death (SCD) in a wide spectrum of cardiovascular diseases. Myocardial fibrosis is thought to also cause SCD. We have examined whether QT-dispersion on the surface ECG during life, is related to myocardial collagen content in whole heart autopsy specimens.

Methods: 43 hearts were examined by morphometric analysis of the collagen volume fraction (CVF), using a digital image analysis system. 1,130 myocardial tissue blocks were processed and 25,824 individual fields of myocardium were examined in detail, to calculate the mean-CVF of all 43 hearts. QT and QTc-dispersion were measured manually, by a single, blinded observer, using a digitizer connected to a PC.

Results: The mean age of the patients at death was 72.5 (± 1.7) yrs, range (40.9 to 91.9) yrs. ECG's were obtained 44.0 (± 10.5) days prior to death, range (0 to 364) days. Mean QT and QTc-dispersion were 48.2 (± 3.4) msec and 59.5 (± 4.1) msec-$\frac{1}{2}$, respectively. Mean-CVF was 2.9 (± 0.5)%, range (0.3 to 14.3)%. Results required logarithmic transformation before analysis. Stepwise multiple regression analysis, using 14 clinical variables known to influence QT-dispersion and/or myocardial fibrosis, showed that mean-CVF was the only factor related to QT and QTc-dispersion. The results were highly statistically significant: $p < 0.001$, beta = 0.54 for QT-dispersion and $p < 0.005$, beta = 0.47 for QTc-dispersion.

Conclusion: Our study establishes definitively for the first time, that patchy myocardial fibrosis can be detected during life by QT-dispersion on the surface ECG. It also adds enormous credence to the hypothesis that sudden cardiac death is commonly due to myocardial fibrosis causing electrical inhomogeneity.

P1760 Microvolt T-wave alternans in prediction of ventricular tachyarrhythmic events in patients with non-ischaemic dilated cardiomyopathy

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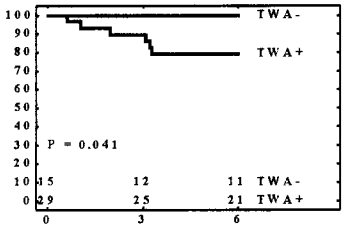
The present study tested the hypothesis whether exercise-induced noninvasive microvolt T wave alternans (TWA) might be of predictive value in patients with non-ischemic dilated cardiomyopathy (DCM). The presence of TWA (CH2000, Cambridge Heart, Bedford, USA) was assessed in patients with DCM who were subsequently followed for at least 6 months for the occurrence of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), or sudden cardiac death (SCD).

Results: A total of 56 DCM patients were studied (age 53 ± 11 years; 38 males; LVEF 28 ± 9%) of whom 16 were recipients of an implanted cardioverter defibrillator and 40 had no history of VT/VF. TWA was positive in 29 patients, negative in 15, and indeterminate in 12. During the 6 months follow-up period, there were 6 events (3 VT and 3 VF) which all occurred among TWA positive patients. The fig. depicts Kaplan-Meier analysis: the 6-months event rate in TWA positive patients was 21%.



Conclusion: The present study demonstrated that microvolt TWA appears to identify DCM patients at high risk for ventricular tachyarrhythmic events. Larger studies are required in patients without prior history of VTE to establish the utility of TWA in these patients.

P1761 Prospective evaluation of the effect of carvedilol therapy on heart rate variability in patients with dilated cardiomyopathy

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Carvedilol has been shown to improve clinical symptoms and left ventricular function in heart failure pts. However, there is limited knowledge of whether carvedilol is able to modify cardiac autonomic tone in these pts. Heart rate variability (HRV) is a noninvasive tool for measuring cardiac autonomic activity. Therefore, the effects of carvedilol therapy on HRV were prospectively assessed in 14 pts (10 m, 45 ± 13 y.) with idiopathic dilated cardiomyopathy (IDC). All pts were in stable clinical condition on constant doses of digitalis, diuretics, and ACE-inhibitors 3 mos before study entry. After a 3- to 4-week titration period, carvedilol was titrated up to 50 mg daily, or the highest dose tolerated (at least 25 mg). Maintenace treatment was then continued for 8 weeks. Digital 24-hour Holter recordings were performed at baseline and after 8 weeks of additional carvedilol therapy. The following standard time domain parameters of HRV were obtained using the Oxford Medilog 2 analysis system: HRm = mean heart rate calculated over 24 hours, SDNN = SD of all normal coupling intervals (NNs), rMSSD = the root mean square of successive differences in RR intervals among consecutive NNs, and pNN50 = percentage of adjacent NNs differing >50 ms.

Results:

	Before carvedilol	Under carvedilol	p-value
HRm (bpm)	88 ± 10	75 ± 10	<0.01
SDNN (ms)	77 ± 21	110 ± 22	<0.001
rMSSD (ms)	19 ± 7	26 ± 7	0.02
pNN50 (%)	1.7 ± 1.3	5.5. ± 4.5	<0.001

Conclusions: Carvedilol therapy leads to a significant increase in HRV parameters related to parasympathetic activity in pts with dilated cardiomyopathy. The prognostic significance of the effect of carvedilol on HRV needs to evaluated in appropriatelly designed prospective studies.

P1762 Different standards of heart rate variability measures for out- and in-hospital cardiological patients

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Values of heart rate variability (HRV) measures differ in healthy subjects and cardiological patients. The aim of the study was to establish standards – criteria for normal and pathological values of HRV for out- and in-hospital patients.

Methods: Prospective study enrolled 1242 consecutive patients, 733 out-hospital and 509 in-hospital, as well as 105 healthy volunteers, aged 51 ± 13, 56 ± 12 and 48 ± 9 years, respectively. 43% were female and 57% male. Arrhythmias of etiology other then coronary artery disease predominate in out-hospital and coronary artery disease in in-hospital pts. HRV was analysed from 24-hour Holter ECG. Limits of normal and pathologic values were determined according to percentiles of distributions of best fitted biomathematical models. Differences between groups were tested by t-test.

Results: Out- and in-hospital patients differ by all HRV measures ($p < 0.001$) (table). All variables differ by age ($p < 0.01$), and slightly by sex. In healthy, out- and in-hospital group, moderately depressed values of LF/HF ratio was 1.4–2.4, 0.8–1.5 and 0.7–1.3, and moderately elevated 4.1–5.8, 4.6–7.5 and 4.4–7.9, respectively.

Means and borderline values of HRV

	SDNN (ms)	rMSSD (ms)	pNN50 %	total power (ms2)	LF (ms2)	HF (ms2)
Healthy – am	147	46	11	4698	1085	401
Borderline	89–109	17–26	1.6–5.2	1401–3103	261–622	85–218
Out-hos – am	146	45	9	4340	841	353
Borderline	72–103	13–22	0.2–1.7	687–1781	89–256	34–89
In-hosp – am	126	40	7	3173	579	237
Borderline	49–86	11–18	0.1–0.7	284–1144	33–134	18–57

am = mean; borderline = moderately depressed; lower values are pathologically diminished!

In conclusion, different HRV standards for out- and in-hospital pts are probably result of different extent of patients daily activities and different kind of their illnesses. So, two standards are proposed for daily work with out- and in-hospital patients.

P1763 Effects of glycemic control on heart rate variability in type I diabetic patients with cardiac autonomic neuropathy

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Background: The presence of cardiac autonomic neuropathy (CAN) is associated with a high risk of cardiovascular events such as ischemia, myocardial infarction, or sudden death. Previous studies have shown that strict glycemic control slows the deterioration of CAN as assessed by standard autonomic function tests (AFTs) but failed to show reversibility. The effect of glycemic control on heart rate variability (HRV) is unknown.

Objective: We evaluated the effect of glycemic control on HRV in type I patients with CAN.

Methods: Ten patients with early and 13 patients with advanced CAN were enrolled in a program of intensified insulin treatment. AFTs and 24-hour time and frequency domain HRV parameters were obtained at baseline, 3, 6, and 12 months.

Results: HbA1C decreased from 9.5 ± 0.4% to 8.4 ± 0.5% ($p = 0.02$) in the early CAN group, and from 9.3 ± 0.4% to 8.2 ± 0.5% ($p = 0.006$) in the advanced CAN group. Both time and frequency domain HRV indices tended to improve in patients with early CAN. The ultralow (ULF), very low (VLF), low (LF) and high (HF) frequency powers increased in patients with early CAN (Table). The improvement in HF at 12 months over baseline indicates increased parasympathetic tone. By contrast, these parameters continued to deteriorate in patients with advanced CAN. AFTs showed no significant change in both groups.

Effects of glycemic control on HRV

Groups	HRV	Baseline	3 months	6 months	12 months
Early CAN	ULF	7494 ± 1284	8430 ± 2191	8180 ± 2857	7611 ± 3606#
	VLF	737 ± 163	984 ± 505	1124 ± 624	982 ± 722*
	LF	229 ± 95	394 ± 292	462 ± 318	626 ± 563*
	HF	62 ± 30	106 ± 77	132 ± 90	183 ± 168*+
Advance CAN	ULF	5990 ± 1897	4404 ± 855	4687 ± 985	6114 ± 849
	VLF	693 ± 213	631 ± 240	572 ± 180	483 ± 84
	LF	193 ± 75	173 ± 84	171 ± 76	144 ± 33
	HF	65 ± 32	56 ± 26	46 ± 21	46 ± 8

#$p < 0.01$ compared with the advance CAN group; * $p < 0.05$ compared with the advance CAN group; +$p < 0.05$ compared to baseline.

Conclusions: A reversible metabolic component of CAN exists in a subgroup of patients even after many years of type I diabetes. Power spectral analysis of HRV allows early identification of potential reversibility as early as 1 year after the institution of strict glycemic control.

P1764 Redefining limits for the low-frequency area of heart rate variabilty helps detecting sympathetic activation

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Sympathetic overactivity has been associated with sudden death in patients with heart disease. A reliable measure of sympathetic activation does not exist and its controversial whether the low-frequency area (LF: 0.04–0.15 Hz) of heart rate variability (HRV) is suitable for measuring sympathetic activity. We hypothesized that the LF area was too broadly defined and a narrower low-frequency band was better suited for detecting sympathetic activation.

Methods: Fourteen healthy subjects were examined for one hour of supine rest and one hour of 60 degr. head-up tilt during control circumstances, with beta-blockade (metoprolol) and with muscarinic blockade (atropine). The time-series of RR-intervals was dividided into successive 5-min time-series and Fourier analysis was performed. The LF area was divided into subbands (0.04 – 0.06 Hz, 0.06 – 0.08 Hz, 0.08 – 0.10 Hz, 0.10 – 0.12 Hz and 0.12 – 0.15 Hz). Powers from each 5-min analysis were then averaged for the supine period and for the tilted period.

Results: The total LF power of HRV did not change significantly with tilt. Analysis of the LF subbands revealed that in the area 0.06–0.10 Hz power rose during tilt (496 ± 22 msec2 to 992 ± 35 msec2, $p < 0.01$). The rise was abolished by betablockade (565 ± 44 msec2 to 465 ± 29 msec2, ns) and was seen again during muscarinic blockade (8 ± 1 msec2 to 29 ± 2 msec2, $p < 0.01$).

Conclusion: Total low-frequency power of HRV seems to be a poor measure of sympathetic activation in contrast to power in the 0.06–0.10 Hz area. The limits of the LF area should possibly be redefined if HRV is going to be useful in assessing autonomic activity.

P1765 Association between rate corrected QT interval and coronary risk factors: results from a cohort of 2764 apparently healthy subjects

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Prolongation of corrected QT interval ($QTc = QT/RR^{\frac{1}{2}}$ where RR = 60/heart rate) is a risk factor of sudden death in patients without intraventricular conduction defects and cardiac dysfunction, independent of age, history of myocardial infarction and heart rate. However, there is little information concerning the QT duration and its relation with coronary risk factors in apparently healthy subjects. Between 1994 and 1996, 2764 subjects (1484 women, 1280 Men, aged 30 to 64 years) without bundle branch block, previous myocardial infarctions, known ischemic heart disease, or diabetes and who were not taking medication that might affect QT duration had a 12-lead electrocardiogram recorded in the frame of an ongoing follow-up study, the D.E.S.I.R. study (Data from an Epidemiological Study on the Insulin Resistance Syndrome) and a determination of fasting glucose and insulin, serum lipid concentrations, tobacco and alcohol consumptions and physical activity. QT was measured automatically with a dedicated algorithm (Cardionics®) and the formula used for rate-correction was based on the best-fit regression between variables: QTk = (QT/RR)power(k) (k estimated by 0.352 for men and 0.345 for women). In men (mean QTk = 377 ± 17 ms), after adjusting for age, there was an inverse correlation between QTk and glycated hemoglobin (HbA1c) ($R = -0.12$, $p < 0.001$) and fasting insulin ($R = -0.07$, $p < 0.01$). Results remained significant after adjustment on body mass index, arterial pressure, and serum lipids. In women (mean QTk = 383 ± 17 ms), there was an inverse correlation between QTk and HbA1c ($R = -0.12$, $p < 0.001$) and fasting plasma glucose ($R = -0.12$, $p < 0.001$) and results also remained significant after adjustment on other parameters. Alcohol consumption did not affect QTk duration nor in men or women whereas high tobacco consumption ($p = 0.02$) and high physical activity ($p < 0.0001$) were associated with an increase in QTk in men.

Conclusion: After adjusting for heart rate, QT duration was influenced by glucose homeostasis, tobacco consumption and physical activity in healthy subjects. These findings may help to understand the mechanisms of sudden death in apparently healthy subjects.

P1766 Baroreflex sensitivity and heart rate variability in patients with and without sustained T-wave alternans after an acute myocardial infarction

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Background: T-wave alternans (TWA) at microvolt level during exercise has been shown to be a risk marker of ventricular tachyarrhythmias. We studied possible relation of TWA to other arrhythmic risk markers of autonomic nervous system, i.e. baroreflex sensitivity (BRS) and traditional and new dynamic measures of heart rate variability (HRV).

Methods: Occurrence of sustained TWA during ergometer exercise test, BRS by phenylephrine method, standard deviation of all R-R intervals (SDNN) and short-term (detrended fluctuation analysis, DFA1) and long-term (1/f slope) fractal correlation properties of HRV from 24-hour ECG recordings were assessed in a prospective consecutive series of 162 patients after an acute myocardial infarction. QT interval dispersion (QTd) and signal-averaged ECG (SAECG) were also analyzed.

Results: There were no significant differences in either BRS or any of the HRV measures between TWA+ and TWA- patients (table). Neither did SAECG nor QTd differ between these groups.

	TWA+ (n = 24)	TWA- (n = 138)
BRS	7.2 ± 6.1	8.4 ± 7.2
SDNN	95.3 ± 22.4	98.9 ± 33.0
DFA1	1.20 ± 0.19	1.26 ± 0.26
1/f slope	−1.30 ± 0.19	−1.31 ± 0.19

Conclusions: Presence of TWA during exercise shortly after an acute myocardial infarction is not related to BRS, HRV or to other noninvasive markers of ventricular tachyarrhythmias. Future follow-up study will reveal the predictive value of TWA in arrhythmic risk stratification in relation to other arrhythmia risk factors.

P1767 Improved risk assessment in patients with chronic heart failure and healthy controls using nonlinear heart rate variability analysis

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Background: Mortality is high in patients with chronic heart failure (CHF). Analysis of heart rate variability (HRV) has been shown to bear prognostic information in CHF patients. In this study, we evaluated the prognostic value of a new quantitative parameter of nonlinear HRV, alpha-comb, in CHF patients and healthy controls.

Methods: We applied a geometrical description of 3-dimensional Poincare plots, i.e. a graphical description of all heart beats present in a 24 hr electrocardiogram. The result of this procedure, the parameter alpha-comb, was obtained in 100 patients with mild to moderate CHF (age 59 ± 7 yr [mean ± sd], left ventricular ejection fraction [LVEF] 0.29 ± 0.09) and in 96 age-matched healthy controls.

Results: During up to 7.5 years follow up, 30 of the CHF patients died, 26 of cardiac death. The mean alpha-comb was 1.5 ± 1.1 in nonsurviving CHF patients, 2.0 ± 1.1 in surviving CHF patients and 2.6 ± 0.7 in healthy controls. In univariate and multivariate survival analysis, the relative risk for cardiac death of an alpha-comb below 2.0 was 9.6 (95%CI 2.9–32.2, $p < 0.001$) and 6.3 (95%CI 1.8–21.8, $p < 0.01$), respectively. For an LVEF below 0.30, this was 4.7 (1.8–12.4, $p < 0.01$) and 4.3 (95%CI 1.4–13.7, $p < 0.05$), respectively. Adding the criterium of an alpha-comb < 2.0 to an LVEF < 0.30 resulted in a sensitivity for cardiac death of 73% with a specificity of 83%, which is remarkably high in such a patient population. Conventional time and frequency domain parameters of HRV were not significantly related to survival.

Conclusions: Alpha-comb, a new quantitative non-linear HRV parameter based on a geometrical description of 3-dimensional Poincare plots, provides a risk assessment for cardiac mortality in CHF patients which is significantly better than that of standard HRV parameters. Compared to LVEF, the prognostic value of alpha-comb is at least as good, and, moreover, complementary. Further studies will be needed to confirm these data.

P1768 Is heart rate variability regulated from an open loop system from blood pressure variability?

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Variations in heart rate (HRV) are known to be regulated by blood pressure via the baroreceptors. Mechanical denervation of the baroreceptors gives rise to an increase in blood pressure variability. The aim of this study was to study the effect of chemical abolition of HRV with atropine on blood pressure variability (BPV).

Methods: Ten healthy volunteers (5 men and 5 women) were examined twice during three hours of rest in supine position. The first day served as control condition, and on the second day the subjects received a bolus injection of atropin 2 mg intravenously, followed by an infusion of atropin 8 microg/(kg body weight * h). ECG and finger systolic blood pressure (Finapress) were recorded during the whole experiment. Paired series of RR-intervals and blood pressure were analyzed in the frequency domain with Fourier spectral analysis.

Results: As expected HRV were significantly decreased after parasympathetic blockade in all frequency bands (Total Power, ULF, VLF, LF and HF). However in SPV no changes at all were found in the same bands as shown in table 1.

Table 1. HRV and BPV during control period and atropine infusion in the different frequency bands. (Mean ± SE)

	RR control	RR atropine	BP control	BP atropine
log(ULF)	19.1 ± 1.1	17.0 ± 1.4*	14.9 ± 1.1	15.0 ± 1.1
log(VLF)	17.8 ± 0.2	14.8 ± 0.3*	12.9 ± 0.2	13.0 ± 0.2
log(LF)	17.0 ± 0.2	13.2 ± 0.4*	12.0 ± 0.2	12.0 ± 0.2
log(HF)	16.3 ± 0.4	10.9 ± 0.5*	10.4 ± 0.2	10.4 ± 0.2
LF/HF	2.3 ± 0.5	15.3 ± 4.3*	5.7 ± 0.8	5.9 ± 1.6
log(TP)	20.1 ± 0.8	18.0 ± 1.1*	15.8 ± 0.8	15.8 ± 0.9

*p < 0.01 compared to control.

In conclusion: BPV was not affected at all by atropine. This finding makes the classical view of HRV and BPV as a closed loop feedback system unlikely. Blood pressure affects HRV by the baroreceptors, but the influence of HRV on BPV seems negligible. It seems that the interaction from BPV to HRV is a simple feed forward network with no back propagation.

P1769 Prognostic value of heart rate variability and its evolutionary pattern very early after acute myocardial infarction

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Background: Although experimental data have shown that speed of recovery of heart rate variability (HRV) after acute myocardial infarction (AMI) is related to clinical outcome in animals, no relevant information is available on humans. Furthermore, the prognostic significance of HRV very early after the acute event has not been studied comprehensively.

Methods: 108 successive pts aged 59 ± 8 years old that all received thrombolysis for AMI (5 ± 3 hours after onset of symptoms) were subjected to 24-hour ECG recording as soon as thombolysis had ended (D0) the next day (D1) and 5 ± 1 days after admission (D5). HRV was assessed and the pts were followed-up for a period of three years. Resuscitated cardiac arrests were considered cardiac deaths for the purposes of the study.

Results: During follow-up 11 pts were resuscitated or died of cardiac cause. Comparisons are shown in the table (non-survivors typed in italics).

HRV	D0	D1	D5	F
SDNN	*72 ± 20*	*62 ± 21*	*70 ± 24*	0.843
SDANN	*62 ± 19*	*52 ± 20*	*63 ± 21*	0.858
RMSSD	*35 ± 13*	*27 ± 13*	*26 ± 12*	0.911
SDNN	87 ± 36	76 ± 29	89 ± 27*	
SDANN	74 ± 30	68 ± 22*	79 ± 22*	
RMSSD	41 ± 25	35 ± 30	34 ± 16	

* = p < 0.05 from non-survivors for the same HRV measure at the same day, F for ANOVA test (interaction of repeated HRV measurements × death effect).

Conclusions: Very early after AMI, evolutionary pattern of HRV did not differ between pts that survived or died of cardiac cause in the long term. However, HRV may yield prognostic information 24-hours after the acute event, possibly offering a clinical benefit due to earlier risk stratification.

P1770 Relation between QT variability and autonomic cardiac function before episodes of non-sustained ventricular tachycardia in hypertrophic cardiomyopathy

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We analysed the dynamic changes in the QT interval in relation to autonomic cardiac control immediately before episodes of non-sustained ventricular tachycardia (NSVT) in patients with hypertrophic cardiomyopathy (HCM).

Methods: The study group consisted of 17 patients with HCM (11 men, 6 women) with a mean (SD) age of 60 (10) years, who had at least one episode of NSVT recorded in ambulatory 24-hour Holter monitoring (ELA MEDICAL). All sinus complexes were averaged over 30 s periods, creating 2880 templates. For each template, mean corrected QTe (time interval between the onset of QRS and the offset of the T wave), mean corrected QTa (time interval between the onset of the QRS and the peak of the T wave), their standard deviations (SDQTe and SDQTa), QTe/RR and QTa/RR were calculated. Spectral HRV was expressed as low (LF) (0.039 to 0.148 Hz) and high (HF) (0.160 to 0.398 Hz) frequency components and LF/HF was used as an index of sympathovagal balance of the heart. Five-minute segments were analysed, immediately before and 1 hour after episodes of NSVT. In order to examine the relationship between autonomic balance and ventricular repolarisation we plotted the LF/HF ratio against the Qtec and QTac using linear correlation and regression analysis.

Results: In total, 42 5-minute segments (21 episodes) were analysed. QTac was significantly higher and SDQTa lower before than 1 hour after NSVT (322 ± 20 vs. 313 ± 22, $p < 0.006$ and 2.8 ± 1.1 vs. 4.7 ± 3.6, $p < 0.03$, respectively). No differences were found in QTec, SDQTe, QTe/RR and QTa/RR. The LF/HF ratio was higher before the NSVT (3.78 ± 2.8 vs. 1.39 ± 2.3, $p < 0.02$). There was a significant correlation between the LF/HF ratio and QTac only during 5-minute periods before NSVT ($r = 0.85$, $p < 0.0001$).

Conclusion: In patients with HCM the QTac interval is prolonged before episodes of NSVT and this prolongation is related to sympathetic predominance.

P1771 Identification of sleep-related breathing disorders from the very low component of the heart rate variability

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Cyclical low oscillations of the heart rate during night had previously been described in sleep-related breathing disorders. Thus, ECG Holter monitoring with spectral analysis of the heart rate variability (HRV) could represent a simple screening tool for detection of obstructive sleep apnea syndrome (OSAS).

The purpose of the present study was to evaluate the diagnostic yield of such method in patients referred to our sleep laboratory for clinically suspected OSAS. We correlated in 124 patients (98 males) mean (±SD) aged of a 53.8 ± 11.2, the frequency-domain HRV variables obtained from 24 h ECG Holter monitoring and respiratory disturbances indexes (RDI) assessed with complete polysomnography. The presence of an abnormal periodic breathing pattern was characterise in time-scale and evaluate on the plot of the spectrum for the interbeat interval increment as a function of inverse beat number. The occurrence of repetitive sleep apnea was associated with a spectral peak at about 0.02–0.05 $beat^{-1}$. The power spectral density of the very low frequency (VLFpsd) band (0 to 0.05 $beat^{-1}$) and the percentage of these component (%VLF) on the total power spectral density was computed.

There were no differences in clinical characteristics between patients with and without OSAS. The apparence of a VLF peak (mean frequency 0.03257 ± 0.009 $beat^{-1}$) was detected in 51 out of the 54 OSAS patients. We founded a high sensitivity (94.4%), a high specificity (97.1%) for this unique criteria. Using ROC curves, the %VLF appeared as the most powerfull separator for OSAS ($W = 0.80$, $p < 0.0001$), followed by the VLFpsd ($W = 0.79$, $p < 0.0001$). A positive correlation was founded between the RDI and, the two continuous previously described variables of HRV (%VLF: $r = 0.56$, $p < 0.001$; VLFpsd, $r = 0.50$, $p < 0.01$).

Frequency-domain analysis of HRV could thus represent an efficient tool in screening OSAS. The ease of use and of interpretation is of interest considering the high prevalence of OSAS in a general middle-agged population.

P1772 QT dispersion in patients with different aetiology of left ventricular hypertrophy

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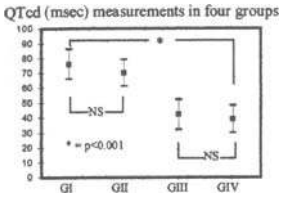
QT dispersion (QTd) is associated with abnormal ventricular repolarisation and cardiac arrhythmias. Left ventricular hypertrophy (LVH) is an adaptive mechanism to pressure overload and may play an important role in the development of serious cardiac arrhythmias. The purpose of this study was to detect the QTd in patients (pts) with different etiology of LVH.

Methods: We studied 86 patients with 3 different etiology of LVH and 30 healthy individuals. Study population was divided into four groups. In Group I. there were 52 pts (mean age: 54 ± 12, 36 male) with essential hypertension. Group II. Consisted of 35 pts (mean age: 50 ± 10, 26 male) with valvular aortic stenosis. There were 29 elite athletes in Group III. (Mean age: 58 ± 11, 25 male) and were 30 healthy subjects (mean age: 56 ± 9, 23 male) in Group IV. Patients in Group I. and II. had normal coronary angiograms. QTd was measured from surface ECG and Bazett's formula was used to correct QTd (QTcd) for heart rate. Left ventricular mass was determined by echocardiography (Deveruex formula) and left ventricular mass index (LVMI) was calculated in relation to body surface area.

Results: The QTd was significantly higher in Group I. and II. than Group III. and IV. ($P < 0.001$).



Group	QTcd (mesc)	LVMI (g/m2)
I	73 ± 8	196 ± 15
II	70 ± 9	184 ± 12
III	42 ± 10	221 ± 20
IV	39 ± 9	94 ± 15

Conclusion: Although left ventricular hypertrophy develops both in pathological and physiological conditions, QTd is associated with only pathological conditions. Even significant degree of left ventricular mass increase due to sportive endurance training does not induce QTd. These healthy individuals are probably less prone to develop serious ventricular arrhtyhmias.

P1773 Prognostic value of repolarisation analysis in patients with hypertrophic cardiomyopathy – comparison of QTc and QTd measurement

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We compared the prognostic value of repolarisation analysis in standard ECG and 24 h QTc measurement in pts with hypertrophic cardiomyopathy [HCM].

Material and methods: Retrospective study – standard 12-leads ECG (50 mm/s) and Holter recordings of 50 HCM in age 15–50 y (on no medications) was performed. QT, QTd and QTc (Bazett formula) were measured in standard ECG and QT, QTc beat by beat during 24 h ECG.The presence of more than one risk factor [RF > 1] (family history of SCD, history of syncope, history of VT, blood pressure decrease during exercise test) was treated as high risk. During the follow up (12–66 months) 7 sudden deaths were recorded. This group [SCD] was compared with 43 survivors [sHCM].

Results: QTc was prolonged in SCD group in standard and Holter ECG – 474 ± 45 vs 425 ± 31 ms ($p = 0.001$) and 465 ± 15 vs 416 ± 27 ms ($p < 0.0001$). QTd was also increased in SCD group – 57 ± 16 vs 40 ± 13 ms ($p = 0.002$). These pts had also more clinical RF (1.8 ± 1 vs 0.9 ± 0.9, $p = 0.02$). Prognostic value of different parameters is presented in the table.

Table

	SCD (7 pts)	sHCM(43 pts)	Sens.	Spec.	Pred. accurac.
QTcECG > 440 ms	7 pts	14 pts	100%	67%	72%
QTcECG > 450 ms	4 pts	12 pts	57%	72%	70%
QTcHol > 440 ms	7 pts	6 pts	100%	86%	88%
QTcHol > 450 ms	7 pts	4 pts	100%	91%	92%
QTd > 50 ms	5 pts	11 pts	71%	74%	74%
>1 RF	5 pts	14 pts	71%	67%	69%

Conclusions: 1. Prognostic value of repolarisation alterations analysis seems to be high in HCM pts. 2. The highest predictive accuracy was obtained with 24 h QTc analysis. 3. This results should be verified in prospective study.

P1774 The effect of heart rate on T-wave alternans with or without organic heart disease

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Microvolt T wave alternans (TWA), that measured by a spectral method (CH2000. CAMBRIDGE HEART. Inc), has been associated with increased susceptibility to life-threatening ventricular tachyarrhythmias (VT). However, not a small number of false positive results are concerned.

Methods: The aim of this study is to evaluate the effect of heart rate on TWA of patients with or withiut organic heart disease (OHD) and/or VT. We measured TWA during right atrial pacing in consecutive 127 patients (60 ± 18 years, M/F = 74/53) undergoing electrophysiologic study. Twelve pts have OHD and VT, 40 pts: OHD+/VT−, 5 pts: OHD−/VT+, 70 pts: OHD−/VT−. Recordings of TWA were made with atrial pacing at 80, 90, 100, 110, and 120 beats/min (bpm). Positive TWA was defined as an alternans voltage 1.9 μV for a period at least 1 minute in at least VM, X, Y, Z, or adjacent two precoidal leads and an increasing alternans voltage with pacing rate.

Results: The number of TWA positive patients at each group.

	80	90	100	110	120 bpm
OHD+/VT+	2 (17%)	6 (50%)	8 (67%)	9 (75%)	11 (92%)
OHD+/VT−	1 (3%)	5 (13%)	8 (20%)	15 (38%)	16 (40%)
OHD−/VT+	0	1 (20%)	1 (20%)	1 (20%)	1 (20%)
OHD−/VT−	0	0	2 (3%)	8 (11%)	14 (20%)

TWA was not seen at sinus rhythm in any group.

The predictive value of TWA for OHD+/VT+ at each pacing rate.

bpm	Sens.	Spec.	P.P.V	N.P.V	Accuracy
120	0.916	0.691	0.261	0.986	0.717
110	0.750	0.752	0.265	0.962	0.752
100	0.666	0.891	0.421	0.957	0.867
90	0.500	0.941	0.500	0.941	0.894
80	0.167	0.990	0.333	0.909	0.902

P.P.V: Positive Predictive Value, N.P.V: Negative Predictive Value

Conclusions: 1). Sensitivity increased with incresing pacing rate, but specificity was declined. 2). Pts with OHD+ have high incidence of false positive results with increased heart rate, that should be paid attention.

P1775 A new index of heart rate variability

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Background: Analysis of heart rate variability (HRV) over a 24-hour period has been studied in both time and frequency domains. All methods suffer from poor repeatability and a simple, easy to understand outcome. For this reason, a new index of HRV was developed.

Methods: Scattergrams (Poincare plots) of 24-hour normal to normal RR interval variability were calculted for 210 middle aged healthy subjects (173 men, 37 women, mean age 49.5 ± 6.0 years). All had been examined by a physician and none had signs or symptoms of cardiovascular disease. The plots were divided into 256 squares each of $0.01s^2$ area. In each square, the total number of points was counted. If N1 and N2 represent the two highest counts from any of the squares, NN represents the total number of all normal RR intervals and NN50 is the number of intervals that differ from successive intervals by more than 50 ms, then the new index is as follows:

HRV fraction = [1 − (NN1 + NN2)/(NN − NN50)].100%

which is a number that varies between 0 to 100%.

Results: The mean normal value was 52.7 ± 8.58% with a 96 percentile range of 35.12–70.28%. The HRV fraction was significantly lower in females than in males (48.74 ± 8.43% versus 53.58 ± 8.39% $p = 0.002$).

In 165 patients, day to day reproducibility was assessed. The correlation co-efficient for the HRV fraction was 0.781 compared to 0.666 for the triangular index.

Conclusion: The new HRV fraction is simple to compute and easy to understand (cf LV ejection fraction) and overcomes many of the limitations of existing measures of HRV. It has been shown to have greater prognostic value than other time domain indices in a separate study of perioperative morbidity and mortality.

P1776 Ultrashort-term heart rate variability increaces and long-term variability decreaces prior to spontaneous ventricular fibrillation

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Decreaced heart rate variability (HRV) is recognized as a long-term predictor of sudden death in post-myocardial infarction patients. It is not known if acute changes in HRV precede the onset of ventricular fibrillation (VF). The purpose of this study was to determine if changes in HRV occur prior to spontaneous VF.

Methods: The Medtronic Jewel + TM ICD stores 1000 RR intervals prior to the last detected episode of VF and 1000 RR intervals prior to interogation. We compared time domain analysis of HRV for the intervals recorded immediately prior to detected VF with HRV for baseline RR intervals recorded at routine ICD follow-up. Twelve episodes of VF were analyzed in 10 patients (8 men, 2 women; ages 62 ± 11 years; LV ejection fraction 25 ± 12%). Spontaneous VF was diagnosed by stored electrograms as the abrupt onset of a polymorphic rhythm with mean cycle length < 250 ms. Episodes of VF preceded by ventricular tachycardia were excluded. Ultrashort-term HRV, was measured by the number of normal intervals which differed from the preceding interval by >50 ms (pNN50). Long-term variability was measured by the standard deviation of the average RR intervals of 5 successive 200 interval segments (SDANN).

Results: The mean VF cycle length was 220 ± 45 ms. pNN50 (ultrashort-term variability) increased prior to VF; 22 ± 18 vs 64 ± 72, p = 0.03), suggesting an increase in vagal tone. SDANN (long-term variability) decreased prior to VF; 44 ± 41 ms vs 18 ± 14 ms, p = 0.03. Sinus cycle length was not significantly different: 820 ± 135 ms at baseline vs 780 ± 220 ms prior to VF; p = NS.

Conclusion: Ultrashort-term HRV increaces and long-term HRV decreases immediately prior to VF. Calculation of pNN50 and SDANN may permit ICDs to predict spontaneous VF.

P1777 Failure of heart rate variability measurements to predict all cause cardiac mortality post-infarction

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Purpose: This study aimed to determine the predictive power of heart rate variability [HRV] in a cohort of infarct patients discharged from hospital on optimum post MI drug therapy.

Methods: 204 consecutive post-MI patients were studied in the period 1996–97. 135 (66%) had received thrombolysis on admission. At discharge 163 (80%) were taking Aspirin, 135 (67%) B-blockers, 83 (41%) ACE-inhibitors, 36 (18%) statins and 30 (15%) warfarin. HRV was measured 3–6 days post MI, from an ECG record of 1024 QRS sinus complexes. Patients were followed for 1 year or until death.

Results: During follow up, 19 (9.3%) patients died, 16 (7.8%) of cardiac causes (cardiac failure 3, reinfarction 7, sudden 6). No patient was documented to have sustained VT. There was no statistically significant difference in mean (standard deviation [SD]) of any time domain or frequency domain measurements of HRV between survivors and patients who died of cardiac causes.

HRV variables measurements

	Survivors (n = 185)	Cardiac deaths (n = 16)
Mean RR (ms)	973 (173)	934 (217)
SDNN (ms)	46 (31)	37 (22)
Mean DRR (ms)	26 (45)	23 (25)
SDSD (ms)	22 (26)	21 (26)
RMSSD (ms)	35 (52)	31 (36)
LF/HF ratio	22 (1.6)	23 (1.7)

SDNN = SD of all RR intervals; DRR = difference between all RR, SDSD = SD of successive difference between RR; RMSSD = root mean square of successive difference; LF/HF = lower/ high frequency power ratio.

Conclusion: Contrary to previous studies, HRV failed to predict all cause cardiac mortality. Probable explanations for this include low overall cardiac and sudden death rates. Both the negative result and low event rates however may be explained by the increased use of thrombolysis during MI and/or by beta blocker and ACE-inhibitors use during recovery.

P1778 Postural heart rate variability for predicting mortality after acute coronary syndrome

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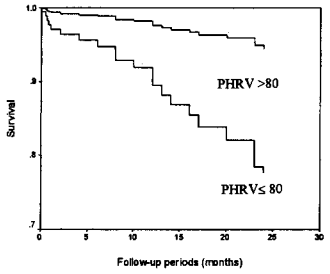
Background: Heart rate variability (HRV) derived from standard 24-hour electrocardiogram (SHRV) on patients after acute myocardial infarction has been used to assess autonomic control of heart rate and to predict mortality. However, this technique is expensive and time consuming.

Objective: To evaluate a new, simple, inexpensive and easy to perform HRV technique, derived from supine-upright difference in RR intervals called "Postural Heart Rate Variability (PHRV)", as a predictor of mortality after acute coronary syndrome.

Methods & Results: 100 consecutive patients (mean age 63 years, range 29–86 years, 60 males and 40 females) admitted to the coronary care unit with diagnosis of acute coronary syndrome (acute myocardial infarction and unstable angina), in sinus rhythm and hemodynamically stable state, were studied. SHRV and PHRV were assessed from each patients simultaneously during the acute phase of acute coronary syndrome. Baseline clinical characteristics and all drugs used were recorded. Primary end-point was all-cause mortality. Patients were followed up for 24 months (mean 17.7 months), 30 died and 39 developed congestive heart failure (CHF). There were moderate correlation between SHRV and PHRV (r = 0.53, p < 0.05). The PHRV of the dead vs survivors were 64.4 ± 43.5 vs 95.8 ± 73.9 ms, p < 0.05, and of those with and without CHF 67.5 ± 43.6 vs 101.5 ± 78.8 ms, p < 0.05. Lower PHRV were also observed in patients with diabetes (DM) and hypertension (HT). Different cut-off values of PHRV were searched for calculating sensitivity and specificity and then plotted on Receiver Operator Characteristics curve (ROC curve). PHRV ≤ 80 ms provided sensitivity of 86.7%, and specificity of 40.6% with positive and negative predictive values in these population of 33.9% and 86.7% respectively. PHRV ≤ 80 ms had Odd Ratios for predicting all-cause mortality 4.9 (1.1–22.2) p = 0.03, after adjusted for age, heart rate, CHF, DM, HT, history of angina, smoking, CABG/PTCA and drugs used.



Conclusion: A simple technique of heart rate variability, derived from supine-upright RR intervals called Postural Heart Rate Variability, was found to correlate moderately with standard 24-hour heart rate variability method. It can be used as an independent predictor for mortality after acute coronary syndrome.

P1779 Baseline heart rate is an independent risk predictor in patients with coronary artery disease

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We investigated the impact on long-term mortality of heart rate (HR) among 11,575 unselected patients (pts) with coronary artery disease (CAD) screened but not included in the BIP Study. The characteristics and outcome of pts divided into three subgroups according to their baseline HR (Group 1 – HR < 65 b/min (n = 2370); Group 2 – 65–75 b/min (n = 6018); and Group 3 – >75 b/min (n = 3126) were as follows:

	Group 1	Group 2	Group 3
Men (%)	80	79	76
Age (mean)	60.2 yrs	59.8 yrs	59.6 yrs
Prior MI (%)	67	72	73
Diabetes (%)	15	21	27
Hypertension (%)	34	32	36
Smoking (%)	11	11	13
Total cholest. (mean)	222.2 ± 34	224.7 ± 34	224.2 ± 35
NYHA ≥ 2 (%)	24	28	34
Aspirin (%)	61	57	55
β-Blockers (%)	53	33	22
Ca-Blockers (%)	50	51	50
Digoxin	3	4	7
Crude 5 yr mort. (%)	8.7	12.9	18.4
Hazard Ratio*	1.0	1.47	2.06
and 95% CI	–	(1.26–1.72)	(1.75–1.43)

**Adjusted for: age, gender, prior MI, diabetes, NYHA class, β-Blockers, Ca-Blockers and ACE-I use.*

Conclusion: This study suggests that the baseline HR is an independent mortality predictor in pts with CAD. However, it remains to be proven that reduction of HR will improve the outcome of pts with CAD.

P1780 Effects of β-blockade on the circadian profile of time domain heart rate variability in patients surviving acute myocardial infarction

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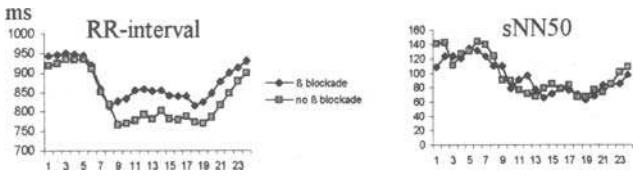
Beta blockade (BB) has proven to be of beneficial effect in patients (pts) recovering from acute myocardial infarction (AMI). However, data on the effects of BB-therapy on heart rate variability (HRV) – marker of sympathovagal balance – are surprisingly rare.

Methods: We enrolled 185 consecutive pts 13 ± 2.5 days after AMI (83 anterior, 102 inferior; 137 underwent thrombolytic therapy). 126 pts received metoprolol 50–200 mg/day, 59 pts had no BB therapy. There were no significant differences between the two groups regarding age, gender, peak creatine kinase level, left ventricular ejection fraction, infarct site and size. HRV parameters (sNN50, pNN50, SDNN, rMSSD and RR-interval) were analysed from 24-hour-Holter monitoring and were calculated as hourly mean values.

Results: Pts with BB therapy exhibited significantly longer RR-intervals at daytime. At nighttime the course of RR-cycle lenght was not significantly different from that in pts without BB. The morning decrease was sharper in pts with no BB therapy. Time domain HRV parameters showed a circadian profile, however, there were no significant differences in pts with and without BB therapy in both, day- and nighttime.



Conclusion: BB therapy dampens the day-night-difference of RR-cycle lenght in pts after AMI, but it does not affect the circadian profile of time domain HRV. Our finding suggests, that hourly measured time domain HRV is independent of any BB therapy in pts after AMI.

P1781 Determinants of the parasympathetic enhancement during the "diving" reflex

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The origin of the diving reflex (apnea + face immersion in cold water, causing sustained vagal activation) is unclear. To assess the relative contribution of apnea, immersion and water temperature, we recorded RR interval (RR), calibrated respiration and systolic blood pressure (SBP) in 11 volunteers (29 ± 2 yr) breathing through a snorkel, before (4 minutes, NO-APN) and during 40 s apnea (APN), while the face was maintained in air (AIR), warm (28°C, WW) or cold (12°C, CW) water. We measured ventilation and sympatho-vagal balance by spectral analysis (low- and high-frequency, respiratory components, HF and LF, markers of vagal and sympathetic activity) of RR and SBP. Compared to NO-APN-AIR, NO-APN-CW and NO-APN-WW increased RR, RR variability (standard deviation, SD) and%HF, while reduced%LF (mean: from 772 ± 26 to 834 ± 37 to 822 ± 32 ms, $p < 0.05$; SD: from 48.8 ± 4.2 to 66.9 ± 6.2 to 57.9 ± 6.1 ms, $p < 0.05$; HF: from 42.7 ± 7.6 to 51.4 ± 5.9 to 53.3 ± 6.8%, $p < 0.05$ LF: from 52.9 ± 7.4 to 36.8 ± 4.2 to 38.4 ± 7.4%, $p < 0.005$), without change in breathing frequency and depth. WW and CW conditions gave similar results. SBP remained unchanged in NO-APN conditions (both mean and spectral values). APN provoked no change in RR, markedly reduced all HF (absence of breathing), but increased the RR-LF (from 6.38 ± 0.25 to 6.90 ± 0.17 ln-ms^2, $p < 0.005$) and SBP-LF powers (from 2.28 ± 0.29 to 3.44 ± 0.21 ln-mmHg^2, $p < 0.005$), regardless of AIR, WW or CW.

The evident vagal activation seen during the "diving" reflex appears to be due to water immersion in itself rather than the apnea, with little or no effect of water temperature

P1782 Cardiocirculatory coupling during sinusoidal baroreceptor stimulation and fixed-frequency breathing

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The question, as to whether respiratory sinus arrhythmia (RSA) is mainly created by a central coupling between respiration and heart rate, or by baroreflex mechanisms, is controversial. In the case of a major contribution of baroreflexes to RSA, cardiocirculatory coupling during breathing, and during cyclic baroreflex stimulation, should show similarities.

We applied a sinusoidal stimulus to the carotid baroreceptors (neck suction, NS) and generated heart rate fluctuations of the same magnitude as RSA with a frequency near, but different from the breathing frequency (0.2 Hz vs. 0.25 Hz) and at a lower frequency (0.1 Hz) in 17 healthy subjects, aged 29–39 years. Measurements were performed supine and upon 60° tilting, to assess the effects of changed autonomic activity. The data were analyzed by Fourier transform, transfer function and phase analysis.

Respiratory fluctuations in systolic blood pressure (SBP) preceded sinus arrhythmia with a time lag equal to that between baroreceptor stimulation and oscillations in RR intervals (0.62 ± 0.18 s vs. 0.57 ± 0.28 s). Although NS at 0.1 Hz largely increased SBP fluctuations, the spontaneous phase relations between blood pressure (leading) and RR intervals (lagging) remained unchanged. During NS at 0.2 Hz, RR interval fluctuations generated only a minor response in SBP (five times less than spontaneous respiratory blood pressure fluctuations). Head-up tilt increased the time lag between NS and the other signals.

The observed similarities between the effects of baroreceptor stimulation and spontaneous sinus arrhythmia do not support the hypothesis that the origin of RSA, in healthy subjects, is predominantly a central phenomenon which secondly generates fluctuations in blood pressure. The lack of increase in SBP fluctuations during 0.2 Hz NS suggests that respiration affects blood pressure mainly by mechanical (stroke volume) rather than autonomic mechanisms, and that RSA depend on blood pressure fluctuations and not vice versa.

P1783 Assessment of QT dynamicity by evaluation of QT/RR relation from 24-hour Holter ECGs in patients after myocardial infarction

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To evaluate the QT dynamic in patients (pts) after acute myocardial infarction (MI), 14 pts (age 60 ± 7 years, 12 men) who died suddenly (SCD) within 1 year after MI and 14 pair-matched (age, sex, left ventricular ejection fraction, infarct site, thrombolytic therapy) pts who remained event-free after MI (survivors) for ≥3 years were studied. Fourteen normal subjects served as controls (CON, age 55 ± 9 years, 11 men). QT and RR intervals were automatically measured on a beat-to-beat basis with visual control from 24-h ambulatory ECGs using Pathfinder 700 (Reynolds Medical, UK). Mean hourly values of the QT/RR slope ($QT = \alpha + \beta RR$) and corrected QT interval at 1000 ms of RR interval ($QT1s = \alpha + 1000\beta$) were derived for each subject. The circadian rhythm of ventricular repolarisation was examined by harmonic regression analysis.

Results 1) There was a trend towards a significant difference in 24-h mean value of QT1s between study groups (408 ± 26 v 381 ± 43 and 386 ± 22 ms, $p = 0.06$ by ANOVA). A significant difference was found between SCD and CON (408 ± 26 v 386 ± 22 ms, $p = 0.02$). 2) The QT1s differed significantly between study groups ($p = 0.038$) only in day time (09:00–19:00), during which period QT1s was significantly longer in SCD than in CON (409 ± 33 v 380 ± 27 ms, $p = 0.02$), and tended to be longer than in survivors (409 ± 33 v 379 ± 42 ms, $p = 0.08$). 3) The 24-h mean value of QT/RR slope was significantly different between study groups ($p = 0.04$), showing significantly steeper slope in SCD than in CON (0.15 ± 0.07 v 0.09 ± 0.02, $p = 0.008$). 4) During the day, the QT/RR slope differed significantly between study groups ($p = 0.04$) and the difference was less marked at night ($p = 0.08$). The slope was significantly steeper in SCD than in CON in both day and night ($p < 0.05$). 5) A marked circadian variation of QT1s and the slope was observed in CON, which was blunted in survivors and SCD.

Conclusions Abnormal repolarisation behaviors, characterised by longer QT1s and impaired adaptation of QT to variations in RR intervals, were found in SCD. Lethal ventricular tachyarrhythmias may be provoked by the altered repolarisation dynamics in pts after MI.

P1784 New algorithm for QT dispersion analysis in XYZ-lead Holter ECG: description and validation

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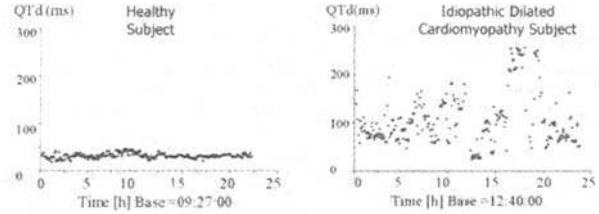
QT dispersion (QTd) in surface ECG has been proposed as a simple measure for arrhythmic risk assessment. QTd analysis in 3 orthogonal leads (OL) correlates with 12 leads measurements. The automatic measurement of QT in digital Holter recordings has been developed and validated, however, automatic QTd analysis in Holter is not widely available. The aim of this work is to develop and validate a new computer algorithm for beat-to-beat analysis of QTd (QTmax-QTmin) in Holter recordings.

Material & Methods: The proposed algorithm has been organized in three steps: 1) a single-lead detector of significant points is applied to each of the 3 leads, 2) the QT interval is measured in each lead and finally 3) the QT dispersion is obtained. A set of 1000 beats (50 initial beats of 20 subjects) of 3 leads (X,Y,Z) digital Holter ECG recordings (200 Hz, Burdik USA) from the IDEAL database were used for the validation of the algorithm. These beats present different T-wave morphologies and different noise levels. The automatic results (AUT) have been compared with those obtained manually by two cardiologists (C1&C2).

Results: Total number of beats analyzed 810/1000 (noisy beats rejected). Mean value of QTd was: 10.6 ± 2.8 ms C1; 11.2 ± 2.7 ms C2; 10.6 ± 1.7 ms AUT. Mean ± SD values of differences were AUT-C1 = 0.62 ± 12 ms, AUT-C2 = −0.34 ± 11.9 ms, C1-C2 = 0.26 ± 13.1 ms.



24-hours dyamic behavior of QTd.

Conclusions: 1) A new automatic algorithm for QTd analysis in digital Holter recordings is described; 2) Automatic QTd measurements are comparable to manual measurements; 3) Automatic QTd analysis provides an objective measure (unaffected by inter observer variability) of dispersion of repolarization allowing therefore to study its dynamic behavior what may be of potential clinical benefit.

P1785 Morlet wavelet analysis of Holter recordings in acute anterior myocardial infarction patients may be used for early prediction of patent infarct related artery after thrombolysis

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Wavelet (WV) transform is a non stationary spectrotemporal analysis technique enabling detection of small, transient signals hidden in the QRS complex and the ST segment of the ECG. The objective was to study whether WV transform through-out the QRS and ST segment in acute myocardial infarction (AMI) pts can predict patent infarct related artery following thrombolytic treatment.

Methods: 25 pts with anterior AMI, without history of previous MI, aged 21–70, underwent thrombolysis during the first 6 hrs after onset of pain. All pts had 2 lead Holter recordings for the first 48 hrs following onset of thrombolysis and for 24 hrs prior to discharge (7th or 10th day). During stay all pts underwent coronary angiography. 19 had patent infarct related artery and 6 non patent. Holter data (V1 lead) were digitized at 800 Hz for Morlet WV analysis. Three frequency bands were examined. Band 1: 200–160 Hz, 2: 150–100 Hz, 3: 90–50 Hz. WV parameters averaging was done over 3–5 consequitive beats at the onset of lysis 1, 2, 4, 6, 12, 18, 24, 48, 168 or 240 hrs after lysis. The parameters used were the Mean (MN) and Maximum (MX) values of the WV in all 3 bands in the QRS, the ST, the last 40 msec of QRS (J-40) and the first 40 msec of ST (J+40).

Results: We observed statistically significant differences of all but 3 of the above mentioned parameters between pts with patent and non patent infarct-related artery at the 6th hr after lysis. Discriminant analysis of the WV parameters showed that 6 hrs following lysis results in the following Wavelet Parameter Index (WVI):

$$WVI = -2,767 * MN3QRS + 36,544 * MX3QRS + 1213,852 * MN1(J+40) + 0.942 * MN3(J-40) - 322.62 * MX1ST - 1,581$$

where 1, 2, 3 represent the frequency bands. If WVI < 1.84 the artery was considered patent, otherwise non patent (table).

	WVI < 1.84	WVI ≥ 1.84
Pts with patent infarct related artery (n = 19)	n = 18	n = 1
Pts with non patent infarct related artery (n = 6)	n = 0	n = 6

p = 0.0001, Sensitivity = 95%, Specificity = 100%, Positive Predictive Accuracy = 100%, Negative Predictive Accuracy = 86%

In conclusion Wavelet parameter Index (WVI) can predict as early as 6 hours following lysis the patent infarct related artery in AMI pts and might be a useful tool for noninvasive assessement of successful thrombolysis.

P1786 Qt dispersion in patients with arrhythmogenic right ventricular dysplasia

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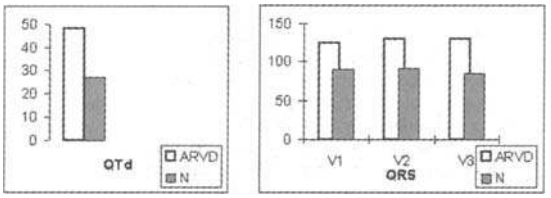
Arrhythmogenic right ventricular dysplasia (ARVD) is characterized by recurrent ventricular tachycardia (VT) of RV origin. Nonuniform recovery of ventricular excitability may facilitate the development of VT of reentrant mechanism.

We analyzed 17 patients with well-documented ARVD (RV tachycardia with left bundle brunch block (LBBB) morphology, positive echo- and angiocardiography criteria, late potentials (LP). The mean age was 37 ± 13 years old and eleven patients were males (65%). All patients were off antiarrhythmic drugs. The QT and the T peak-T end (Tp-Te) intervals, QT dispersion (QTd), QRS duration and T wave morphology were evaluated using the precordial leads V1-V6 and were compared with data of 15 sex- and age- matched healthy subjects. Patients with right bundle brunch block (RBBB) pattern were excluded. Data were manually measured twice by the same observer.

Results: The QTd was significantly different in ARVD patients compared to normal subjects ($p < 0.05$). The QT interval and QRS duration were significantly longer in the ARVD group. There was no difference in the Tp-Te interval between the two groups. LP were present in 13 patients (76%); the T wave was negative in 71% of the ARVD patients in lead V2 and 65% in V3; No intra-observer difference in measurements was present.



Conclusion: The QTd and the QRS duration were significantly increased in patients with ARVD compared with normals. In the absence of complete or partial RBBB pattern, the QT dispersion and the QRS width in the surface ECG separated the ARVD patients from the normal subjects. They might therefore be useful as simple screening criteria in apparently healthy subjects with an episode of monomorphic VT of LBBB morphology or with a history of not yet documented paroxysmal tachycardias.

P1787 QT interval dynamicity in patients with coronary artery disease

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It has been well known that repolarisation abnormalities are related with the development of serious ventricular arrhythmias and show circadian variations. The purpose of this study was to investigate the QT dynamicity in a group of patients with coronary artery disease (CAD) proved by coronary angiography.

Methods: Twenty-hour Holter recordings were obtained from 50 healthy subjects (25 women, mean age 43 ± 11 years) and 84 patients with CAD (40 women, mean age 45 ± 10 years) using Ela Medical Holter system. Algorithm automatically measured the QT end (QTe), RR interval (ms), and the slopes of the linear regressions of QTe plotted againts the corresponding RR interval (QTe/RR) from the entire 24 hours tracing and four segments of 6 hr defined: morning (06–12), day (12–18), evening (18–24), night (00–06).

Results: QTc end values:

	24 hour	Morning	Day	Evening	Night
Patients	436 ± 34	442 ± 23	437 ± 29	438 ± 27	435 ± 32
Controls	423 ± 34	428 ± 26	426 ± 31	424 ± 19	422 ± 16
P value	0.05	0.04	0.05	0.03	0.02

Slopes of QTe/RR:

	24 hour	Morning	Day	Evening	Night
Patients	0.14 ± 0.1	0.11 ± 0.07	0.14 ± 0.1	0.15 ± 0.2	0.16 ± 0.1
Controls	0.18 ± 0.05	0.14 ± 0.1	0.16 ± 0.2	0.17 ± 0.1	0.18 ± 0.1
P value	0.04	0.05	0.06	0.07	0.06

Conclusions: These results show that patients with CAD have abnormal repolarisation behaviour, characterised by increased mean QTc end and depressed adaptation of QT to variations in RR interval especially during the morning. These findings may be an explanation for the increased sudden cardiac death risk during morning hours.

P1788 Relation between early and late phases of ventricular repolarization and cardiac cycle length in 1,100 normal subjects

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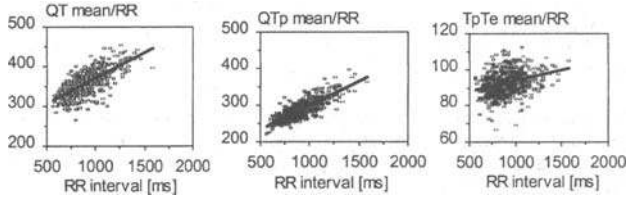
The characteristics of the T wave and QT interval components have been hypothesised to be as important as the QT interval duration itself. Investigation of physiologic difference in phases of ventricular repolarisation and their relation to cardiac cycle length may explain mechanisms of arrhythmogenesis.

Methods: QT, QT_{peak} (QT_p) and T_{peak}-T_{end} (T_pT_e) intervals were evaluated in 1100 healthy volunteers (age 33 ± 12; 910 men) by QT Guard software (Marquette Medical Systems). To assess relation between phases of repolarization and cardiac cycle length, the slopes of linear regressions of QT, QT_p and T_pT_e intervals plotted against the corresponding RR interval were compared.

Results: In all subjects, QT and QT_p interval were strongly dependent on RR interval ($r = 0.82$ and 0.81, respectively; $p < 0.0001$), while T_pT_e interval showed only a weak correlation with heart rate ($r = 0.30$, $p < 0.02$). QT/RR and QT_p/RR slopes were significantly steeper than that of T_pT_e/RR (0.1311 and 0.1283 vs 0.0116; $p < 0.05$; see Figure). The steepness of QT/RR and QT_p/RR slopes decreased, and in T_pT_e/RR slopes increased with age. This was more pr onounced in women, whereas the same relation in men remained stable in all age groups.



Conclusion: QT_p interval strongly depends on heart rate, while T_pT_e interval is less rate-dependent suggesting stronger autonomic modulations of the early phase of ventricular repolarization. Prolonged early phase of repolarization at slower heart rate may be responsible for mechanisms of arrhythmogenesis.

P1789 QT interval dynamicity during direct PTCA: effects of reperfusion on ventricular repolarization in acute myocardial infarction

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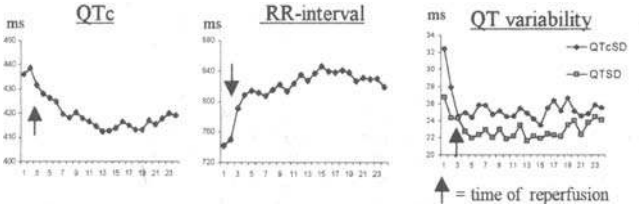
Effective treatment of acute myocardial infarction (AMI) may reduce possible substrates for serious arrhythmias. We sought to evaluate the influence of early coronary artery reperfusion by primary angioplasty (PA) on beat-to-beat QT interval dynamics, a measure of temporal fluctuations of ventricular repolarization.

Methods: We prospectively investigated 89 consecutive patients (pts) (17 female, 72 male; 59.3 ± 3.2 years of age) with a first AMI (45 inferior, 44 anterior). Peak creatine kinase level was 1090 ± 854 U/l. Reperfusion was successfully achieved by PA in all pts (TIMI flow before reperfusion 0.65, after reperfusion 2.71). Continuous beat-to-beat QT interval measurement was performed from 24-hour Holter monitoring, which was initiated at admission.

Results: Reperfusion of the infarct related artery in AMI caused a significant continuous decrease of both, parameters of QT interval (QT, QTc, Qta, Qtac) and QT interval variability (QTSD, QTcSD, QTaSD, QTacSD). RR-interval increased significantly after reperfusion.



Conclusion: Reperfusion leads to a significant continuous decrease of the QT interval and beat-to-beat QT interval variability, reflecting heterogeneity of ventricular repolarization. Reduction of QT interval variability and its associated risk of malignant ventricular arrhythmia may contribute to explain the beneficial effect of early reperfusion by PA in AMI.

P1790 Effect of short-term exercise rehabilitation on heart rate variability, exercise tolerance and total ischaemic burden in patients after myocardial infarction

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The favourable effect of long-term physical training on the autonomic nervous system has been proved, whereas the effect of short-term rehabilitation in patients after myocardial infarction (MI) is still not clear.

The aim of the study was to assess exercise tolerance, heart rate variability (HRV) and total ischemic burden (TIB) in 24 hr ECG recording (HM) and exercise stress test (EXT) in patients after MI undergoing a 27-day exercise rehabilitation.

Material and Methods: 115 patients after a first MI were randomized to two groups matched for age, sex, infarct location, left ventricular function and work capacity (WC). Group A (64 patients) underwent a 27-day early postdischarge training; group B (51 patients) was not exercised. In all patients echocardiography, HM and EXT were performed at baseline and at 27 days.

Results: At baseline both groups were similar with respect to EXT duration, time-domain HRV parameters, (LVEF) and TIB.

	SDNN (ms)	rMSSD (ms)	pNN50 (%)	EX Time (s)	W (Watt)
Group A: n = 64					
At baseline	96.3 ± 26.0	24.1 ± 13.5	4.5 ± 6.6	516.9 ± 194.4	98.8 ± 26.9
p	p < 0.001	p < 0.001	p < 0.001	p < 0.001	p < 0.001
After training	123.9 ± 29.4	28.9 ± 8.7	7.6 ± 6.0	670.3 ± 244.5	124.6 ± 32.6
Group B: n = 51					
At baseline	106.6 ± 30.0	26.1 ± 11.3	5.5 ± 6.3	499.9 ± 188.7	101.0 ± 26.9
p	p > 0.05	p < 0.001	p < 0.001	p > 0.05	p > 0.05
At end of study	108.0 ± 26.3	21.0 ± 7.3	2.8 ± 3.7	495.9 ± 193.0	100.0 ± 27.4

After training HRV parameters and WC increased significantly in group A. Early training did not affect LVEF in group A (60 ± 7.9 vs 63.0 ± 10.3%) and LV size. In group B the indices of parasympathetic activity deteriorated. TIB remained unchanged in both groups. In group A the circadian pattern of SMI was changed – the number of SMI episodes in the morning hours was lower.

Conclusion: Short-term physical training in patients after a first MI improves HRV parameters and exercise tolerance. This is not associated with TBI reduction, but the circadian pattern of SMI is changed.

P1791 Double Inheritance of a mutation in the long QT syndrome

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Long QT syndrome (LQTS) is a familial cardiac disorder characterized by prolonged ventricular repolarization and syncope or sudden death due to ventricular tachyarrhythmias. In the autosomic dominant form, (Romano-Ward syndrome), affected subjects are heterozygous carriers of a mutation in one of the LQTS genes KCNQ1, HERG, KCNE1 or SCN5A. In the recessive form associated with congenital bilateral deafness, (Jervell and Lange-Nielsen), affected subjects are either homozygous carriers of a mutation *in* KCNQ1 or KCNE1 or heterozygote compound carriers. However, one case of homozygous mutation *in* KCNQ1 has been reported without deafness. The prevalence of double inheritance of a mutation in a LQTS genotyped population is unknown.

Methods: 54 genotyped Romano-Ward families were analyzed. All subjects underwent clinical examination, a 12-lead ECG and DNA analysis. Subjects were considered as affected in case of QTc > 460 ms or QTc > 440 ms associated to bradycardia or abnormal T wave, or syncope or torsades de pointes.

Results: A single mutation was found in KCNQ1 in 35 families and in HERG in 15 families. In 2 families, the probands were homozygous carriers of a mutation in KCNQ1 (A300T in one family and R533W in the other) without any deafness. In a third family, the proband and her most severely affected sister were carriers of 2 mutations, one in HERG (2592+1G-A) and one in KCNQ1 (A341E). In a fourth family, both parents of the proband were carriers of a mutation in KCNQ1 (1893insC). However, none of their children including the proband are homozygous carriers so far.

Conclusion: Double inheritance of a mutation in one of the LQTS genes can be evidenced without deafness. Genetic testing should be performed in both sides of the family of affected subjects.

P1792 Demonstration of two different ion channel mutations in long QT syndrome probands

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Four disease genes, KvLQT1, HERG, SCN5A, and KCNE1 are implicated in the Long QT Syndrome (LQTS). Recent evidence suggests that the clinical manifestation of the disease may be largely heterogeneous within the same family or within patients with the same molecular defect. Thus, genetic or epigenetic factors play a critical role in the clinical phenotype. We tested the hypothesis that additional mutations may be present in genotyped individuals and account for phenotypic differences within the same family. We screened the entire coding sequence of the four LQTS genes in 20 genotyped patients affected by the Romano-Ward variant of LQTS. In three probands (15%) we were able to demonstrate the presence of two simultaneous genetic defects not present in 200 control individuals (400 chromosomes). In family 1 the proband, a 5 year old boy with prolonged QT interval and a history of syncope, inherited two mutations, one in KvLQT1 from the asymptomatic father (QTc: 435 ms) and one in HERG from the asymptomatic mother (QTc: 430 ms). In family 2, two missense KvLQT1 mutations were present in the proband, a 16 old girl with a history of exercise-induced syncopal episodes, one located in the S6 transmembrane (tm) segment, inherited from the father, and one in the carboxy terminus, inherited from the mother. In family 3, the proband inherited from the mother a missense mutation in the S5 tm segment of HERG and presented a splice error mutation in exon 21 of the SCN5A gene. In vitro expression of mutations identified in family 1 confirmed loss of function thus establishing a pathogenetic link with the disease.

These data demonstrate for the first time the simultaneous presence of two independent mutations in LQTS patients. They also support the hypothesis that multiple defects of cardiac ion channels may act as modifiers of the clinical phenotype in LQTS. Finally, these results point to the presence of a higher than expected prevalence of silent carriers of genetic defect of cardiac ion channels in the general population.

P1793 Clinical consequences of homozygous premature truncation of the HERG protein

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In Long QT Syndrome (LQTS) heterozygosity for a given mutation in one of the three K^+ channel genes ($LQT_{1, 2 or 5}$) gives rise to prolongation of the cardiac action potential, because the aberrant protein encoded by the mutated gene exerts a dominant negative effect on channel function with resultant less K^+ current. Homozygosity for mutations in KVLQT1 and KCNE1 have been associated with the recessively inherited Jervell and Lange-Nielsen syndrome. HERG, involved in LQT_2 is the gene encoding the rapid component of the delayed rectifier I_{Kr}. In a consanguineous family a stillbirth was followed by the premature birth of a child in distress due to severe ventricular arrhythmias in the presence of marked QT-prolongation. LQTS was diagnosed, β-blocker therapy installed and a pacemaker implanted. The patient developed well and remained symptom-free after 1.5 years. All 15 exons of the HERG gene were amplified from genomic DNA and analyzed by SSCP. We identified a duplication of bp 557 to 599 in exon 4, resulting in a frameshift and a premature stop codon in the S1 domain. In the index patient this duplication was present on both alleles, so no functional HERG protein is anticipated. The same mutation was found heterozygously in both parents, and was not present in a healthy sister. Analysis of DNA isolated from amniotic fluid cells and paraffin-embedded tissues derived from the stillborn brother revealed that he also carried the duplication homozygously.

It is concluded that absence of I_{Kr} gives rise to a severe cardiac phenotype with no indication of malfunction of any other organ, suggesting specific cardiac expression of I_{Kr}. In contrast to murine models, lack of I_{Kr} is not lethal in humans.

P1794 Clinical course of the disease in the family members of Jervell-Lang-Nielsen syndrome and LQT1 syndrome probands

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Background and Purpose: The LQTS pts with the Jervell-Lange-Nielsen syndrome (JLN) have longer QTc and more severe course of the disease than pts with the Romano-Ward syndrome. The JLN is mainly caused by mutations of the KVLQT1 gene encoding IKs potassium channel. The same gene is also mutated in LQT1 patients. We aimed to determine and compare the clinical course of the disease in non-deaf affected family members (AFM; defined as QTc > 0.46 sec) of JLN patients and AFM of KVLQT1 probands.

Methods and Results: We identified 27 non-deaf AFM from 40 JLN families and 108 AFM from 10 LQT1 families. Results of univariate comparison between two groups are shown in the Table below. The multivariate Cox model predicting first CE event showed that AFM from LQT1 families had significantly higher (HR = 4.63; p = 0.003) risk of CEs than non-deaf AFM from JLNS families. Male gender was the only other independent predictor of cardiac events (HR = 1.75; p = 0.04) in AFM from JLNS and LQT1 families.

Affected JLN vs LQT1 Family Members

	AFM of JLN (N = 27)	AFM of LQT1 (N = 108)	p value
Age at last contact (yrs)	40 ± 24	33 ± 23	0.730
Females	15 (56%)	57 (53%)	0.796
1st degree relationship to proband	11 (41%)	39 (36%)	0.656
QTc	0.49 ± 0.02	0.51 ± 0.04	0.003
Beta-blockers	4 (15%)	53 (49%)	0.001
Cardiac Events	4 (15%)	51 (47%)	0.002
Median age at 1st cardiac event	15	9	0.363

Conclusions: Affected family members from LQT1 families have higher risk of cardiac events than non-deaf affected family members from JLNS families. This observation suggests different penetrance of the mutant KVLQT1 gene in the JLN and LQT1 families.

P1795 QT interval in twins

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Dominant long QT syndrome causing syncopal attacks and sudden death, has been mapped to several gene loci and functional mutations in these ion channel genes have been identified[1]. The recessive Jervell and Large Neilsen syndrome causing prolonged QT interval and deafness can be related to "disruptive" mutations in the KVLQT1 gene. Although it appears that the likelihood of sudden death from a given cardiac event differs depending on the gene that is mutated to produce LQT, the influence of other background genetic or environmental factors is unclear.

The study cohort was comprised of 301 female Caucasian twin pairs [103 monozygotic (MZ) and 198 dizygotic (DZ) pairs] aged 18–71 years ascertained through a national media campaign in the UK. Zygosity was determined by questionnaire and confirmed with DNA fingerprinting. QT interval and interbeat interval (RR) were measured "blind" by a trained observer from routine 12 lead ECG traces and the corrected QT (QT_C) was calculated from the equation $QT_C = QT/\sqrt{RR}$.

Mean QT_C (SD) values were 413 (25) ms for MZ and 412 (25) for DZ twins. QT_C was significantly correlated with age ($r = 0.24$, $p < 0.001$). Intraclass correlations were larger than zero for both MZ ($r = 0.30$, $p < 0.001$) and DZ twin pairs ($r = 0.20$, $p < 0.0025$) pointing to a significant familial resemblance. The difference between rMZ and rDZ suggests a small heritability.

Maximum Likelihood model fitting confirmed a significant age effect (ACE *with age* vs. ACE *no age:* χ^2 [1] = 29.0, $p < 0.001$) and a significant familial resemblance that could be explained either by additive genes (AE vs. E: χ^2 [1] = 11.2, $p < 0.001$) or common environment (CE vs. E: χ^2 [1] = 10.7, $p < 0.005$). However, the model including age, additive genetic and unique environmental influences gave the most parsimonious explanation of the data, based on the lowest AIC. In this model age explained 6% (95% CI: 2–10) and additive genetic factors (i.e. the heritability) 25% (95% CI: 11–38) of the variance, the remaining variance being due to unique environment or measurement error.

Thus we find a small heritability for QT_C, which in conjunction with unique environmental effects are the major influences on QT variability.

P1796 Identification of a de-novo mutation in sudden infant death syndrome

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Sudden infant death syndrome (SIDS) is a death of a apparently healthy infant dying unexpectedly. It is the leading cause for death among infants between one month and one year of age. There have advanced a number of theories on causes of SID including cardiac disorders, respiratory infections, abnormal function of the nervous system with pathological breathing and sleep patterns. Recently, prolongation of the QT interval was suspected to be involved in a significant number of SIDS victims. To test the hypothesis we performed genetic analysis of the four known genes causing the long QT syndrome (LQTS) in infants with premature unexpected death.

DNA from 20 SID victims was prepared and PCR products (150–400 bp) of *KVLQT1* (LQT1), *HERG* (LQT2) *SCN5A* (LQT3) and *KCNE1* (LQT5) were generated. Single strand conformation polymorphism (SSCP) was then performed followed by sequence analysis of abnormal band shifts in SSCP on an ALF*express* DNA Sequencer connected to an external thermostatic circulator.

In one of the 20 samples we were able to detect one missense mutation in the SCN5A gene, which was localized in the DIII S4–5 region of the α-subunit of the sodium channel and leads to an aminoacid change from alanine to proline (Ala1330Pro). ECG analysis of the deceased infant showed a prolonged QT-interval of 0.6 sec, both parents had normal QT-intervals (0.40 and 0.42 sec). Sequence analysis failed to detect the same mutation in the parents, paternity was proved with paternity analysis.

Our results show that the congenital long-QT syndrome has to be taken into consideration as a potential cause for SIDS. Further studies are necessary to assess its incidence in SIDS victims.

PREDICTORS OF SUDDEN CARDIAC DEATH

1797 Left ventricular ejection fraction predicts sudden rather than non-sudden cardiac death?

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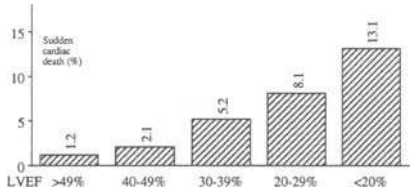
In patients following myocardial infarction (MI-pts.) left ventricular ejction fraction (EF) has shown to be predictive for non sudden cardiac mortality rather than sudden cardiac death (SCD). Thus, it is questionable wether EF should be used for risk stratification to select candidates for an implantable cardioverter/defibrillator (ICD). In a prospective risk stratification study 928 consecutive acute MI-pts (707 males, mean age: 59 ± 9 yrs) underwent radionuclide ventriculography 10–15 days after the acute event. Mean EF was 46 ± 15%. EF ≥ 50% was found in 44% (n = 407) of pts, 40–49% in 25% (n = 232), 30–39% in 16%, (n = 153), 20–29% in 11% (n = 99), and <20% in 4% (n = 38). The mean follow up was 28 ± 16 months.



Conclusions: This is the first study which demonstrates that even a very low EF predicts SCD and thus is helpful to identify candidates for a prophylactic ICD implantation.

1798 Risk of sudden and non-sudden cardiovascular death in patients with congestive heart failure following an acute myocardial infarction

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Congestive heart failure (CHF) following acute myocardial infarction (MI) is known to be associated with an increased risk of both death of all-cause and sudden cardiovascular death (SCD). The aim of the present study was to compare the incidence of SCD and non-sudden cardiovascular death (non-SCD) in consecutive MI patients with or without congestive heart failure (CHF) and to identify risk markers of SCD within the CHF-group.

Methods: We analysed data from 6676 consecutive patients admitted alive with acute MI to 27 Danish hospitals over a period of 2 years. The patients were screened for the TRACE study. Follow up was 2–4 years and all deaths were classified by an event committee. SCD was defined as cardiovascular death within one hour of onset of symptoms. CHF was defined as requirement of treatment for CHF during hospital stay and/or at discharge.

Results: Of the 5983 patients alive at discharge 2952 (49%) had CHF. During follow-up 1659 deaths occurred of which 535 were classified as SCD and 726 as non-SCD. Presence of CHF significantly increased the all causes mortality (ACM) as well as mortality due to both SCD (SCM) and non-SCD (non-SCD) at all times ($p = 0.0001$ between CHF/no-CHF in all three types of mortality).Multivariate regression analysis proved CHF to have value predicting any type of death independent of other known risk factors. Within the group having CHF we found age, left ventricular systolic dysfunction, previous MI and history of arterial hypertension to be independently associated with SCD.

	ACM (%) 1-yr/2-yr/3-yr	SCM (%) 1-yr/2-yr/3-yr	Non-SCM (%) 1-yr/2-yr/3-yr
No CHF	7/10/14	2/4/5	3/5/6
CHF	22/33/40	8/12/15	11/17/20

Conclusion: CHF following MI is independently associated with an increased absolute risk of both SCD and non-SCD. Age, left ventricular systolic dysfunction, previous MI and history of arterial hypertension are independent risk markers of SCD within the CHF-group.

1799 Comparison of measures of autonomic tone and the signal-averaged ECG for risk stratification after myocardial infarction: results of a prospective long-term follow-up trial in 411 consecutive patients

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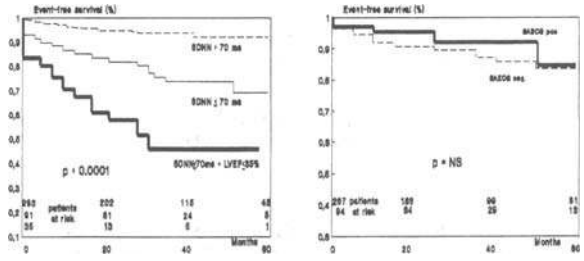
Data on the prognostic value of the signal averaged ECG (SAECG; time domain) with respect to vulnerability to ventricular tachyarrhythmias (VT/VF) post myocardial infarction (MI) compared to heart rate variability in patients treated to contemporary guidelines are sparse.

Methods: A total of 411 consecutive MI pts underwent noninvasive risk stratification at hospital discharge (8 ± 6 days after MI) including SAECG (time domain; late potential positive with 2 of 3 criteria: QRS > 114 ms; LAS > 38 ms; RMS40 < 20 μV) and heart rate variability (HRV) from 24 hour Holter recording (SDNN; cut-off value: 70 ms).

Results: In 42/411 pts a prospectively defined endpoint (death; sustained VT/VF; resuscitation from cardiac arrest) occurred after 33 ± 26 months of follow-up. The figure depicts Kaplan-Meier survival analysis for HRV (left) and SAECG (right). *On* multivariate analysis, only HRV and LVEF were independent risk markers.



Conclusion: In patients with MI treated according to modern therapeutic guidelines (open infarct artery; beta-blocker therapy), analysis of the SAECG in the time domain is not useful for risk stratification. Measures of autonomic tone, in contrast, yield a high predictive value with respect to identifying high-risk pts.

1800 Is abnormal signal-averaged electrocardiogram in time or frequency domain analysis an independent predictor of mortality post acute myocardial infarction and what is the optimal time of recording?

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Background: In previous studies an abnormal (abn) signal-averaged electrocardiogram (SAECG) was founded to be an unfavorable predictor after acute myocardial infarction (AMI); however there seems to be no agreement on its independent predictive value, the appropriate mode of analysis and the optimal time to be recorded, elements that comprise the aim of this study.

Methods: We prospectively studied 705 pts, aged 63.5 ± 0.47 (SE) yrs, in sinus rhythm, with a first AMI. SAECG (ART, 40 Hz filtered, noise level < 0.5 μV) was recorded in all pts in the 1st (before thrombolysis), 3rd and 7th day post AMI. As late potentials (LP) in time domain (Td) analysis in pts with QRS on the surface ECG < 120 ms were taken fQRS > 114 ms and either LAS > 38 ms or RMS < 20 μV whereas in pts with QRS ≥ 120 ms were taken fQRS > 155 ms and either LAS > 55 ms or RMS < 17 μV. In frequency domain analysis, spectral temporal mapping (STM) was considered abn if a normality factor < 30% was derived from analysis (ART, FFT plus, TM software) of x, y or z lead. Twenty-one other variables from clinical (Killip class at admission, maxCPK and maxCPK-MB), ECG (presence or absence of BBB, site of AMI, QRS score (day 8), for estimation of infarct size [based on R and Q wave duration and R/Q and R/S ratio] Lown ≥ IVa ventricular arrhythmias on Holter (day 1) number of vessel diseased on angiography and ejection fraction on echo (day 8)) were considered.

Results: During follow-up of 28.5 ± 0.75 (SE) months there were 118 (18.5%) cardiac deaths. In multivariate logistic regression analysis only age (p = 0.000) and EF (p = 0.000) were the independent prognostic indices of mortality whereas Killip class at admission and LP on day 1 had independent marginal significance (p = 0.06, p = 0.07 respectively).

Conclusions: In pts with a first AMI only age and EF were the strong independent indices of mortality. LP in Td on day 1 before thrombolysis and Killip class at admission were associated to mortality with a trend.

1801 Fractal analysis of heart rate variability as a predictor of mortality after acute myocardial infarction

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Depressed heart rate variability (HRV) and reduced left ventricular (LV) systolic function are known risk markers for mortality in patients after an acute myocardial infarction (AMI). The aim of this study was to compare fractal and traditional HRV measures in predicting mortality in a consecutive series of patients surviving an AMI.

Methods: A population of 479 patients was studied in four centers (Nordic ICD Pilot Study). As a measure of LV systolic function, wall motion index (WMI) was assessed by echocardiography. Standard deviation of consecutive RR-intervals (SDNN) was analyzed from a 24-hr-ECG recording 5–14 days after AMI. As a fractal measure, the short-term scaling exponent DFA1, was calculated using detrended fluctuation analysis.

Results: The mortality was 7.1% (34/479) after a follow-up of 13 ± 6 months. In univariate analysis, low DFA1, reduced SDNN and depressed WMI were predictors of mortality (table). In multivariate Cox regression analysis, including also clinical variables, reduced DFA1 was the most powerful predictor of death, relative risk of death being 1.7 (95% confidence interval 1.1–2.8).

Parameter	Odds Ratio	95% C.I.*	PPA**
DFA1 < 0.85	4.3	1.6–11.6	22%
SDNN < 70 ms	2.3	1.1–4.9	12%
WMI < 1.3	2.0	1.0–4.1	11%
DFA1 < 0.85 and WMI < 1.3	10.8	3.2–36.1	42%

*C.I. = confidence interval, **PPA = positive predictive accuracy.

Conclusion: Fractal analysis gives more powerful prognostic information than traditional analysis of HRV or measure of LV function. Combination of impaired LV function and altered fractal HR dynamics has high accuracy in predicting mortality of patients surviving AMI.

1802 Identification of patients at risk of sustained monomorphic ventricular tachycardia after myocardial infarction using body surface potential mapping

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Among various approaches to identify subjects at risk of sustained monomorphic ventricular tachycardia (SMVT) after myocardial infarction (MI), body surface potential mapping (BSPM) has been shown to provide valuable noninvasive information on arrhythmogenic substrate. Predictive value of different parameters obtainable from BSPM is unknown.

Methods: Simultaneous ECG recordings (5 sec) from 80 regularly spaced unipolar leads over the torso, standard 12 leads, and orthogonal XYZ leads were obtained (500 Hz sampling frequency, 12 bit per sample) in a training study population (18 post-MI patients with documented SMVT, age 54.8 ± 13.7 years and 20 post-MI without VT during 6 months follow-up, age 59.7 ± 11.5 years). QRS and QTc duration was measured from XYZ leads. The QRST-area was calculated in each lead and spatial features of its body surface distributions were represented by Karhunen-Loeve (K-L) coefficients. Single-beat late potentials were extracted by singular value decomposition (SVD) of the QRST interval and subsequent time-domain analysis was performed.

Results: First 16 K-L coefficients (F 1–16), QRS, QTc, and the results of the time-domain analysis of SVD signal were used to enter forward stepwise discriminant analysis. Five best discriminant parameters were selected (QRS, F 12, F 4, F 1, QTc), and subsequently tested in 52 subjects (26 post-MI patients with documented SMVT, mean age 59.0 ± 7.4 years, and 26 post-MI without VT during 6 months follow-up, mean age 58.7 ± 11.0) who underwent the same recordings. Sensitivity and specificity of this technique to identify subjects with VT was 80.8% and 73.1%, respectively.

In conclusion, combination of the above 5 BSPM-derived parameters identifies post-MI patients with SMVT with a very high accuracy.

ABLATION OF ATRIAL FLUTTER

1803 Prediction of definitive atrial flutter radiofrequency ablation based on simplified assessment of complete cavotricuspid isthmus block

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Complete cavotricuspid isthmus block (IB) was assessed by a simplified method in 40 patients after successful radiofrequency ablation of atrial flutter (AF).

Methods: A quadripolar catheter was placed on the lateral right atrium. After AF termination, counterclockwise IB was assessed by low lateral atrial pacing (quadripolar catheter) and by recording atrial septal activation with ablation catheter. Clockwise IB was assessed by recording right lateral atrium activation during CS os pacing with ablation catheter. Complete IB was defined by shortening the interval between the double potential recorded by ablation catheter on the lesion (A1, A2) when pacing high lateral compare to low lateral atrium pacing. Data from 10 patients (R) with either reinducible AF by atrial pacing (6) or spontaneous AF recidives (4) were compared with data from 30 patients (S) with definitive success (follow-up: 8 ± 6 months).

Results: R and S patients exhibited bidirectional IB without differences for lateral or septal atrium activation times when pacing the opposite side. Complete IB was achieved for 27 group S patients but was absent in all R patients ($p < 0.05$). When switching from low to high lateral atrial pacing, Spike-A1 increased (18 ± 10 and 19 ± 12 ms resp. in S and R; NS), while Spike-A2 decreased for S and increased or remained stable for R (resp.: −5 ± 15 vs 10 ± 12 ms; $p < 0.01$). A1A2 shortening was S: −19 ± 20 vs R: −9 ± 10 ms ($p < 0.01$).

Conclusion: AF recurence or inducibility was possible despite conventional criteria of bidirectionnal IB. Demonstration of complete IB by this simple method was more effective to predict definitive succes of AF radiofrequency ablation.

1804 Identification of a conduction gap for successful focal reablation in patients with recurrent atrial flutter after initial bidirectional block

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Of 210 pts referred for catheter ablation of common-type atrial flutter (AFL) between 1/96 and 10/98, 10 pts (9 male, age 60 ± 8 yrs) experienced recurrent AFL during a mean 2.8 mos FU; bidirectional isthmus conduction block (CB) had been achieved in the initial procedure with 14 ± 9 RF pulses. The aim of the study was to further characterize the electrophysiological properties of recurrent AFL and to localize a conduction gap (CG) in the initially created linear lesion using either conventional techniques and/or the electroanatomical mapping system CARTO.

Methods and results: Of the 10 pts, 6 had counterclockwise AFL, 3 clockwise AFL and 1 both types. The mean cycle length of recurrent AFL was not different compared to that before the first procedure (234 ± 26 ms vs. 244 ± 41 ms, n.s.). CGs along the prior linear lesions were identified during coronary sinus pacing in 6 pts and during AFL in 3 pts by using local electrogram criteria (double or fragmented atrial potential in the initial linear lesion or CARTO); single CGs were identified at the annular district in 2 pts, at the intermediate district in 2 and at the caval district in the remaining 5 pts. In 1 pt, no attempts were made to find a CG, but bidirectional CB was achieved by creating an additional linear lesion. 2.1 ± 1.4 RF pulses delivered at sites of CG resulted in bidirectional isthmic CB in 9 pts. No AFL recurred during 15 ± 10 mos FU.

Conclusion: The recurrence rate of AFL after initial bidirectional CB was 4.8%. In pts with recurrent AFL, the CG along the initial linear lesion could readily be identified by local electrogram criteria (single or fragmented atrial potential) as well as by the CARTO system. The CG could be closed with only a few RF pulses.

1805 Unidirectional conduction block on the crista terminalis during sinus rhythm in the patients with and without typical atrial flutter

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Purpose: It has been revealed that during the typical atrial flutter(AFL), the tricuspid annulus(TA) is the anterior and the crista terminalis(CT) is the posterior barrier with a block line in the right atrium(RA). We investigate the conduction properties of the CT during sinus rhythm in the patients with and without AFL.

Methods: We performed electrophysiological test in 7 patients with AFL(CL:235 ± 45 ms) and in 5 patients without the history of AFL who had reentrant supraventricular tachycardia. In the patients with AFL, a 10-pole electrode catheter with 2-mm interelectrode distance was positioned along the CT under the fluoroscopy guidance, where we could observe the double potentials(DP) during AFL. In the patients without AFL, after the catheter ablation procedures, atrial pacing from the coronary sinus os was performed then the catheter was positioned at the CT where the DP was observed. Atrial pacing from the low septum(LS) and then from the low lateral wall(LL) were performed at pacing cycle length(PCL) from 600 ms to 200 ms during sinus rhythm.

Results: In all patients with AFL, a block line with the DP was observed along the CT during LS pacing regardless of PCL. On the other hand, during LL pacing at shorter PCLs(225 ± 25 ms) the DPs were observed along the CT indicating the presence of a block line, but at longer PCLs the DP couldn't be observed. Similarly in all patients without AFL, LS pacing always demonstrated the presence of a block line with DP along the CT, and LL pacing at shorter PCLs (250 ± 30 ms) also demonstrated the presence of a block line.

Conclusions: It is suggested that the crista terminalis plays a role as a fixed block line in the transverse conduction from septum to lateral wall, but as a functional block line from lateral wall to septum during sinus rhythm.

1806 Atrial fibrillation in patients with typical atrial flutter: is there any role for the crista terminalis?

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Background. The occurrence of atrial fibrillation (AF) in patients with type I atrial flutter (AFI) remains an important clinical problem. In AFL, the Crista Terminalis acts as a functional line of block that prevents the short-circuiting between the posterior (P) and lateral (L) wall (W).

Methods. In 22 patients (61 +− 7 years) with AFL (cycle length 234 +− 23 ms) we compared the electrophysiologycal properties of the CrT in 16 lone AFL and in 6 patients with history of AFL/AF. Multiple electrograms were recorded at the right atrium, coronary sinus and CrT. CrT was identified during AFL by recording double electrograms between the LW and PW. Decremental pacing trains were delivered, from 600 ms to 2 to 1 local capture, at the LW and PW or coronary sinus ostium (CSO).

Results. At least 5 bipolar electrograms were recorded along the CT from the high to the low atrium next to the inferior vena cava. No double electrograms were recorded during sinus rhythm at that area. Fixed transversal conduction block along all the CrT (detected by the appearance of double electrograms at all recording sites and cranio-caudal activation sequence on the opposite side to the pacing site) was observed in 2/16 AFL patients and in 2/6 AFL/AF patients. No differences were observed in the pacing cycle length at which transversal block appeared at the CrT. Nevertheless fractionated electrograms longer than 80 ms were only observed at the CrT in 6/6 AFL/AF and 1/16 AFL patients ($p < 0.01$) at a pacing cycle lengths longer than 300 ms.

Conclusion. Conduction disturbances at the CrT may influence in the appearance of AF in patients with AFL.

1807 Unipolar electrograms to confirm isthmus block after radiofrequency ablation of typical atrial flutter

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Objective: To examine the utility of the unipolar electrograms (UNIP) to confirm bi-directional block along the isthmus between the tricuspid annulus (TA) and the inferior vena cava (IVC). We hyphotesized that pacing from the coronary sinus ostium (CSos), the UNIP recorded at the other side of the line of radiofrequency application, close to the inferolateral TA, could change from a biphasic "RS" morphology (suggestive of conduction along the TA-IVC isthmus) before, to a positive monophasic "R" UNIP morphology (suggestive of termination of the wave front against the line of block) after achievement of clockwise isthmus block (CIB). Similar findings could be observed after counterclockwise isthmus block, (CCIB), pacing from the inferolateral TA.

Patients and Methods: In 15 patients (P) who underwent ablation of atrial flutter (AFI) a line of bi-directional block was created in the TA-IVC isthmus, confirmed by comparing the timing and the sequence of 10 standard bipolar electrograms of a multipolar catheter positioned along the TA. The ablation catheter was used to record the UNIP.

Results: Pacing at a cycle length of 500 ms from the CSos before CIB, the UNIP recorded at the inferolateral TA was "RS" in all P. After CIB, the interval between the stimulus artifact and the UNIP increased a mean of 45 ± 13 ms and changed to "R" in 13 P and to "Rs" in 2 P. Pacing from the inferolateral TA before CCIB, the UNIP obtained at the septal side of the line of block, was "RS" in all P, After CCIB, the interval between the stimulus artifact and the UNIP increased a mean of 40 ± 11 ms and changed to an small "R" in 14 P and to "Rs" in 1 P. Pacing from the CSos, in two P we observed a prolongation time of the stimulus-UNIP interval after RF applications despite showing "RS" morphology. In both of them, after obtaining CIB we observed conversion from "RS" to "R" UNIP.

Conclusion: UNIP are useful to recognize bi-directional TA-IVC isthmus block, even in the presence of slow conduction through the TA-IVC isthmus and could reduce the number of catheters (and recording channels) for RF ablation of AFI.

1808 Specific re-ablation in recurrences of atrial flutter: high-resolution electromagnetic catheter mapping of gaps within the tricuspid annulus–inferior caval vein–isthmus

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The endpoint of catheter ablation of the tricuspid annulus (TA)-inferior caval vein (ICV)-isthmus during treatment of atrial flutter (AFL) is complete bidirectional conduction block. An incompletely damaged isthmus, with a small gap and slow conduction, may reveal double potentials and reversal of conduction around the annulus during pacing of the coronary sinus (CS), thereby simulating conduction block but allowing clinical recurrences and complicating re-ablation.

In 16 patients (pts) with recurrences of AFL after ablation or with induction of an incompletely damaged isthmus during the initial ablation session, three-dimensional (3-D) maps of the TA-ICV isthmus were constructed for precise definition of the individual isthmus anatomy (Carto system). High-density electro-anatomical mapping during CS stimulation allowed precise identification of discrete gaps within the noncontiguous lesion lines. In 9 pts, an incompletely damaged isthmus could be identified although the recording of double potentials and complete reversal of conduction around the TA simulated conduction block. In 8 pts, the gap was found close to the TA, in 5 pts close to the ICV, and in 3 pts in the middle part of the isthmus, respectively. The electromagnetic navigation system allowed precise re-navigation to the predetermined sites of conduction breakthrough. In all pts, specific gap ablation was successfully performed with 3.2 ± 3.3 radiofrequency pulses for induction of complete conduction block.

High-resolution electro-anatomical re-mapping of the isthmus after ablation allowed precise verification of the linearity of the lesions along with proof of induction of complete conduction block and differentiation from incomplete block through small gaps exhibiting slow conduction. Precise 3-D re-navigation to the gaps substantially facilitated specific re-ablation in AFL recurrences.

POTASSIUM CHANNEL AND THE LONG-QT SYNDROME

1809 Human atrial conduction properties correlate with the relative expression of connexins 40 and 43

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Background: As a major determinant of intercellular conductance, gap-junctional coupling is also considered a principal determinant of myocardial conduction velocity. The aim of this study was to test the hypothesis that the quantities of the predominant atrial gap junctional proteins, connexin40 (Cx40) and connexin43 (Cx43), affect the atrial conduction velocity in humans.

Methods: Epicardial mapping was performed on 16 patients undergoing cardiac surgery using an array of 56 unipolar electrodes with 3.5 mm interelectrode spacing, before atriotomy or cardioplegia. During sinus rhythm, the conduction velocity was measured over the trabeculated portion of the right atrial free wall. An excision biopsy from the mapped region was processed for quantitative confocal immunodetection of Cx40 and Cx43. Six highly confocal (<1 μm) randomly selected fields were acquired for each patient. Using differential wavelength filtering, connexin labelling, connective tissue autofluorescence and lipofuscin autofluorescence were quantified using PCimage analysis software.

Results: There was no correlation between the conduction velocity and the quantities of Cx40, Cx43 or total connexin signal (Cx40+Cx43). However, the ratio of expression of connexins correlated with conduction velocity during sinus rhythm ($p < 0.005$, $r^2 0.58$), such that as the proportion of Cx40 increased (and Cx43 decreased), the conduction velocity decreased. Furthermore, during pacing the ratio of expression of connexins correlated with the degree of decrementation of atrial conduction velocity ($p < 0.005$, $r^2 0.51$), such that atria with the lowest proportion of Cx40 showed the greatest decrementation. There was no correlation between conduction velocity and the quantity of connective tissue autofluorescence.

Conclusions: In human atria, the relative expression Cx43 and Cx40 correlates with right atrial conduction velocity during sinus rhythm. Interactions between different connexin types may be an important determinant of atrial conduction velocity and may also influence interval dependant conduction properties.

1810 Phenotypic characteristics of long-QT syndrome patients with different mutations of the SCN5A sodium channel gene

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Background and Purpose: Several mutations of the SCN5A gene have been reported in the LQT3 variant of the long QT syndrome. To further characterize phenotype by mutation in LQT3, we identified two large LQT3 families, one with the KPQ mutation, and the other with the D1790G mutation. Both mutations cause abnormal inactivation of the sodium channel, yet, only the KPQ causes also sustained inward sodium current.

Methods: The family carrying KPQ mutation consisted of 160 family members (42 genetically tested) and family carrying D1790G mutation consisted of 101 family members (66 genetically tested).

Results: Comparison of gene mutation carriers is provided in the table below.When comparing cardiac events (syncope, aborted cardiac arrest, or cardiac death prior to beta-blocker therapy) in all family members regardless of genotyping and ECG data, there were 13 (8%) pts with cardiac events in KPQ family and 6 (6%) pts with cardiac events in D1790G family (ns). There were 3 cases of cardiac events with documented sinus arrest (without torsade de pointes) in D1790G family and none in KPQ family. The median age at first event was higher in KPQ than D1790G families (18 vs. 10 years, respectively; $p = 0.11$).

LQT3 Pts with KPQ and D1790G Mutations

	KPQ (n = 15)	D1790G (n = 26)	p value
Median age at diagnosis (yrs)	18	18	ns
Median follow-up (yrs)	9	10	ns
Males	11 (73%)	12 (46%)	0.114
HR (bpm)	71 ± 18	83 ± 25	0.111
QTc (ms)	530 ± 50	494 ± 46	0.025
QTmc (ms)	403 ± 87	352 ± 73	0.057

Conclusions: Two different intragenic mutations of the SCN5A sodium channel gene channel contribute to somewhat distinct phenotypic presentation of LQT3 patients. In comparison to KPQ patients, those with D1790G mutations exhibit shorter QTc, higher heart rate, earlier onset of cardiac events, and possibly increased risk of sinus node arrest.

1811 The rapid and the slow component of the delayed rectifier potassium current in undiseased human ventricular myocytes

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There are large inter-species variations in the delayed rectifier potassium current (I_K). The very few available data regarding I_K in man originate from diseased hearts in the presence of Cd^{2+} and Ba^{2+}, which cations fundamentally alter the properties of IK.

Methods: Therefore, the characteristics of I_K (including activation and deactivation kinetics) were studied in 32 myocytes isolated from 16 undiseased human left ventricle, by applying the whole cell configuration of the patch-clamp technique at 37 C°. Nifedipine was used to block I_{Ca}.

Results: The E-4031 sensitive rapid component of I_K (I_{Kr}) was found to be present in all myocytes. The current-voltage relationship of the I_{Kr} tail current showed apparent inward rectification. The activation of the current started at −10 mV and reached its maximal amplitude (0.274 ± 0.062 pA/pF, n = 10) at 20 mV. The activation of the I_{Kr} was fast (τ = 36.6 ± 3.2 ms, n = 6) with relatively slow biexponential deactivation kinetics (τ_1 = 600.0 ± 53.9 ms and τ_2 = 6792 ± 875.7 ms, n = 5). In the presence of forskolin in the extracellular and phosphate in the intracellular solutions, an E-4031 insensitive and chromanol 293B sensitive tail current, which represented the slow component of I_K (I_{Ks}), was also observed. The maximal amplitude of I_{Ks} tail was 0.206 ± 0.035 pA/pF at 50 mV, n = 6, ie. 75% of the amplitude of I_{Kr}. The time constant for activation of I_{Ks} was rather slow (1096.8 ± 126.5 ms, n = 6) and for deactivation it was relatively rapid (109.9 ± 11.6 ms, n = 12)

Conclusion: It is concluded that both I_{Kr} and I_{Ks} exist in undiseased human ventricle. The recorded I_K resembled I_K detected in dog ventricular myocytes but substantially differed from I_K measured in myocytes from guinea pig ventricle. I_{Kr} and I_{Ks} probably play an important role in the frequency dependent and pharmacological modulation of repolarization in human ventricle.

1812 External pH modulates HERG potassium channel properties

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Among factors which are involved in early ventricular arrhythmias during acute myocardial ischemia, decrease in pHo is certainly of special importance. Although pH was shown to modulate ionic membrane currents including potassium channels, its effects on HERG (human eag-related gene) are still unknown. We expressed HERG, known to encode the cardiac potassium channel IKr, in CHO cells and investigated effects of external pH (pHo) using the whole-cell patch-clamp technique. HERG currents were elicited from a holding potential of −80 mV by depolarizing pulses (−50 to +40 mV, 10 mV steps) followed by repolarization to −60 mV. When pHo was lowered from 7.4 to 6.0, current amplitude was decreased and kinetics of activation and deactivation were faster. For example, for a +10 mV pulse, current amplitude decreased from 1503 ± 356 to 1284 ± 404 pA (*P < 0.05) and rapid time constants (bi-exponential fitting) of activation and deactivation decreased respectively from 181 ± 18 to 88 ± 31 ms and from 143 ± 16 to 61 ± 11 ms (*P < 0.05). However, the half activation voltage ($V\frac{1}{2}$) was not significantly changed. When pHo was rised from 7.4 to 8.0, activation was accelerated and $V\frac{1}{2}$ negatively shifted. For example, for a +10 mV pulse, activation time constant changed from 127 ± 26 to 46 ± 5 ms and $V\frac{1}{2}$ was shifted from −2.1 ± 4.7 to −24.5 ± 3.8 mV (*P < 0.0025). (*data expressed as mean ± SEM; n = 5)

We conclude that alterations of HERG channel by pHo, particularly the faster deactivation observed at low pHo, could have consequences for the onset of arrhythmias during cardiac ischemia.

1813 Human inward rectifier K^+ currents are affected by a G-protein β3 subunit gene polymorphism

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A C825T-polymorphism has been recently identified in the gene encoding for the G(beta3)-subunit of pertussis-toxin sensitive G-proteins. When expressed in in-vitro systems, the T-allele gene produces the splice variant G(beta3)-s, resulting in enhanced activity of signal transduction. Here we tested the hypothesis, that patients carrying the T-allele exihibit the G(beta3)-s phenotype and that the resulting enhancement of signal transduction should be detectable in the acetylcholine stimulated K^+ current (IK,ACh), an effector system directly activated by G(beta,gamma) dimers. Patients undergoing cardiac surgery (mainly coronary bypass) were genotyped for the C825T-polymorphism. Atrial inward rectifier K^+ currents (IK1, IK,ACh) were studied with single cell voltage clamp techni-ques. IK1 was measured with depolarizing ramp pulses and quantified as inward current at −100 mV corrected for cell capacitance. The values were (mean ± s.e.m; in pA/pF): CC-allele carriers −5.00 ± 0.40 (CC; n = 80 cells/26 patients), CT −4.53 ± 0.38 (n = 93/23) and TT −7.94 ± 0.72 (n = 25/7); p < 0.05 for TT vs. CC and CT (one-way ANOVA). The increased background IK1 is not affected by atropine (1 μM), excluding spontaneously active M2-acetylcholine receptors. Upon activation of IK,ACh by superfusion with carbachol (2 μM), current increased by (in pA/pF) −5.81 ± 0.43 in CC (n = 66), −6.62 ± 0.36 in CT (n = 86), and −4.95 ± 0.75 in TT (n = 19), p < 0.05 for TT vs. CT. In contrast to the above hypothesis, the T825-allele is not associated with enhanced IK,ACh but background IK1 is increased in homozygous T-allele carriers instead. The nature of this finding remains to be elucidated.

1814 Mitochondrial ATP-sensitive K channels mediate anti-infarct tolerance afforded by activation of adenosine A1 and bradykinin receptors in the heart

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We examined if mitochondrial ATP-sensitive K channels (mitoKATP) are effectors at the end of signals from A1 and bradykinin (BK) receptors.

Methods: Isolated buffer-perfused rabbit hearts were used. [Protocol 1] Infarction was induced by 30-min global ischemia/2-h reperfusion, and its size was measured by tetrazolium and expressed as a% of area at risk (%I/R). The heart received no drug, A1 receptor agonist (1 uM R-PIA), a mitoKATP opener (100 uM diazoxide), a protein kinase C (PKC) inhibitor (200 nM calphostin C), a mitoKATP blocker (30 uM 5-hydroxydecanoate, 5-HD), or combination of these agents before ischemia. [Protocol 2] Infarction was induced by 30-min coronary occlusion/2-h reperfusion with or without preischemic infusion of BK (500 nM), a selective blocker of sarcolemmal KATP (HMR1883, 20 uM), 5-HD, or combinationn of these agents. [Protocol 3] Mitochondria were isolated from hearts with or without 30-min global ischemia after diazoxide or vehicle infusion. Their respiratory functions were determined.

Results:[Protocol 1] R-PIA reduced%I/R from 50 ± 7 in the control to 13 ± 3. This protection was abolished by calphostin C (%I/R = 54 ± 4) and by 5-HD (%I/R = 60 ± 9). Diazoxide mimicked the effect of R-PIA (%I/R = 11 ± 4), and this effect of diazoxide was abolished by 5-HD (%I/R = 45 ± 7) but not by calphostin C (%I/R = 13 ± 7). Neither calphostin C nor diazoxide alone modified%I/R. [Protocol 2] BK reduced%I/R from 38 ± 5 in the control to 12 ± 3. This effect was abolished by 5-HD(%I/R = 43 ± 8) but not by HMR1883 (%I/R = 12 ± 3). HMR1883 alone had no effect on%I/R (42 ± 8). [Protocol 3] State III respiration and respiratory control index were reduced after 30-min ischemia, and these changes were significantly attenuated by diazoxide pretreatment.

Conclusion: These results support the hypotheis that signals from A1 and BK receptors, via PKC, lead to opening of mitoKATP, which reduces mitochondrial damage and lethal injury in the cardiomyocytes during ischemia.

MANAGEMENT OF VASOVAGAL SYNCOPE

1815 Mechanisms of vasovagal syncope: an age-dependent phenomenon?

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Age related physiologic changes in cardiovascular regulation are well recognized. Although recent data suggest triggering mechanisms of vasovagal (VV) syncope are likely protean, age-dependent hemodynamic responses to orthostatic stress in pts with VV syncope have not been defined. In this prospective study, we examined age-dependent cardiomotor (HR, SV), vasomotor (BPs, TPR), and preload (EDV) conditions in 45 pts with tilt table (70°, up to 45 mins)-induced VV syncope. Pts were divided into 3 age groups: Group I, age < 30 yrs (mean 17 ± 4 yrs, n = 15); Group II, age 30–59 yrs (mean 42 ± 9 yrs, n = 15); Group III, age ≥ 60 yrs (mean 70 ± 7 yrs, n = 15). Hemodynamic parameters were monitored continuously by impedance cardiography and photoclamp plethysmography. Results are summarized below:

At baseline supine, HR was indistinguishable among 3 groups, while SV (ml): 125 ± 22, 96 ± 27, 78 ± 27, (p = 0.004, ANOVA, group I, II, III, respectively), and EDV (ml): 192 ± 43, 163 ± 46; 126 ± 43 (p = 0.002) were significantly lower in the older pts, while TPR (dyne.s.cm^3): 966 ± 297, 1386 ± 594, 1713 ± 538 (p = 0.0002) was significantly higher in the older pts. In response to tilt (at 1 min), before any symptoms developed, a 45% ± 16% increase in HR occurred in group I pts while only a 13% ± 16% increase occurred in group III pts (p = 0.0004). The difference in HR response was associated with significant differences, between group I & III pts, in SV: −33% ± 15% vs −2% ± 20%, (p = 0.001), in EDV: −23% ± 17% vs 9% ± 24% (p = 0.0001) and in TPR: 22% ± 54% vs 2% ± 16% (p = 0.04).

Conclusions: 1) Lower SV and EDV at baseline in older pts suggest intravascular volume depletion may be a significant component of VV syncope in the elderly. 2) Increases in HR and TPR in response to tilt, consistent with sympathetic activation, are more pronounced in the younger pts preceding syncope. 3) Diverse age-dependent mechanisms are present in pts with VV syncope.

1816 Paroxetine prevents refractory vasovagal syncope in young patients

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Serotonin may play a major role in the mechanisms leading to neurocardiogenic vasovagal syncope. To establish whether serotonin re-uptake inhibition by paroxetine could prevent refractory vasovagal syncope in young patients the following study was undertaken.

Methods. Forty-six consecutive young patients (19 male and 27 female, mean age 33.7 ± 6.5 years) with recurrent syncope and positive tilt test, and in whom previous therapies with beta-blocking, vagolytic, negative inotropic or mineral corticoid agents were ineffectual, poorly tolerated or contraindicated, randomly received either paroxetine at 20 mg once a day or placebo tablets. The response to head-up tilt test was reevaluated after one month of treatment, and the clinical effect was noted over a mean follow-up of 30.5 ± 9.6 months.

Results. After one month of treatment 14 patients (60.9%) in the paroxetine group as compared with 9 patients (39.1%) in the placebo group became tilt negative (p < 0.001). Over a 30 month follow-up 19 patients (82.6%) versus 11 patients (47.8%) in the paroxetine and placebo groups, respectively (p < 0.0001) remained symptom-free and no spontaneous syncope was experienced. Side effects of paroxetine administration were negligible and only one patient (4.3%) asked to be discontinued from the drug for severe recurrent headache.

Conclusions. Paroxetine was found to significantly improved symptoms of young patients with vasovagal syncope in whom previous traditional therapies were ineffectual, poorly tolerated or contraindicated.

1817 Specificity and positive rate of head-up tilt testing potentiated with sublingual nitroglycerine in elderly patients with unexplained syncope

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Introduction. Head-up tilt testing (HUTT) potentiated with nitroglycerine is extensively used to increase the diagnostic yield of unexplained syncope, but the method is not extensively performed, and its diagnostic value is not already proved in an elderly population. The aim of the study is the assessment of the specificity and total positive rate of potentiated HUTT in detecting the vasovagal origin of unexplained syncope in an elderly population.

Methods. 128 elderly patients (mean age 71.6 ± 5.1 years) with syncope of unknown origin and 101 subject in a control group (mean age 70.1 ± 4.7 years) were studied. The patients and the control subjects were tilted upright to 60 degrees for 45 minutes. If syncope did not occur, sublingual nitroglycerine (0.4 mg) was administered, and observation was continued for 10 minutes. Positive responses to HUTT were defined as the reproduction of syncope or presyncope according to VASIS definition.

Results. During the unmedicated phase syncope occurred in 26 (20%) patients and in no members of the control group. After nitroglycerine was administered, syncope occurred in 53 (41%) patients and in 2 (2%) members of the control group. The total positivity rate of the test was 62% with a specificity of 98%.

Conclusions. HUTT potentiated with sublingual nitroglycerine provides an adequate specificity and positivity rate in elderly patients with unexplained syncope; therefore it can be proposed as a useful diagnostic tool also in an elderly population.

1818 Psychiatric profile of patients undergoing head-up tilt test for evaluating recurrent unexplained syncope

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Background: Anxiety disorders and panic attacks are generally associated with a variety of symptoms patterns most commonly including palpitations, tachycardia or lipothymia, but in some cases including syncope (S).

Methods: The aim of the study was to assess relationship between symptoms of psychiatric disorders (PD) and recurrent unexplained S of presumed vasovagal origin. The study group consisted in 40 patients (aged 42 ± 18 years) undergoing 60° head-up tilt test for evaluating recurrent unexplained S (group S), and 40 age- and sex-matched control patients free of known chronic PD admitted in our departement for arrhythmia (group C). All of them underwent a semi-standardized psychiatry questionnaire (MINI International Neuropsychiatric Interview) with ICD-10 (International Classification of disease, 10th revision) criteria in order to assess their profile. For the purpose of analysis, responses were categorized into scores of 0 to 20 (absence) and > 20 (presence) for anxiety, 0 to 15 (no symptoms), 15 to 20 (moderate) and > 20 (severe intensity) for depression according respectively to Hamilton anxiety and MADRS scales.

Results: General PD were found in 65% (n = 26) of group S patients and 35% (n = 14) of group C patients (p = 0.01). Detailed analysis revealed that sub-profiles of anxiety disorders and panic attacks were more frequent in group S patients when compared to controls (12 vs 5, and 8 vs 4 respectively), whereas sub-profile of depression was similar in both group (6 vs 5, ns). In addition, group S patients had a mean score of 25 ± 5 for anxiety compared with 22 ± 4 in group C (p = 0.004), whereas mean score for depression did not significantly differ between the 2 groups (23 ± 5 vs 25 ± 5, ns). Considering group S patients, no difference could be found between those with positive (n = 25) and negative (n = 15) head-up tilt results with respect to age, sex, number of syncopal episodes and sub-profiles of anxiety, panic attacks or depression.

Conclusion: Patients with unexplained S of presumed vasovagal origin have more frequent episodes of anxiety disorders and panic attacks on standardized investigation when compared to age- and sex-matched control patients with arrhythmias. This may have an impact on their management and clinical outcome.

1819 Autonomic function testing in patients with various types of vasovagal syncope

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Objective of this study was to determine if differences in basal autonomic tone are observed between patients with various types of vasovagal syncope (VVS).

Methods: In 60 patients with clinicaly suspected VVS head- up tilt testing (HUT) was performed. HUT was positive in 39 pts (12 men, age 34 ± 13) and negative in 21 pts (11 men, age 32 ± 15). Type of vasovagal reaction was classified according to VASIS classification as mixed (type I, 24 pts), cardioinhibitory (type II, 7 pts) and vasodepressor (type III, 8 pts). Expiratory-inspiratory ratio (E/I) during deep breathing, 30:15 ratio during active standing-up and the Valsalva ratio (VR) were used to evaluate vagal responsiveness. Maximal increase ase in HR after standing-up (ΔF) and the increase in plasma noradrenaline and adrenaline levels in response to standing for 5 minutes (ΔNA, ΔA) were considered as markers of sympathetic responsiveness. In addition spectral analysis of heart rate variability was evaluated in each group of patients.

Results: No significant differences in autonomic tone were observed between pts with various types of reactions during HUT. Results are summarised bellow.

	Type I	Type II	Type III	Negative HUT
E/I	1.29 ± 0.12	1.36 ± 0.11	1.27 ± 0.12	1.24 ± 0.09
30:15 ratio	1.08 ± 0.10	1.11 ± 0.14	1.13 ± 0.17	1.15 ± 0.32
VR	1.70 ± 0.035	1.60 ± 0.31	1.76 ± 0.037	1.59.0 ± 0.35
ΔF	26.70 ± 10.02	30.21 ± 6.92	31.99 ± 10.03	29.85 ± 13.38
ΔNA (pg/ml)	293.2 ± 175.2	232.0 ± 100.9	308.1 ± 54.1	308.6 ± 140.9
ΔA (pg/ml)	60.4 ± 47.1	62.9 ± 48.3	64.2 ± 28.7	59.1 ± 29.0
LF (ms^2)	191.66 ± 94.0	167.14 ± 96.0	198.57 ± 124.2	197.6 ± 119.6
HF (ms^2)	174.16 ± 75.9	155.42 ± 71.8	177.71 ± 103.4	177.33 ± 91.6
LF/HF (ms^2)	1.10 ± 0.14	1.02 ± 0.14	1.10 ± 0.05	1.08 ± 0.17

In conclusion: Different hemodynamic reactions during HUT cannot be explained by differences in basal autonomic tone in patients with VVS.

1820 Midodrine hydrochloride in the treatment of vasovagal syncope and essential hypotension: haemodynamic effects and the influence on life quality

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The **aim** of this of this prospective, nonrandomized study was to evaluate the usefulness, haemodynamic effects and the influence on life quality (LQ) of alpha-agonist midodrine hydrochloride, which was use in the treatment of vasovagal syncope and essential hypotension.

Methods: 44 patients (mean age 36 year, 19 men) with history of recurrent syncope and positive of head-up tilt testing were included (28 patients with type I, 11 patients with type II, 5 patients with type III according to VASIS classification) in the study. In all patients before oral therapy with midodrine was started ambulatory blood pressure monitoring ABPM) was performed. Initial dose was 2.5 mg two times daily. When necessary the dose was increased to 5 mg two times daily.). LQ was evaluated using validated questionnaire of the Psychological General Well-Being (PGWB) index.

Results: After midodrine hydrochloride treatment 90% of patients had no inducible presyncope or syncope on repeated tilt table testing. Midodrine produced significant increase in systolic (22 ± 3 mm Hg, $p < 0.01$) and diastolic (11 ± 1 mm Hg, $p < 0.001$) blood pressures compared to placebo (2 ± 5 and 2 ± 3 mm Hg, respectively). Upright blood pressure 12 hours after administration was significantly greater with midodrine (116 ± 6/7 ± 6 mm Hg) vs. placebo (84 ± 7/54 ± 4 mm Hg, $p < 0.05$). Motionless standing time, a measurement of functional capacity, also improved with midodrine (238 ± 43 vs. 77 ± 28 seconds). The well-being was worse in compare with that of control group at baseline (PGWB total mean score for syncope-hypotension patients was −78.1 vs. control 95.6). It improved on midodrine treatment by 11.2 ($p < 0.001$).

In conclusion midodrine appears to be highly effective in preventing and treatment of all types of vasovagal syncope and essential hypotension and it improve LQ at that patients.

TRIGGERS FOR ATRIAL FIBRILLATION

1821 Trends in complexity of atrial arrhythmias before atrial fibrillation onset

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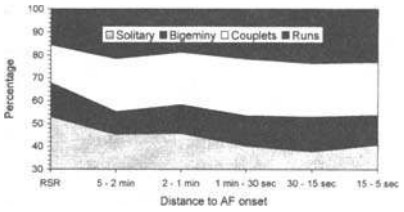
It is now becoming apparent that in a subset of subjects with paroxysmal atrial fibrillation (AF), a focal atrial tachycardia is responsible for the arrhythmia. It is known that atrial premature beats (APB's) increase before AF onset, but the pattern of arrhythmia has not been studied.

Methods: Holter recordings were performed on 177 subjects with paroxysmal atrial fibrillation. All recordings were subjected to standard automated analysis and manual editing. AF episodes were identified by a previously validated technique and this information combined with the beat interval data. APB's (approximated by short RR intervals) were identified and classified as being solitary, part of a couplet, a bigeminal rhythm or a run. The proportion of APB's belonging to each classification at each timepoint prior to AF onset was calculated.

Results: 600 episodes from 76 recordings in 39 pts (24 male, 62 ± 13 years old) met the selection criteria. The proportion of all APB's which were solitary fell from 53% remote from AF to 41% 5 seconds before AF onset ($p = 10^{-8}$, see figure). This fall was largely due to an increase in atrial couplets (17% → 23%, $p = 10^{-4}$) and runs (16% → 23%, $p = 10^{-5}$) with the number of bigeminal beat remaining unchanged (15% → 13%, p = NS).



Conclusion: Prior to AF onset, the complexity of APB patterns increases, suggesting that these arrhythmias may progress to an atrial tachycardia underlying the AF in some subjects.

1822 Predominant origin of ectopy triggering atrial fibrillation from the pulmonary veins: mapping and ablation in 100 patients

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Curative catheter ablation of atrial fibrillation (AF) may target either the substrate (linear ablation) or the initiating trigger. This report presents the results of mapping and ablation of ectopy triggering AF in 100 consecutive patients.

Methods: These patients (pts) included 77 men and 23 women with a mean age of 53 ± 12 years; 29 had structural disease. Spontaneous initiations of AF were mapped using multielectrode catheters in the pulmonary veins (PV). The accuracy of mapping was confirmed by RF ablation resulting in acute disappearance of ectopy and AF.

Results: Of 181 foci (1 focus = 47; 2 foci = 23; 3 foci = 20; >3 foci = 6 pts) 3 were from the lateral right atrium, 2 from the septum and the posterior left atrium in 4. 172 trigggers (95%) originated from the PV: left superior (65) and inferior (42), right superior (50) and inferior (15). AF was initiated in most cases by 2 or more consecutive focal discharges with an irregular cycle length of 182 ± 57 ms. Ablation was performed along the intra PV course of foci between the source and the exit. 7 pts had adverse effects (1 tamponnade, 1 stroke, 5 PV stenosis of whom 4 were asymptomatic). During a follow-up of 7 ± 6 months, 65 patients were free of recurrence of AF without anti-arrhthymic drugs.

Conclusions: The PV are the main source of ectopy initiating paroxysms of AF. Catheter ablation of these triggering foci leads to cure of AF.

1823 Differences in pulmonary vein electrograms between patients with paroxysmal atrial fibrillation and controls

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Introduction: The pulmonary veins (PV) have been recently documented to be the almost exclusive source of trains of ectopics which initiate paroxysms of atrial fibrillation. Electrogram markers of pulmonary vein arrhythmogenic capability have not been described.

Methods: Bipolar electrograms (EGM) recorded in sinus rhythm from within 2, 3 or 4 pulmonary veins in 15 control patients (11 M, 4 F, mean age 45 ± 15 years, no structural heart disease, no atrial fibrillation) were compared with those at ablation sites in 14 age matched patients (12 M, 2 F, 43 ± 6 years) with pulmonary vein ectopy initiated atrial fibrillation. The presence of local venous activity, its complexity, electrogram duration, delay between atrial and local pulmonary vein activity (in sinus rhythm), amplitude ratios, PV-atrial conduction times (CT) and PV precocity relative to the P wave during ectopy produced by mechanical stimuli and spontaneous ectopy (in controls and patients respectively) were compared.

Results: The following significant ($p < 0.05$) differences were found:

	No of PV EGM deflections	Total EGM duration	PV-Atrial CT	PV Precocity
Controls	1.6 ± 0.7	63 ± 14 ms	68 ± 25 ms	−43 ± 26 ms
Patients	2.2 ± 0.9	79 ± 19 ms	105 ± 40 ms	−80 ± 33 ms

Conclusions: There are significant differences (ranging from obvious to none) in electrogram complexity and veno-atrial conduction dynamics between controls and arrhythmogenic pulmonary veins probably related to anatomy, anisotropic behaviour and gap junction distribution.

1824 Postoperative electrophysiologic evaluation of radiofrequency pulmonary veins isolation

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Purpose: The aim of this study is to assess the left atrial electrophysiologic properties after bilateral pulmonary veins isolation (BPVI) using intraoperative radiofrequency ablation.

Methods: We evaluated prospectively 20 Pts (mean age 59 ± 11 years) with rheumatic mitral valve disease and atrial fibrillation (AF) submitted to concommitant valve surgery and BPVI. After AF surgery, epicardial pacing electrodes were placed on the LA posterior wall, in and out of the isolated zones, and on the right ventricle. In the 11 sinus rhythm Pts, before discharge, simultaneous electrograms of all sites were acquired at rest and during pacing of isolated zones and non-isolated atrial tissue. The resting amplitude of electrogram signals in and outside atrial isolated zones were compared. During programmed electrical stimulation, one milisecond pulses were used and stimulus amplitude was progressively increased (maximum 28 mA) until atrial capture occurred. Minimum stimulus amplitude required for atrial capture was recorded for each pacing site.

Results: In all sinus rhythm Pts, electrogram amplitude inside the isolated zones was <25% of non-isolated atrial tissue. Pacing within the isolated zones required a significantly higher pulse amplitude for atrial capture detection (13.5 ± 9.3 mA vs 8.5 ± 4.5 mA for pacing of non-isolated atrial tissue). In two Pts, no atrial capture was detected when pacing isolated right pulmonary veins, even with maximum pulse amplitude.

Conclusion: Radiofrequency applications caused a significant decrease in atrial electrogram signal amplitude. Pacing of isolated atrial tissue required higher pulse amplitudes for capture detection in non-isolated atrium zones. Further studies are needed to define the criteria for electrically isolated zones and to establish their correlation with efficient supression of AF.

1825 Paroxysmal atrial fibrillation of focal origin: high recurrence rate after initial successful catheter ablation

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Recent reports indicate that paroxysmal atrial fibrillation may be of focal origin, amenable to radiofrequency catheter ablation (ABL) therapy.

Methods: We screened pts with frequent (>2 episodes/week) refractory paroxysmal atrial fibrillation and identified those with frequent monomorphic atrial extrasystoles (AES) or atrial tachycardias on resting or Holter ECG, with the aim ABL. The origin of the atrial extrasystoles or tachycardias was mapped during the ablation procedure. The procedure was declared successful if after ABL no further atrial ectopic activity was observed during 60 min. The pts were followed in the hospital by continous Holter monitoring over 72 hours.

Results: In 13 pts meeting the above inclusion criteria, catheter ablation eliminated a single atrial focus (location of the focus: inside the pulmonary veins [PV] 10, right atrium 3). In 6 of 10 pts with focus ablation in the PV, recurrence of atrial ectopic activity was noted on Holter monitoring after 12–36 h. In one pt a second PV focus (previously not apparent) was identified and successfully ablated; in 3 patients the same focus was reablated with primary success during a second procedure, but with recurrence of 2; 2 pts have not been restudied but the origin of the recurrent atrial activity appears different than the ablated focus based on resting ECG analysis. Overall 9 of the 13 pts are off antiarrhythmic drugs and without symptoms (mean follow up 14 ± 12.5 months).

Discussion: Atrial fibrillation of focal origin can be identified by careful analysis of resting and/or Holter ECG. ABL therapy has a high acute success rate; however, there appears to be a high recurrence rate for foci located in the PVs, and repeat procedures are necessary. In addition, foci previously not apparent can be seen after initially successful focus ABL.

EXERCISE TESTING IN HEART FAILURE AND HYPERTENSION

1837 Enhancement of exercise hyperpnea is a powerful prognostic marker independent of peak oxygen consumption in chronic heart failure

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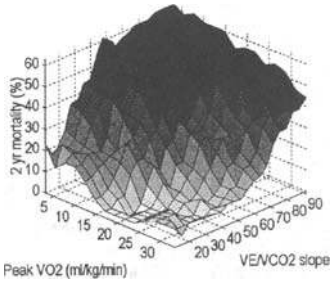
Background: Reduced peak oxygen consumption (peak VO_2) during exercise is a known adverse prognostic factor in chronic heart failure (CHF). However increased exercise hyperpnea (VE/VCO_2 slope), may also be an adverse marker.

Methods: 301 CHF patients underwent cardiopulmonary exercise testing, using a modified Bruce protocol. Peak VO_2 and VE/VCO_2 slope were determined with a pneumotachograph and mass spectrometer.

Results: During a median follow-up of 33 months, 87 patients died. Univariate Cox proportional-hazards analysis revealed powerful predictive value in both peak VO_2 and VE/VCO_2 slope ($p < 0.0001$ for each). More importantly, bivariate mortality analysis identified independent prognostic value peak VO_2 ($p = 0.0003$) and VE/VCO_2 slope ($p < 0.0001$). The graph demonstrates the relationship of mortality to peak VO_2 and VE/VCO_2 slope, using a model which does not assume linearity of risk or of interaction between peak VO_2 and VE/VCO_2 slope.



Conclusion: During cardiopulmonary exercise testing, the VE/VCO_2 slope gives valuable prognostic information independent of peak VO_2. In the worst prognostic group by peak VO_2 (<10 ml/kg/min) patients are classifiable by VE/VCO_2 slope into a range of 2-year mortalities from 20% to 60%. Even in the best prognostic group by peak VO_2, enhanced VE/VCO_2 slope identifies a subgroup at elevated risk.

1838 Kinetics of oxygen consumption recovery after a symptom-limited exercise test in chronic heart failure: an index of habitual physical activity and deconditioning

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In daily life, chronic heart failure (CHF) patients (pts) typicallly complain symptoms long after exercising, and a prolonged post-exertional kinetics of oxygen consumption (kVO_2) has been described.

Methods: The relationship between kVO_2 after incremental exercise test and habitual physical activity and deconditioning has been investigated in 85 CHF pts (59 + 8 yrs, 87% male, in NYHA class I–III, mean EF 22 ± 8%), who performed an incremental bicycle exercise test limited by fatigue or dyspnea (mean peak VO_2 16.4 ± 4 ml/kg/m'). Recovery was defined as the period starting when the workload was removed and the analysis of VO_2 vs time was assessed in the first 3 min following effort. kVO_2 recovery was evaluated as T1/2, the time to reach 50% of peak value. Habitual physical activity level was evaluated by an interviewer-determined scoring (AcS range 0–9) considering leisure-time, occupational activities and hospital admissions. T1/2 was significantly negatively correlated to peak VO_2 ($r = -0.65$, $p < 0.01$) and AcS ($r = -0.62$, $p < 0.01$). T1/2 was significantly prolonged in pts with different fuctional capacity (A, 34 pts; peak VO_2: ≤15 ml/kg/m' T1/2 129 ± 13 sec., B, 37 pts; peak VO_2: 15–20 ml/kg/m' T1/2 95 ± 20 sec.; C, 14 pts; peak VO_2 ≥ 20 ml/kg/m' T1/2 75 ± 7 sec., $p < 0.01$). Pts with prolonged T 1/2 (group A ≥ 120 sec and group B ≥ 90 sec) compared with those with shorter T1/2 (group A < 120 sec and group B < 90 sec) had a significantly lower AcS (group A: 3.8 ± 2 vs 4.9 ± 2, Group B: 4.8 ± 2 vs 6.3 ± 1, $p < 0.05$), whereas peak VO_2 was similar (group A: 12.7 ± 1 vs 13.3 ± 2 ml/kg/m', group B: 16.3 ± 1.5 vs 17.2 ± 2 ml/kg/m', NS). In group C, AcS and peak VO_2 were similar in pts with short T1/2 (<60 sec) or prolonged T1/2 (≥60 sec).

In conclusion, in CHF, kVO_2 is negatively correlated to peak VO_2 and AcS and it's notably delayed in pts with severe funtional impairment. In pts with similar peak VO_2, a prolonged kVO_2 is associated with a lower AcS, as a result of greater activity restraint during daily life. Thus the analysis of kVO_2 may enhance the understanding and management of symptoms in CHF pts.

1839 Resting pulmonary function is an important determinant of exercise capacity in patients with heart failure

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In patients (pts) with heart failure (CHF) the mechanisms responsible for exercise intolerance have not been fully defined. Abnormalities in pulmonary function seem to play a relevant role in determining the peak exercise oxygen uptake (VO_2). In order to clarify the relative contribution of resting hemodynamic profile and pulmonary function, 162 male pts (mean age 59 ± 9 yrs) with CHF (NYHA class II–IV, LVEF: 23 ± 7%) underwent spirometry, lung volumes (TLC) and diffusion (DLCO), mouth inspiratory and expiratory pressures (MIP, MEP; 91 pts). Right heart catheterization and a symptom-limited cardiopulmonary exercise test were performed within 3–4 days.

Results: mean value peak VO_2 was 13 ± 4 ml/kg/m. Resting hemodynamic parameters did not show any significant correlation with peak VO_2; furthermore, there were no differences in hemodynamics between pts with peak VO_2 ≤ or >14 ml/kg/m. On the other hand, there was a significant correlation ($p < 0.05$), although of low degree, between peak VO_2 and forced vital capacity ($r = 0.35$). DLCO was significantly higher in pts with peak $VO_2 > 14$, compared to those with $VO_2 \leq 14$ ml/kg/m (21.6 ± 6.9 vs 17.7 ± 5.5, $p < 0.001$). Using a stepwise regression analysis, the respiratory and/or hemodynamic parameters which significantly correlated with peak VO_2 resulted to be DLCO (most important) and MEP with an overall R value of 0.60.

Conclusion: these data confirm previous studies showing a poor correlation between resting indices of cardiac function and exercise capacity. On the other hand, several pulmonary function parameters were related to peak VO_2. Particularly, lung diffusion and respiratory muscle function (as assessed by MEP) seem to be important determinants of exercise intolerance in heart failure.

1840 Increased sympathetic nerve activity during repetitive rhythmic forearm exercise in patients with chronic heart failure

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Sympathetic nerve activity is increased at rest in patients with chronic heart failure(CHF), but less is known about sympathoexcitation during exercise in patients with CHF. Accumulation of muscle metabolites during rhythmic exercise cause an increase in sympathetic nerve activity by stimulation of the muscle metaboreflex in patients with CHF. The aim of this study was to evaluate whether muscle sympathetic nerve activity(MSNA) is further accelerated with repetitive rhythmic exercise in patients with CHF.

Methods: Fifteen patients with CHF(LVEF 38 ± 10%) and 10 age-matched controls were studied. Each subjects performed two equivalent symptom limited rhythmic handgrip(RHG) exercise at 30% of maximal voluntary contraction separated by 5 min rest. MSNA was recorded micronerographically from the left peroneal nerve. Heart rate and blood pressure were measured during RHG.

Results: CHF patients fatigued prematurely during RHG. Heart rate and blood pressure response during the first and second RHG were similar in both groups. At rest, the discharge rate of MSNA was higher in CHF patients than in controls(21 ± 8 vs 42 ± 6, $p < 0.05$). MSNA burst frequency was similar in both groups (44 ± 5 vs 51 ± 11: NS) at the end of first exercise. After the cessation of RHG, MSNA rapidly returned to the baseline in both groups. However, MSNA at the end of second RHG was higher in CHF patients than in controls (59 ± 9 vs 42 ± 6, $p < 0.05$). Furthermore, the increase in MSNA from rest was larger during the second RHG compared to the first RHG in CHF patients(42% vs 33%, $p < 0.05$), but there was no significant difference in controls (110% vs 105%, NS).

Conclusions: Repetitive RHG exercise caused increase in sympathetic nerve activity in patients with CHF, which have a role in the progression of heart failure with excessive daily activity.

1841 Influence of arterial baroreflexes on postexercise blood pressure response in patients with left ventricular dysfunction

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Arterial baroreflexes regulate cardiovascular response to exercise in patients with normal humans and left ventricular(LV) dysfunction, but less is known about the relation between arterial baroreflexes and postexercise blood pressure (BP) response in patients with LV dysfunction. The aim of this study was to examine the influence of arterial baroreflex sensitivity (BRS) on central and peripheral hemodynamic responses during recovery from maximal exercise.

Methods: BRS was assessed by the regression line between phenylephrine-induced increase in systolic blood pressure and attendant changes in the R-R interval in 40 uncomplicated patients with LV dysfunction (LV ejection fraction < 45%). All the patients underwent symptom-limited bicycle exercise and hemodynamic variables were observed during recovery.

Results: In all patients, the average BRS was 5.6 ± 2.6 msec/mmHg. At 2 and 5 minutes of recovery, mean BP had a positive correlation with systemic vascular resistance ($r = 0.72$, and 0.62: $p < 0.01$), but not with cardiac output. BRS correlated inversely with mean BP ($r = -0.57$ and -0.55: $p < 0.05$) and systemic vascular resistance ($r = -0.53$ and -0.47: $p < 0.05$). Moreover, BRS had modest but significant correlation with percentchange decrease in mean BP from peak exercise to 2 and 5 minutes of recovery ($r = 0.40$ and 0.35: $p < 0.05$), indicating that patients with lower BRS have a higher systemic vascular resistance and mean BP during recovery than those with normal BRS.

Conclusions: Decrease in BRS reflect delayed postexercise BP response in patients with LV dysfunction.

1842 Hypertensive patients have significantly higher MDA and VIP levels during exercise compared to normal individuals

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Lipid peroxidation, has been proposed to play a relevant role in the development and progression of atherosclerosis. This process is mediated by O_2 radicals and among its final cytotoxic products the most important are aldehydes, malyndialdehyde (MDA) being the most significant one. The vasoactive intestinal polypeptide (VIP) is a systemic and coronary vasodilator with some positive inotropic properties. This study was designed in order to evaluate MDA and VIP plasma changes in both hypertensive patients (pts) before the initiation of any medical treatment and in normotensive volunteers during exercise test.

Methods: 20 pts (16 M, 4 F) mean age 56.8 ± 5.2 yrs and mean body mass index (BMI) 24.1 ± 2.3 with essential hypertension (Group H) and 14 normotensive volunteers (12 M, 2 F) mean age 55.9 ± 4.8 yrs and BMI 23.7 ± 3.1 (Group N) were studied. The two groups were matched for age and BMI. An exercise test according to Bruce protocol was performed in all, hypertensives and normotensives. Coronary angiography has been performed also in the whole study population in order to exclude coronary artery disease. The plasma MDA and VIP concentrations were determined at rest (baseline) and at peak exercise by the thiobarbituric acid assay and by RIA method respectively.

Results: The results of our measurements are shown below:

	Group H (n = 20)	Group N (n = 14)	
MDA (baseline) μmol/ml	102 ± 0.32	120 ± 0.75	p = NS
MDA (peak exercise) μmol/ml	144 ± 0.53	129 ± 0.35	p = NS
	p < 0.001	p = NS	
VIP (baseline) pmol/ml	13.41 ± 3.07	9.21 ± 2.50	p < 0.001
VIP (peak exercise) pmol/ml	16.57 ± 3.20	10.22 ± 2.13	p < 0.001
	p < 0.01	p = NS	

Conclusions: The results of our study suggest that: 1) Hypertensive pts have significantly higher peroxidation during the exercise test compared to normal volunteers. 2) Hypertensives have significantly higher VIP levels at rest and during exercise than normal volunteers. This phenomenon may be the expression of a massive vasodilators mobilization in order to protect the myocardial perfusion.

BENEFITS OF PHYSICAL TRAINING

1843 Exercise tolerance and quality of life after myocardial infarction with respect to patency of the infarct-related artery: interim results of The Open Artery Trial (TOAT study)

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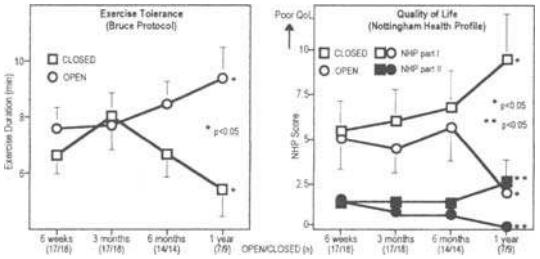
Introduction: The TOAT study is a randomised trial of intervention v medical management in asymptomatic patients following anterior myocardial infarction (AMI). 12 month follow-up data on exercise tolerance (ET) and quality of life (QoL) is presented.

Methods: Symptom-free patients <75 yrs with an occluded left anterior descending artery (LAD) are randomised 5–28 days post 1st Q-wave AMI to: OPEN (PTCA + stent to LAD + medical therapy), or CLOSED (medical therapy alone). Follow-up at 6 weeks and 3, 6, and 12 months post AMI includes ET (Bruce protocol) and QoL (Nottingham Health Profile – NHP).

Results: To date, 37 patients with similar baseline characteristics have been randomised; 18 to OPEN (14 M, 4 F, age 57.3 ± 8.3 yrs) and 19 to CLOSED (14 M, 5 F, age 58.2 ± 11.0 yrs). Data expressed as mean ± SEM.



Conclusions: Delayed intervention is associated with significantly improved ET and self perceived QoL (NHP part I), in addition to a significantly enhanced lifestyle (NHP part II) 12 months post AMI. Intervention even in the absence of symptoms may be beneficial.

1844 Exercise training benefits patients with ischaemic and non-ischaemic cardiomyopathy

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Exercise training improves symptoms, exercise capacity and haemodynamics in heart failure. It is not known whether this response differs with the cause of heart failure, as non-ischaemic cardiomyopathy (CM) patients may have skeletal as well as cardiac muscle abnormalities.

Method: Compared ischaemic (isch) CM and non-ischaemic (non-isch) CM patients randomised to 12 weeks of exercise training. Before and after the program, they underwent: cardiopulmonary exercise tests, New York Heart Association (NYHA) classification, quality of life questionnaires, right heart catheterisation and measurement of heart rate variability (HRV), plasma noradrenaline (NA), adrenaline (Adr) nitrates, endothelin (ET), atrial (ANP) and brain natriuretic peptides (BNP) and N-Terminal BNP (NT-BNP).

Results: 51 patients underwent exercise training (26 isch CM, 25 non-isch CM), 44 men/7 women, age 55 ± 12 years and LVEF 0.26 ± 0.08 units. The isch CM group was significantly older than the non-isch CM group (63 vs 48 years, $p = 0.0003$) with higher levels of ANP (71 vs 44.7 pmol/l, $p < 0.04$), BNP (38.9 vs 28.6 pmol/l, $p < 0.05$), NT-BNP (218 vs 141 pmol/l, $p < 0.04$) and ET (2.71 vs 2.11 pmol/l, $p < 0.03$) and more impaired HRV. Despite this, they did not differ significantly in response to exercise training. Isch CM (% Change) vs Non-isch CM (% Change): Heart Rate −7% vs −7%, Blood Pressure −15% vs −8%, Pulmonary Capillary Wedge Pressure −11% vs −15%, Pulmonary Vascular Resistance −25% vs-6%, Systemic Vascular Resistance −13% vs −15%, NYHA Class −36% vs −26%, Peak Oxygen Uptake 4% vs 11%, Exercise Duration 25% vs 38%, NA −16% vs −27%, Adr −72% vs −31%, ANP −15% vs −23%, BNP −16%vs −21%, NT-BNP −27% vs −23%, ET −9% vs −1%, Nitrates 13% vs −6%.

Conclusions: Exercise training leads to similar improvements in symptoms, exercise capacity, haemodynamics and neurohormonal abnormalities regardless of the patients' age or the underlying diagnosis.

1845 Effects of long-term moderate exercise training on functional capacity, quality of life and sexual behaviour in chronic heart failure

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Recent reports have shown that short-term exercise training (ET) improves the aerobic capacity of patients with chronic heart failure (CHF). However, the effects of long-term ET on functional capacity, quality of life (QOL) and sexual activity are not well defined.

Methods: Fifty-nine patients (57 ± 14 years) with stable CHF in sinus rhythm were randomized into 2 groups. A group (T = 30) underwent supervised ET at 60% of peak VO_2 3 times a week for 8 weeks, then twice a week for 12 months. A group (NT = 29) was not exercised. Medications were not changed during the study. At baseline, 2nd and 14th month all patients underwent a symptom-limited incremental exercise test with gas exchange analysis on a cycle ergometer. At same times, QOL was assessed by the Minnesota Living with Heart Failure Questionnaire and sexual activity profile (SAP) by questionnaire.

Results: Significant changes were observed only in trained patients. Peak VO_2 increased by 18% at 2 months ($P < 0.005$) and 21% at 14 months ($P < 0.001$). QOL also improved in trained patients and paralleled peak VO_2 ($r = 0.80$; $P < 0.001$). In group T, SAP was unchanged at 2 months. However, SAP was significantly improved from baseline at 14 months (score: +22%; $P < 0.01$ T vs NT) and was correlated with changes in QOL ($r = 0.73$; $P = 0.01$).

Conclusions: Long-term moderate ET significantly improves functional capacity as well as QOL. Both improvements were evident after 2 months and were maintained at 14 months. The beneficial effect of ET on SAP was more delayed and was correlated with changes in QOL.

1846 Correction of coronary endothelial dysfunction in patients with coronary artery disease by regular physical exercise

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Endothelial dysfunction is a key feature of early atherosclerosis contributing to myocardial ischemia in patients (pts) with coronary artery disease (CAD). This study was designed to determine whether exercise training corrects coronary endothelial dysfunction in pts with CAD.

Methods: 18 patients were prospectively randomized to a training group (T) or an inactive control group (C). At beginning (B) and after 4 weeks (E), pts received serial intracoronary infusions of acetylcholine (ACH) to assess endothelium-mediated vasodilation. Average peak flow velocity (APV) was invasively measured using a Doppler flow wire, vessel diameter was determined by quantitative coronary angiography.

Results: At B pts in T and C had similar responses to acetylcholine doses of 0.072, 0.72, and 7.2 μg/min with respect of percentage of change in vessel diameter and APV. After exercise training ACH-induced coronary artery vasoconstriction was significantly blunted in response to 7.2 μg/min ACH by 61% (from −0.41 ± 0.06 to −0.16 ± 0.08 mm; $p < 0.01$ vs. C). In training pts the percent change in APV at the initial study in response to increasing doses of acetylcholine were 13 ± 7, 37 ± 12, and 78 ± 17 percent. The responses to acetylcholine after 4 weeks of exercise training were 29 ± 8, 76 ± 21 and 144 ± 31 pecent, respectively ($p < 0.01$ vs C). Coronary flow reserve as assessed by adenosine infusion increased by 28% (from 2.8 ± 0.2 to 3.6 ± 0.3; $p < 0.05$ vs. C).

Conclusions: In patients with CAD physical exercise improves endothelium-dependent vasodilation of coronary conduit and resistance vessels, probably because of endothelial relaxing factors released in response to cell membrane shear stress induced by pulsatile blood flow.

1847 Effects of physical training on peripheral markers of endothelial dysfunction in patients with chronic heart failure

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Objective: Previous studies have shown an abnormal expression of cellular adhesion molecules and cytokines in patients with chronic heart failure (CHF), which may be related to endothelial dysfunction characterizing this syndrome. Our study investigates the effect of physical training on serum activity of some peripheral inflammatory markers associated with endothelial dysfunction, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), soluble intercellular adhesion molecule-1 (sICAM-1) and vascular cell adhesion molecule-1 (sVCAM-1) in patients with CHF.

Methods: Serum levels of GM-CSF, sICAM-1 and sVCAM-1 were determined by commercially available ELISA tests in 12 patients with stable CHF (ischaemic heart failure 6/12, dilated cardiomyopathy 6/12, NYHA II–III) before and after a 12-week program of physical training in a randomized cross-over design. In addition, the functional status of CHF patients was evaluated by using cardiorespiratory exercise stress test (VO_2max). Patients with infections, malignancies or other inflammatory diseases were excluded from the study.

Results: Physical training produced a significant reduction in serum GM-CSF (26.9 ± 2.1 vs 18.7 ± 1.3 pg/ml, $p < 0.001$), sICAM-1 (378 ± 36 vs 327 ± 34 ng/ml, $p < 0.02$) and sVCAM-1 (1275 ± 121 vs 1134 ± 116 ng/ml, $p < 0.04$) as well as a significant increase in VO_2max (14.9 ± 0.6 vs 16.3 ± 0.7 ml/kg/min, $p < 0.05$). A significant correlation was also found between percentage changes in VO_2max values and sICAM-1 ($r = -0.71$, $p < 0.02$) as well as sVCAM-1 levels ($r = -0.66$, $p < 0.04$).

Conclusions: Physical training causes a significant decrease in peripheral inflammatory markers associated with endothelial dysfunction in patients with CHF. These changes may be related to the training-induced improvement in functional status of CHF patients.

1848 Physical training copes pain in syndrome X

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Background and aim: No effective and rational treatment for patients with Syndrome X (Sdm X, anginal chest pain, positive exercise stress test and angiographically normal coronary arteries) has previously been reported. The aim was to test if Sdm X, as a chronic pain disorder may respond to physical training both as regards pain experience and physical capacity.

Methods: 14 female patients aged 41–65 years continued a rehabilitation programme consisting of 30 min exercise on a bicycle ergometer at 50% of max exercise capacity 3 days/week for 8 weeks. Exercise testing before and after the training period with peak VO_2 measurement.

Results: Exercise capacity increased markedly, 28 ± 10% after training (from 98 ± 9 W to 126 ± 13 W, $p < 0.0003$) and peak VO_2 with 18 ± 10% (from 1.2 ± 0.1 l/min to 1.5 ± 0.2 l/min, $p < 0.003$). The time to pain onset was prolonged with 90 ± 44% (from 3 ± 1 min to 6 ± 2 min, $p < 0.002$). Posttraining pain intensity at pre-training peak exercise load decreased by 41 ± 37%, $p < 0.05$. Maximum pain score, however, remained unchanged. There was an increase in max heart rate (from 137 ± 11 to 152 ± 10 bpm, $p < 0.001$), max systolic blood pressure (from 193 ± 12 to 204 ± 12 mmHg, $p < 0.05$) and double product (from 235 ± 30 to 310 ± 29 bpm · mmHg · 10^{-2}, $p < 0.001$) during exercise.

Conclusion: Syndrome X patients are physically deconditioned but improve their exercise capacity, peak VO_2 and time to pain onset after 8 weeks of physical training. This is the first study showing that physical training is a new and effective treatment in this patient group improving coping of pain.

PHARMACOLOGICAL THERAPY OF ATRIAL FIBRILLATION

1849 Intravenous versus oral amiodarone for the conversion of atrial fibrillation of recent onset

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In a prospective, randomized, placebo-controlled study, we compared the efficacy and safety of amiodarone (amio), administered orally (p.os) versus intravenously (iv), for the treatment of recent onset atrial fibrillation (AF).

Methods: We studied 204 patients (95 men), aged between 34 and 86 years (mean 65 + 11) with AF lasting < 48 hours. Fifty-five pts received amio p.os 2000 mg over 24 hours divided into 4 doses, and then 200 mg × 4 the next day), 80 received amio iv (300 mg for 1 hour followed by 20 mg/kg for the next 24 hours, and then 15 mg/kg the next day), while 69 were given placebo (the first 24 hours iv, the next day orally). Cardiac output (CO) and cardiac index (CI) were evaluated invasively before and 24 hours after the start of amio administration in 28 pts (15 iv and 13 p.os group).

Results: There were no significant differences in the basic clinical data between the three groups. Conversion to sinus rhythm was achieved within 48 hours in 49 of the 55 pts (89.09%) receiving amio p.os, in 71 of the 80 (88.75%) receiving the drug iv, and in 42 of the 69 (60.86%) of the controls (p: NS for iv versus p.os group, $p < 0.05$ for both groups versus controls). The mean time to conversion was 15 + 12 hrs, 10 + 11 hrs and 9 + 11 hrs in the three groups, respectively ($p < 0.05$ for oral group versus the others). The smaller the LA the greater the probability of conversion. Amio delivered iv decreased CO and CI at 24 hours. This decrease was non-significant but might have become so if more patients had been studied.. In the iv amio group 8 pts had a fall in blood pressure and 12 pts had thrombophlebitis, but interruption of therapy was not necessary. No other complications were seen.

Conclusions: Amio, whether delivered p.os or iv, is highly effective for the conversion of recent onset AF to sinus rhythm; neither manner of administration is statistically superior to the other. Oral administration appears to have fewer side effects than iv, while iv has a more rapid action.

1850 Oral dofetilide for conversion of atrial fibrillation/flutter to sinus rhythm: time to cardioversion and duration of hospital stay

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Dofetilide (D), a new class III antiarrhythmic, converts up to 30% of patients (pts) with chronic atrial fibrillation/flutter (AF/AFI) to sinus rhythm (SR). Timing of conversion (CV) and proarrhythmic events were examined during the administration of D in patients with AF/AFI. Two double blind placebo controlled trials, SAFIRE-D and EMERALD, enrolled 996 patients with AF/AF1. Of these 638 [564 AF/74 AFI, mean age 65.6 yrs, mean duration of AF/AF1 4.1 months, 49% NYHA class II heart failure] were randomised to D [125, 250, 500 ug BID]. Since D is predominantly renally excreted, pts with renal impairment received a lower dose according to a pre-specified algorithm. Following the initial dosing, QT interval was measured and the dose was reduced or stopped if QT prolongation was excessive. Pts were monitored in hospital and DC cardioverted if they did not cardiovert within 72 hours of starting D.

Results: In total, 13 of 217 (6%), 22 of 215 (10%), and 61 of 206 (30%) pts in the 125, 250 and 500 ug D groups respectively pharmacologically cardioverted (CV). The timing of cardioversion for the three groups combined is summarised below.

Time from first dose (hrs)	0–6	0–12	0–18	0–24	0–30	0–72
Cumulative (%) converting	28	33	45	65	87	100

Four of the 5 cases (1 male; 4 female; 1 pt 250 μg; 4 pts 500 μg) of torsades de pointes occurred during the first 3 days. The overall prevalence of torsades de pointes was 0.8%. Therefore, the following approach is suggested for CV with D to minimise proarrhythmia risks. Initial drug administration should occur in hospital with ECG monitoring. Dosing should be based on calculated creatinine clearance and QT interval response. For pts who do not convert within 24–30 hours of D therapy, DC-CV should be considered. Pts should be monitored for the first 5 doses of D, or for a minimum of 12 hours after electrical or pharmacological CV to normal SR, whichever is longer.

Conclusion: Based on the fact that 87% of the pts who cardioverted on D did so within 30 hours, we conclude that this approach should minimise hospital stay while allowing for identification and treatment of any proarrhythmias.

1851 Comparative efficacy and safety of intravenous antiarrhythmic agents for conversion of recent onset atrial fibrillation

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Active management of pts with recent-onset atrial fibrillation (AF) to restore sinus rhythm may be warranted to alleviate symptoms, reduce the risk of thromboembolism or avoid/shorten hospitalisation. Although attempted pharmacological cardioversion is widely practiced as first line treatment, little is known about the comparative efficacy and safety of available agents. We have reviewed all published studies since 1980 involving conversion of recent-onset AF by IV antiarrhythmic agents. 22/46 studies were selected based on the following criteria: [i] randomized enrollment, [ii] recent-onset AF (≤7 days), [iii] detailed data about drugs' efficacy and safety. Efficacy rates in termination of AF were analyzed at <3 hrs and 12–24 hrs. Data from multiple studies are presented as pooled estimates of the percentage of pts converting to sinus rhythm (±95% CI). Occurrence of atrial flutter (Fl.) and/or severe tachyarrhythmias (Arr.) are reported as major adverse events:

	Pts	<3 h (% ± 95% CI)	Pts	12–24 h (% ± 95% CI)	Fl or Arr. (n.)
Flecainide	240	77 (65–90)*§		N/A	3/240
Propafenone	173	53 (42–64)*	147	73 (55–91)*	2/173
Amiodarone	95	47 (18–76)*	169	78 (68–89)*	0/95
Ibutilide	37	46*	N/A	3/37	
Digoxin	173	22 (17–28)	136	49 (46–53)	2/173
Placebo	299	15 (8–22)	290	44 (40–49)	2/299

(*$p < 0.001$ vs placebo, §$p < 0.001$ vs amiodarone and propafenone).

Although only limited data are available for some drugs, using meta-analysis techniques, flecainide emerges as the most effective agent for rapid conversion of AF with a good safety profile. Amiodarone and propafenone are as effective but with a slower onset of action. These findings may have important clinical and cost implications for shortening or avoiding hospitalisation and merit further investigation.

1852 Dose response of azimilide for prevention of atrial fibrillation or flutter

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Azimilide (AZ), an investigational class III antiarrhythmic agent, was studied in 3 randomized, placebo controlled trials with a total of 906 patients using once daily doses of 35, 50, 75, 100, and 125 mg or placebo in patients with symptomatic atrial fibrillation or atrial flutter (AF/FL), two-thirds of whom had structural heart disease. In each study the primary outcome variable was the first symptomatic recurrence of supraventricular tachycardia documented using transtelephonic ECG monitoring. Efficacy data from all 3 trials was tested for a dose-response relationship using a log-rank trend test with placebo = 0 mg and all 5 AZ doses. Data were stratified by trial to control for variation in placebo group event rates.

Results: The log-rank trend test was statistically significant with chi-square = 10.3 and p = 0.001. The 125 mg dose demonstrated a statistically significant treatment effect with hazard ratio (HR)(Placebo:AZ) of 1.81 (95% CI 1.27, 2.57). The 100 mg dose was evaluated in 2 separate studies with HRs of 1.32 (p = 0.15) and 1.38 (p = 0.08). The pooled HR for the 100 mg dose was 1.35 (95% CI 1.05, 1.72; p = 0.02) Torsade de pointes occurred in 5 patients on AZ and in no patients on Placebo.

Conclusions: AZ demonstrates a dose-response relationship over the dose range of 35–125 mg once daily in patients with symptomatic AF/FL; doses of 100 mg and 125 mg daily are associated with clinically important antiarrhythmic effects.

1853 Survival in patients treated with azimilide for atrial fibrillation and other supraventricular arrhythmias

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Azimilide is a novel class III antiarrhythmic drug that blocks both IKr and IKs and that was developed for use in patients with supraventricular arrhythmias. Efficacy of azimilide in preventing symptomatic arrhythmia recurrences was tested in 3 randomized, placebo-controlled clinical trials of patients with atrial fibrillation, atrial flutter or paroxysmal supraventricular tachycardia (PSVT). The purpose of this report is to describe the effect of azimilide on survival by pooling data from these 3 trials.

Methods: A total of 1091 patients (958 with atrial fibrillation, atrial flutter or both and 133 with PSVT) were enrolled in the 3 trials. Among these patients 328 were assigned randomly to placebo, and 763 were assigned to azimilide doses between 35 mg daily and 125 mg daily. Patients were followed until their first symptomatic arrhythmia recurrence was documented by electrocardiogram or for a maximum of 9 months (2 studies) or 6 months (1 study) as specified in the respective protocols.

Results: Average length of follow-up was 96.5 days in the azimilide group and 82.5 days in the placebo group. There were 3 deaths in 328 placebo patients and 6 deaths in 763 azimilide patients. The observed mortality rate was 3.0 per 100 patient-years in the azimilide group and 4.0 in the placebo group. The hazard ratio (azimilide:placebo) for mortality was 0.77 with 95% confidence interval (0.19, 3.1).

Conclusion: Although the confidence interval was broad, the point estimate from these pooled data of 3 randomized trials did not demonstrate any substantial favorable or adverse effect of azimilide on mortality in patients with supraventricular arrhythmias.

1854 Chemical cardioversion of acute atrial fibrillation: a randomized, double-blind trial of oral versus intravenous flecainide

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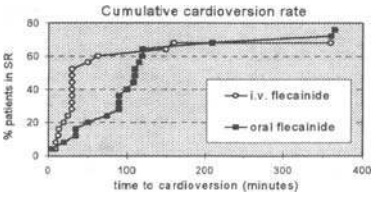
This is the first double-blind trial to compare oral versus intravenous (i.v.) flecainide as a loading dose for the cardioversion of acute atrial fibrillation (AF).

Methods: A randomised, double-blind, double-dummy trial. 50 patients with acute non-rheumatic AF (<48 hrs duration), aged 31–89 years were included. Flecainide was given either as an i.v. infusion (2 mg/kg over 30 mins) or as an oral solution (4 mg/kg) with appropriate placebos. We measured: safety; the time to cardioversion; and the proportions of patients in sinus rhythm (SR) at 2 hrs and at 8 hrs after treatment.

Results: The mean time to cardioversion was 42 mins for i.v. flecainide, and 116 mins for oral flecainide (2 tail t-test, $p < 0.01$). However, there was no significant difference in the proportions of patients cardioverted by 2 hrs (64% both groups) and 8 hrs (68% i.v.; 76% oral) (χ^2 test, n.s.).



Conclusion: These results suggest oral loading doses of flecainide may have a role in the pre-hospital treatment of acute AF.

ATRIAL FIBRILLATION AND EMBOLIC RISK

1855 Prothrombotic alteration of the endothelial haemostatic balance in patients with non-valvular atrial fibrillation

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Background: Systemic hemostatic abnormalities may contribute to the high risk of thromboembolic events in patients (pts) with nonvalvular atrial fibrillation (NAF). The aim of the study was to assess differences in endothelium-dependent coagulation factors in NAF versus sinus rhythm (SR).

Methods: In the LURIC (Ludwigshafen Risk and Cardiovascular Health)-study 1478 consecutive pts who were hospitalized for elective diagnostic coronary angiography were enrolled. Pts with coumarine therapy, acute coronary syndrome, valvular heart disease or any other acute or serious disease were excluded. NAF was documented in routine ECG. Fasting blood samples were drawn in the early morning to minimize circadiane variation.

Results: 1382 pts were in sinus rhythm (age: 61 ± 9 years, 63% male, CAD 80%, CMP 7%) and 175 pts showed atrial fibrillation (age: 65 ± 10 years, 73% male, CAD 74%, CMP 18%). No difference was seen in fibrinogen, factor VII, CRP, D-dimers, prothrombin time, regular alcohol consumption, and arterial hypertension between the two groups.

	SR (n = 1382)	NAF (n = 175)	p
Endothelial Prothrombotic Factors:			
Von Willebrand factor-antigen (U/dL)	164 ± 71	188 ± 82	<0.01
Thrombomodulin (μg/L)	54 ± 26	52 ± 22	0.08
Free protein S (U/dL)	101 ± 28	87 ± 31	0.001
Protein C (U/dL)	111 ± 23	91 ± 26	<0.001
Endothelial Fibrinolytic Factors:			
tPA-activity (IU/ml)	0.7 ± 0.6	0.75 ± 0.7	0.04
PAI-1-activity (IU/ml)	27 ± 56	34 ± 80	<0.001
Thrombotic Clinical Events:			
Venous thrombosis	4.1%	8.1%	<0.001
Stroke/transitoric ischemic attack (TIA)	8.1%	17.7%	<0.001

Conclusion: 1. As expected Pts with NAF had significant more often a history of venous thrombosis and stroke/TIA. 2. The endothelial-dependent hemostatic profile was significantly more prothrombotic in Pts with NAF (increased PAI-1 and vonWillebrand factor, decreased protein C- and free protein S) than in SR. Significant changes in the balance of the endothelial hemostatic system may contribute to the higher rate of thromboembolic events in pts with NAF.

1856 Tissue factor and von Willebrand factor expressions increased in the atrial tissue of the fibrillating atrium

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Right atrial appendage biopsies were collected from 8 pts with atrial fibrillation (AF) and 10 control pts with sinus rhythm (SR) at the time of elective coronary artery bypass grafts.

Method: Double immunohistochemical staining was carried out using monoclonal antibodies against human TF (American Diagnostic Inc.), CD 68 to identify macrophages and EN4 as a specific endothelial cell mark. Also an antibody to vWf (Dako, UK) was used. Immunohistochemical sections were evaluated by two investigators who were blind to the disease entity being investigated and the clinical characteristics of the patients. The total number of macrophages (M) as well as those expressing TF (MTF) were counted. The percentages of macrophages expressing TF (%MTF) were then calculated. The percentage endocardial endothelium expressing vWf was rated as 1, 2, 3 and 4 by two investigators. 1 ≤ 25%, and 4 = 100% expression of vWf.

Results: vWf expression was increased in the AF group ($p = 0.01$). 1/8 pts in AF group expressed <25% vWf, compared to 8/10 in the SR group ($p = 0.015$). No endothelial expression of TF was identified. 3 pts in the SR group were excluded from the TF study because of diabetes mellitus. Results were presented as mean (+sd) and p value below.

	MTF	M	%MTF	vWf
SR	1.23 (0.6)	16.74 (4.4)	7.17 (3.0)	1.4 (1.0)
AF	7.29 (4.5)	32.86 (6.5)	22.41 (14.3)	2.75 (1.0)
p	0.0036	0.0001	0.016	0.011

This report is the first to show an association between AF and both MTF and vWf expressions in the atrial tissue of patients with AF.

Conclusion: These results suggest specific therapy to the prevention of atrial thrombus.

1857 Anticoagulant therapy in atrial fibrillation: experience in an Italian teaching hospital

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Atrial fibrillation (AF)is the most common chronic arrhythmia, and its prevalence has been estimated around 6% among patients older than 65 years. The rate of stroke in patients with AF is 5 times higher than in those without. Oral anticoagulant treatment (OAT)has been shown to reduce by 2/3 the risk of stroke and its administration is currently recommended, particularly in patients older than 65 years. Nevertheless, recent investigations have found a significant underuse of OAT.

Methods: We have carried out an observational cross-sectional study in one Italian University Hospital to evaluate the prevalence of AF among hospitalized patients in a single day and to assess previous and current antithrombotic treatment. In 2 different days 8 trained physicians examined the charts of all hospitalized patients and verified the presence of AF on the ECG.

Results: A total of 1301 charts were examined. The prevalence of AF was 7.9%, 103 patients of whom 11 were present in both visits. The average age was 78.7 (s.d. ± 9.39), 7 patients < 65, and 55 > 75. Males were 44, females 48. There were 78 patients (84.8%) with chronic AF, and 14 (15.2%) patients whose AF was diagnosed for the first time during hospitalization. Among patients with chronic AF, 9 had contraindications to OAT (2 dementia, 3 alcohol abuse, 2 prior falls, 2 prior bleeding). Of the 69 remaining, 24 (34.7%) were treated with OAT (age 72.7 ± 8.04), 18 (26.1%) before hospital admission, whereas 6 (8.7%) were started in hospital. Of the former group 2 also had prosthetic valves, of the latter 2 had OAT started because of venous thromboembolism. Antiplatelets were administered to 33 (42.3%, age 81.7 ± 8.29) patients, 25 (32%) before admission. Of 78 patients, 35 (44.8%) did not receive any antithrombotic therapy before admission, 21(26%) during hospitalization. Patients admitted for acute ischemic stroke were 13 (14.1%, age 81.3 ± 8.46), 12 with chronic AF, and 1 with newly diagnosed AF. None of them was treated with OAT, 10 with antiplatelet agents. Of all patients, 30 (32.6%) had a history of cerebrovascular accidents, 28 of whom had chronic AF. Only 5 (17.8%) were on OAT, 19 (67.8%) were on antiplatelets.

Conclusions: The use of OAT in patients with AF is dramatically low and the rate decreases with increasing age. A high number of patients does not receive any antithrombotic treatment. A significant rate of patients not receiving OAT are admitted for stroke. Hospitalization improves the quality of the treatment, but the results are still poor. Continuous efforts to promote the use of OAT for stroke prevention are necessary.

1858 Anticougulant use in new onset atrial fibrillation: Canadian Atrial Fibrillation Registry (CARAF)

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The Canadian Registry of Atrial Fibrillation (CARAF) is a natural history follow-up registry of 896 patients with new onset atrial fibrillation (AF) with mean follow-up of 3 years. Patients were recruited from emergency departments (445), physician offices (315) and in hospital (136). These patients have been followed annually without directed intervention by the CARAF investigators. Antithrombotic therapy (AT) was done by community physicians. There were 434 men and mean age was 61 years. At 1 year, 27.3% received warfarin, 35.0% ASA, 2.5% both and 35.2% no AT; with virtually no change over 3 years.Warfarin use was greater in chronic AF (111/192, 58%) compared to paroxysmal AF (46/256, 18%) or no recurrent AF (50/334, 15%). In patients with any risk factor for stroke (age > 65 years, diabetes, prior stroke, CHF, or hypertension warfarin use was 35.6% compared to 19.3% for those without any risk factor ($p < 0.001$). Patients with any risk factor were more likely to receive warfarin if they had chronic AF (53.8%) than if they had paroxyxmal AF (23.8) or no recurrent AF (15.8%) ($p < 0.05$). The risk of stroke during the first 2 years of follow-up was 2.4% per year and 60% of strokes occurred in patients not on warfarin at the time of stroke.

Conclusion: In recent onset AF, warfarin use remains low even in patients with known risk factors for stroke and with chronic AF. There appears to be considerable underuse of proven effective therapy in these patients.

1859 Paroxysmal non-rheumatic atrial fibrillation does not show a prothrombotic state

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Anticoagulation is not recommended in paroxysmal atrial fibrillation < 48 hours of duration however prospective studies to assess the presence of a prothrombotic state have not been undertaken in this setting.

Methods: We studied 24 patients with paroxysmal non-rheumatic atrial fibrillation, who restored sinus rhythm by spontaneous or pharmacological cardioversion before 48 hours, without anticoagulant therapy. Atrial mechanic function was assessed by transmitral inflow in transthoracic echocardiography, E wave/A wave ratio (E/A) and A wave velocity time integral/total velocity time integral ratio ($\int A/\int T$) were measured. Thrombomodulin (Th) and von Willebrand factor (vW), markers of endothelial damage, were measured. D-dimer (DD) as hypercoagulable state marker was measured. Blood samples and echocardiographic studies were performed at 1st, 3rd, 7th and 30th days after cardioversion. Results are expressed as median and 25–75th percentile values.

Results: There were no correlation between endothelial cell function markers, DD and echocardiographic findings.

	1st day	3rd day	7th day	30th day	
E/A	0.89 (0.74–0.98)	0.82 (0.70–0.99)	0.79 (0.70–1.22)	0.74 (0.59–1.23)	NS
$\int A/\int T$	0.38 (0.35–0.46)	0.37 (0.34–0.43)	0.34 (0.29–0.45)	0.41 (0.35–0.46)	NS
Th	11.1 (9.8–13.1)	11.5 (8.6–14.8)	10.1 (7.9–14.3)	13.7 (9.6–17.0)	NS
vW	136.0 (105.0–178.5)	123.0 (106.0–169.8)	127.0 (90.5–173.5)	143.0 (107.5–163.0)	NS
DD	2.10 (0.71–7.11)	3.04 (0.63–8.61)	2.89 (0.78–5.85)	1.35 (0.62–1.92)	NS

Conclusions: Patients with paroxysmal non-rheumatic atrial fibrillation did not show a prothrombotic state. The findings of this study support non-anticoagulant-therapy attitude.

1860 Thromboembolic events in non-valvular atrial fibrillation: no evidence of a difference in the endothelial-dependent haemostatic system in dilatated cardiomyopathy versus coronary artery disease

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Background: Systemic hemostatic abnormalities have been described in patients (pts) with nonvalvular atrial fibrillation (AF). The aim of the study was to assess influences of different heart diseases causing AF on the endothelial-dependent hemostatic system.

Methods: In a LURIC (Ludwigshafen Risk and Cardiovascular Health)-substudy 148 pts who underwent elective coronary angiography with AF in routine ECG were enrolled. Pts with coumarine therapy, acute coronary syndrome, valvular heart disease and any other acute or serious disease were excluded. Blood samples were drawn in the morning to minimize circadian variation.

Results: There was no difference in fibrinogen, factor VII, CRP, D-dimers, prothrombin time, regular alcohol consumption and the rate of venous thrombosis between the groups.

	CAD + AF (n = 118, male 76%)	CMP + AF (n = 30, male 90%)	p
Clinical Data:			
Stroke/transitoric ischemic attack (TIA)	21%	13%	**0.001**
Systemic Hypertension	61%	40%	**0.01**
Age	66 ± 10 years	62 ± 10 years	**<0.05**
Endothelial Prothrombotic Factors:			
Von Willebrand factor antigen (U/dL)	181 ± 73	169 ± 72	0.5
Thrombomodulin (μg/L)	51 ± 22	43 ± 18	0.4
Protein S-activity (U/dL)	97 ± 37	93 ± 25	0.2
Protein C (U/dL)	89 ± 27	99 ± 30	0.3
Heparin Co-Factor II (U/dL)	102 ± 13	106 ± 10	0.4
Endothelial Fibrinolytic Factors:			
tPA-activity (IU/ml)	0.74 ± 0.6	0.7 ± 0.7	0.4
PAI-1-activity (IU/ml)	29 ± 37	27 ± 21	0.7

Summery: The increased rate of stroke/TIA in Pts with CAD and NAF may be explained by the higher age of these pts and a higher prevalence of hypertension. It could not be explained by differences in endothelial-dependent fibrinolytic or prothrombotic activity between CAD and CMP.

UNSTABLE ANGINA: PROGNOSIS, BCG AND CRP

1861 Prevalence and predictive accuracy for the detection of coronary artery disease of marked t-wave inversion in multiple precordial leads

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The presence of marked inverted T-waves in multiple precordial leads is considered a sign of high likelihood of significant coronary artery disease (CAD). Its current prevalence and predictive accuracy for the detection of patients (P) with significant CAD are not well known.

Methods: 309 consecutive P (193 males, 116 females; 65 ± 12 yr) without prior CAD diagnostic testing were admitted because of possible unstable angina. P with bundle branch block or previous anterior myocardial infarction were excluded. Each P was analyzed for the presence at admission or the development during the first 24 hours of new and sustained (>24 h) T-wave inversion (>2 mm) in ≥3 precordial leads. We assessed the prevalence of this finding and its potential diagnostic value for the detection of significant (≥70% stenosis) CAD and the identification of significant left anterior descending (LAD) stenosis in the 224 P who underwent coronary angiography.

Results: marked T-wave inversion in the precordial leads was observed in 57 P (18.4%; 95% CI: 14–23%); 53 of them underwent coronary angiography. Sensitivity (Sen), specificity (Spe), and predictive values (PV) of this finding for the detection of significant CAD and LAD stenosis were:

	Sen	Spe	+PV	−PV
CAD (145 P)	25% (36/145)	78.5% (62/79)	68% (36/53)	36% (62/171)
Males (115 P)	26% (30/115)	82.5% (33/40)	81% (30/37)	28% (33/118)
Females (30 P)	20% (6/30)	74% (29/39)	38% (6/16)	55% (29/53)
LAD (97 P)	33% (32/97)	83.5% (106/127)	60% (32/53)	62% (106/171)
Males (73 P)	37% (27/73)	88% (72/82)	73% (27/37)	61% (72/118)
Females (24 P)	21% (5/24)	75.5% (34/45)	31% (5/16)	64% (34/53)

In conclusion, the presence of marked T-wave inversion in multiple precordial leads in P with suspected unstable angina (1) has a prevalence of about 18%; (2) its predictive power for detection of significant CAD is poor; (3) it shows a high specificity and a substantial positive predictive value only in males.

1862 Immediate exercise testing in low risk patients with acute chest pain

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To assess the value of immediate exercise testing (IET) in the triage of patients presenting with acute chest pain a group of 319 consecutive patients was evaluated. Patients included had chest pain with atypical features, non-diagnostic electrocardiogram and no history of coronary artery disease. All patients underwent symptom limited exercise testing according to the Bruce protocol within 24 hours of admission (median 2 hours). Seven patients were admitted because of exercise induced transmural ischemia (4 pts) or arrhythmias (3 pts). Negative IET was present in 195 pts (63%), non diagnostic IET (<70% maximal predicted heart rate) in 69 pts (22%) and positive IET in 48 pts (15%). During 6 month follow-up, 21 patients had adverse coronary events; 11 patients had unstable angina, 8 had myocardial infarction and 2 had sudden death. Patients were divided on the basis of acute (<6 hour) or recent (>6 hour) complaints.

Results:

	Total group (n = 312)	Acute group (n = 104)	Recent group (n = 208)
Sens (%)	24	14	57
Spec (%)	82	82	89
NPV (%)	93	86	97

NPV = negative predicted value

We conclude that immediate exercise testing is useful for the triage of pts presenting with chest pain but has limited value in pts with acute (<6 hr) chest pain.

1863 In unstable angina reduced heart rate variability is not predictive of an adverse in-hospital outcome

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Reduced heart rate variability (rHRV) correlates with in-hospital outcome in patients with acute myocardial infarction. Its potential role for prognostic assessment in unstable angina has not been established. Our objective was to determine the prognostic value of rHRV for prediction of adverse in-hospital outcome in patients with unstable angina (UA).

Methods: 210 consecutive patients (p) with UA without prior myocardial infarction (MI) nor total CK elevation post admission were included. Continuous ECG Holter recording for assessment of silent ischemia and heart rate variability was performed during the initial 24 hours. Measurement of C-reactive protein level (CRP) at admission and a 2-D echocardiogram during the initial 24 hours to detect regional wall motion abnormalities were also performed (median time elapsed since the beginning of pain 12 hours; range 0–24 hours). An in-hospital follow-up period was conducted to determine the occurrence of a primary combined end point of recurrent ischemia (death and/or acute myocardial infarction and/or refractory angina and/or recurrent angina and/or silent ischemia).

Results: Mean age was 66.1 ± 11.3 years, 62.9% were male; 63.3% received prior treatment with aspirin, and 43.8% had ST segment depression (↓ST) on admission ECG. Overall levels of C-reactive protein (CRP) at admission were 0.5 (0.3–1.0)* mg/dl and those of fibrinogen were 333.9 ± 89.6† mg/dl respectively. Prevalence of silent ischemia (SI) was 25.7%. Prevalence of acute left ventricular wall motion abnormalities (LVWMA) was 42.8% (CI 95% 36.0–49.8). The rate of events during the in-hospital period was: death 3.8%, myocardial infarction 8.1%, refractory angina 15.2%, recurrent angina 25.7% and silent ischemia 25.7%. The rate of the primary combined end point of recurrent ischemia (RI) was 42.4% during the in-hospital period.

	p with RI	p without RI	p
n (%)	89 (42.4)	121 (57.6)	-
SDNN†	87.1 ± 27.0	89.0 ± 27.7	ns
SDNN Index†	43.9 ± 18.1	46.2 ± 14.9	ns
SDANN Index†	74.3 ± 24.5	74.9 ± 27.0	ns
pNN50†	8.1 ± 10.6	9.7 ± 10.9	ns
RMSSD†	30.5 ± 16.5	31.6 ± 15.4	ns

(*expressed as median and 25–75% interquartile ranges, †expressed as mean ± SD)

Reduced heart rate variability was also not associated with: elevated CRP levels (>0.3 mg/dl), fibrinogen levels above 400 mg/dl, ↓ST or the presence of LVWMA.

Conclusions: Reduced heart rate variability in patients with unstable angina is not useful as a marker for increased risk of in-hospital recurrent ischemic events.

1864 Prognostic value of clinical and ECG variables in patients with suspected unstable angina: results of the Proyecto de Estudio del Pronostico de la Angina (PEPA)

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Background: Unstable angina (UA) and non-Q wave myocardial infarction (non-Q MI) includes a broad spectrum of patients. However, little prognostic information is available of clinical and ECG variables in large, prospective unselected samples of patients.

Methods: The prognosis of clinical and ECG variables obtained at hospital admission was prospectively evaluated in 4115 consecutive patients considered to have UA or non-Q MI when first seen by a cardiologist. The recruitment period was from October 1995 to September 1996 at 18 centers in Spain.

Results: The total 90 days' mortality was significantly higher ($p < 0.001$) in women, age > 65 y, previous MI, peripheral vascular disease, previous stroke and diabetes. Total 90 days' mortality in the different groups of Braunwald's classification was: Class I: 4.3%, Class II: 1.7%, Class III: 6.7% (NS); Class A: 5.8%, Class B: 5.1% and Class C: 8.9% ($p = 0.03$); previous treatment: without: 4.3%, standard: 6.0%, maximal: 9.0% ($p = 0.03$); abnormalities of ST-T on first ECG: yes 7.1%, no: 2.5% ($p < 0.001$). Only the following, were identified as independent risk for 90 days' mortality in the multivariate analysis (RR; 95% CI): heart failure (1.7; 1.4–1.9), age > 65 y (1.5; 1.3–1.8), diabetes (1.4; 1.2–1.7), ST-T abnormalities (1.4; 1.2–1.7), and peripheral vascular disease (1.3; 1.1–1.6)

Conclusion: Very simple clinical and ECG variables are useful to evaluate the prognosis of patients with suspected UA or non-Q MI.

1865 Superiority of C-reactive protein over the exercise treadmill test for non-invasive risk stratification of patients recovering from unstable angina

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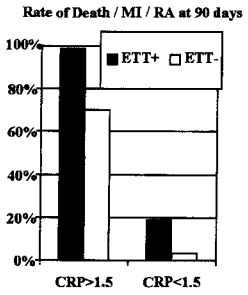
The exercise treadmill test (ETT) is routinely employed for non-invasive risk stratification in patients recovering from an acute ischemic event. In unstable angina, elevated C-reactive protein (CRP) levels were shown to be an independent marker of high risk for recurrent ischemic events. Our objective was to compare the prognostic value of the symptom-limited treadmill test with CRP levels for non-invasive risk stratification in patients (p) with unstable angina discharged without in-hospital events or revascularization procedures.

Methods: During a 6 month period, 105 consecutive p with unstable angina and without prior myocardial infarction nor total CK elevation post-admission were included.

Measurement of CRP was performed at hospital discharge. The ETT was performed at hospital discharge or within the week following hospital discharge. A 90 day follow-up was conducted to determine the occurrence of a primary combined end point (death (D) and/or acute myocardial infarction (MI) and/or refractory angina (RA)).

Results: Mean age was 65.5 ± 11.7 years, 63.8% were male; and 48.6% had ST segment depression (↓ST) on admission ECG. The rate of in-hospital revascularization was 27.6%.



Rate of Death/MI/RA at 90 days.

The rate of in-hospital D and/or MI and/or RA was 21.9% and from discharge to day 90 the rate of the primary end point was 28.6%. A cut-off point of 1.5 mg/dl was established for CRP levels based on the Receiver Operating Curves of the 90-day outcome. CRP at discharge was > 1.5 mg/dl in 29.3% of the p. ETT showed the presence of inducible ischemia in 41.0% of the p. On univariate analysis CRP > 1.5 mg/dl was associated to the highest event rate, but the combination with the ETT results further improved its prognostic significance (shown in figure). In a Cox regression model for predicting the primary end point at 90 days, which included age, ↓ST, silent ischemia, and ETT results, the strongest independent marker was CRP at discharge > 1.5 mg/dl (HR 3.0 CI 95% 1.9–5.0; p < 0.001). The ETT was not an independent predictor in the Cox regression model (HR 0.9 CI 95% 0.7–2.0; p = ns).

Conclusion: In unstable angina CRP at discharge > 1.5 mg/dl is a strong independent marker of an adverse 90-day outcome. These results support the use of a combination of inflammation markers (CRP) and exercise induced ischemia (ETT) to identify p with high or low risk for coronary events.

1866 C-reactive protein level in patients with unstable angina pectoris: association with myocardial perfusion and functional abnormalities on gated SPECT imaging and angiographic morphology

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Elevated C-reactive protein (CRP) has been reported to identify high-risk patients (pts) in unstable angina. We examined the relation of plasma CRP concentration to myocardial perfusion, function and coronary, morphology in pts hospitalized with unstable angina pectoris.

Methods: We studied 96 pts within 6 hours of the onset of symptoms. Blood samples were drawn at admission and at 24 hours to assess CRP levels. Gated SPECT was performed within 1–6 hours after the injection of 30 mCi Tc-99m sestamibi. All pts had coronary angiography in hospital course. SPECT images were interpreted using 20-segments with a 5 point scale (0 = normal, 4 = no uptake) for perfusion and a 4 point scale (0 = absent, 3 = normal) for wall motion. Perfusion index and wall motion index were derived by adding the score of all segments and dividing these by 20. Left ventricular ejection fraction was measured on left ventriculography.

Results: 8 pts had no coronary artery disease (CAD) and none of them had CRP in the 5th quintile (≥2.9 mg/L). The remaining 88 pts with CAD were divided into two groups according to plasma CRP level:

	Quintiles 1–4, n = 72	Quintile 5, n = 16	p
Perfusion index	0.74 ± 0.29	1.01 ± 0.37	0.002
Wall motion index	2.50 ± 0.39	2.21 ± 0.42	0.009
No. of diseased vessels	1.88 ± 0.75	1.91 ± 0.73	NS
Pts with ICT	18 (25%)	6 (37%)	NS
TIMI flow	2.49 ± 0.05	2.05 ± 0.9	0.01
Pts with complex lesion	29 (40%)	8 (50%)	NS
Ejection fraction	59.3 ± 14	49.3 ± 13	0.01

ICT = Intracoronary thrombus

Conclusion: Elevated CRP is associated with a greater degree of myocardial hypoperfusion and wall motion abnormalities and the angiographic findings of lower ejection fraction and decreased TIMI flow.

IMPROVING THE OUTCOME OF ACUTE MYOCARDIAL INFARCTION

1867 Mortality in patients with acute myocardial infarction treated with reperfusion therapy, beyond the clinical trials

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Reperfusion therapy (RT – primary PTCA or fibrinolysis) within the first few hours of acute myocardial infarction (AMI) is a very well established procedure. However, regarding the inclusion and exclusion criteria, the randomised clinical trials rarely express the real world. In the present paper the authors are looking at a single centre registry putting in evidence the most relevant differences with the reference trials.

A consecutive series of 417 patients (pts) with AMI admitted in a single tertiary centre were managed with RT-fibrinolysis – 265 (63%); primary PTCA – 152 (37%). Demographic characteristics, risk factors and previous coronary disease were similar between the two groups. In the group of pts treated with PTCA the anterior topography was more frequently found (69.1% vs 49.4%; p < 0.0001).

Results: In-hospital mortality rate was 10.0% – 42 pts (1ªPTCA – 8.6%; FBR – 10.9%; ns). Mortality was influenced by (survived vs non-survived): age (62.1 vs 71.8; p < 0.0001); gender female (19.5% vs 50.0%; p < 0.0001); Killip cl > I at admission (13.0% vs 33.3%;p = 0.001); late treatment, (<6 hrs – 74.6% vs 59.5%; p < 0.05). Intracranial bleeding was the cause of death in 3 fibrinolysed pts). The outcome was not influenced by reperfusion modality. Mortality by age group was: <60 – 2.5%; 61–70 – 8.8%; 71–80: 19.5%; >80–22.7%. The mean time from symptoms onset to treatment and the prevalence of anterior AMI were the most relevant different baseline characteristics when the present cohort is compared with the reference trials (PAMI, GUSTO I, GUSTO IIb).

Conclusions: In the present cohort mortality rate is slightly higher than reported in published trials, not influenced by reperfusion modality and justified by differences in baseline characteristics: treatment started later and anterior AMI is more prevalent, expressing a higher risk population. Older age, female gender, late treatment and K. Class > I at admission were the predictive factors for death.

1868 Hospital profiles and clinical outcomes stratified by on-site cardiac catheterization availability: an INTIME-II substudy

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Background: Availability of on-site cardiac catheterization strongly influences patient mangement and may be associated with a distinct hospital profile. The relationship between availability of catheterization, hospital profile, and clinical outcomes is not well studied in megatrials of thrombolysis for acute myocardial infarction (AMI).

Methods: We surveyed all 855 hospitals from 35 countries participating in InTIME-II (nPA vs tPA in AMI) regarding location, size, teaching status, patient management, and on-site facilities (catheterization, angioplasty and cardiac surgery). Hospitals were stratified by on-site availibility of cardiac catheterization as: 24 hours, day time only, and no availability.

Results: 100% of hospitals responded to the survey (see table). *Clinical outcomes by catheterization availability and hospital profile will be available after data unblinding in March 1999 and will be presented.

Hospital characteristics

	24 h	Day	None	p (trend)
Number of hospitals	264	215	376	–
City/Referral	88%	75%	52%	<0.0001
< 300 beds	22%	21%	47%	0.01
300–700 beds	41%	52%	42%	0.9
>700 beds	37%	27%	11%	<0.0001
Teaching hospital	79%	69%	47%	<0.0001
Lytic decision by cardiologist	80%	74%	43%	<0.0001
Inpatient care by cardiologist	94%	87%	55%	<0.0001
On-site angioplasty	93%	56%		
% Primary PTCA for AMI	30% **	7%**	–	<0.0001**
On-site CABG	74%	28%	–	<0.0001
30 d event rate (death, MI, stroke)	*	*	*	*

Percentages reflect column percent

Conclusions: In this AMI megatrial, hospitals with 24 hour on-site catheterization tend to be larger, city, teaching hospitals, with patients generally managed by cardiologists. Hospitals with day catheterization had a profile that was intermediate between those centers with 24 h availability and those with no catheterization lab. These differences may be important when comparing clinical outcomes between hospitals stratified by the availability of on-site facitilities.

1869 Non-Q and "incomplete-Q" myocardial infarction after thrombolysis is associated to reinfarction in a six-month follow-up

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Succesful thrombolysis (TL) is associated to a limitation of ECG indexes of necrosis. We explored the rate of development of Q waves at discharge in leads with ST segment elevation (ST↑) on admission, and its prognostic implications in the follow up.

Methods: 7605 pts were discharged alive in the International tPA/SK mortality trial. We analysed the ECG of pts with ST↑ >= 0.1 mV in >= 3 contigous leads on admission, and excluded pts with bundle branch block, poor quality of the ECG or incomplete follow up. An index of Q development in leads with ST↑ was calculated: (n of leads with Q at discharge in leads with ST↑ on admission/n leads with ST↑ on admission) × 100. Six months follow up for reinfarction and death was performed. A total of 5253 pts were included.

Results: 1) no Q development, index 0%, (non Q MI) was observed in 975 pts (18.6%), 2) index 10 to 40% ("incompleted" Q) in 771 (14.7%) and 3) index > 40% ("completed" Q wave) in 3507 (66.7%). Reinfarction is summarised in the table

	Prevalence		Reinfartion		Odds and 95% CI
	n	%	n	%	
Non Q	975	18.6	60	6.2*	1.95 (1.39–2.7)
"Incompleted" Q	771	14.7	45	5.8*	1.84 (1.24–2.6)
"Completed" Q	3507	66.7	114	3.3	1

*p < 0.001 vs "completed Q".

Death rate was 2.8% in the "completed" Q group, 3.5% in the "incompleted Q" group and 3% in the non Q group, p NS. Reinfarction was associated with mortality during follow up: death rate was 28% in the 219 pts with reinfartction and 1.8% in pts without reinfarction, p < 0.001.

Conclusions: non Q MI or incomplete Q development after thrombolysis at discharge predicts a higher risk of reinfarction during the follow up.

1870 Women with acute myocardial infarction are treated less aggressively than men

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Acute myocardial infarction (AMI) in women occurs at higher age and has a higher mortality compared to men. We examined if there is a specific gender difference regarding acute treatment and mortality.

Methods: Within the MITRA study 6066 consecutive patients with AMI were registered in 54 hospitals in south-west Germany from 6/94 until 2/97. The percentage of women was 34% (2033). We examined if there was a gender difference concerning comorbidity, initial presentation, treatment and mortality.

Results:

	Women	Men	p-value
Primary PTCA	6.5%	9.3%	<0.0001
Thrombolysis	41.3%	50.5%	<0.0001
Beta blockers	49.8%	58.6%	<0.0001
Mortality	20.1%	12.2%	<0.0001

There was no significant difference in therapy with ACE inhibitors and Aspirine. Multivariate analysis adjusting for 22 variables (including age) showed that women receive thrombolysis or primary PTCA less frequently than men (OR 0.76; 95% CI 0.62–0.92).

Conclusion: Women with AMI are treated less aggressively than men. The multivariate analysis shows that recanalisation therapy (thrombolysis or primary PTCA) is underused in women. This is associated with a higher hospital mortality.

1871 Prior treatment with aspirin as a predictor of better coronary thrombolysis in patients with acute myocardial infarction

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Prompt and complete recanalization of the occluded infarct-related artery is crucial in limiting the size of the infarct and improving the survival rate. Our objective was to study the relation among prior treatment with aspirin (P-ASA), the achievement of complete coronary reperfusion (CR+), the size of the infarct and the in-hospital survival rate in patients (p) with acute myocardial infarction (AMI) receiving thrombolytic therapy with streptokinase (SK).

Methods: During a 5 year period, 792 consecutive p were admitted to the coronary care unit with diagnosis of AMI. 585 presented ST segment elevation ≥ 1 mm in two or more contiguous leads at hospital admission, receiving SK 233 p (39.8%). We analyzed in this group the relation among P-ASA, the achievement of CR+ (resolution of ST segment elevation ≥ 70% at 60 minutes), the size of the infarct (peak creatine kinase levels) and the in-hospital survival rate.

Results: Mean age was 61.5 ± 13.0 years, 79.4% were male, 29.6% had preinfarction angina (PA), 17.6% had prior history of AMI (P-AMI) and 3.4% had prior history of heart failure (P-HF). The AMI localization was anterior in 126 p and inferior in 107 p. At the time of admission mean systolic arterial pressure (SAP) was 126.5 ± 25.6 mmHg, mean heart rate was 80.0 ± 19.5 bpm and Killip & Kimball classification (KK) was type A in 74.2% of the p, B in 20.2%, C in 2.1% and D in 3.4%. 126 p (54.0%) received P-ASA. 107 p (45.9%) achieved CR+. The rate of in-hospital death was 16.3%. On univariate analysis P-ASA was associated with the highest CR+ rate (70.6% CR+ with P-ASA versus 16.8% CR+ without P-ASA; OR 5.6, CI95% 1.2–26.5; p < 0.01). The peak CK values were 1029.3 ± 771.1 UI/L in the group of p with P-ASA and 2136.4 ± 681.0 UI/L without P-ASA (p = 0.025); and the rate of in-hospital death 7.9% and 26.2% respectively (RR 0.30, CI 95% 0.15–0.60; p < 0.001). In a logistic regression model for predicting CR+, which included age > 70, PA, time "door to SK", P-AMI, P-HF, KK ≥ B and AMI localization, the strongest independent marker was P-ASA (OR 5.4, CI95% 1.2–20.5; p < 0.01). P-ASA was not an independent marker of increased risk for in-hospital death in a logistic regression model adjusted for age > 70, P-AMI, KK ≥ B, AMI localization and SAP < 100 (OR 1.4, CI95% 0.7–3.4; p = NS).

Conclusions: In p with AMI and P-ASA, SK more frequently obtained CR+, resulting in smaller infarct sizes. These results suggest that better platelet inhibition may improve the results of reperfusion strategies in AMI.

1872 Bundle-branch block, acute myocardial infarction and thrombolysis. Too much and too little?

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Purpose: The selection of patients with acute myocardial infarction (AMI) for thrombolytic therapy is of great importance for outcome. This selection is made on clinical symptoms and electrocardiographic (ECG) findings. Patients with bundle branch block (BBB) are a diagnostic problem. Studies on thrombolytics have shown that patients with BBB and AMI have worse clinical outcome compared to patients with normal QRS duration on ECG and they benefit from thrombolytic therapy. We have made a prospective multicenter study addressing the question of early diagnosis, treatment and outcome regarding patients with chronic BBB and clinical suspicion of AMI.

Methods: A prospective multicenter study with 14 Swedish centres. Patients with BBB and chest pain <6 hours on admission and clinical suspicion of AMI were included. ECG was registered on admission and after 12–24 hours. The patients were monitored with continuos vector cardiography for 12–24 hours. Diagnosis of AMI was made with cardio-specific markers.

Results: 265 patients were included. Male/female ratio was 70/30. Mean age was 74.8 years. Left bundle branch block (LBBB) was present in 63% and right bundle branch block (RBBB) in 37%. 121 (46%) had AMI. The use of thrombolytics was as follows: Of all patients 12%, of LBBB and AMI 18% and RBBB and AMI 34%. Of those treated with thrombolytics a substantial percentage did not have AMI (see table).

	All BBB	LBBB	RBBB
AMI	28	14	14
Non AMI	5	3	2

Diagnosis and BBB amongst patients treated with thrombolytics: n = 33

Conclusion: Patients with BBB and clinical suspicion of AMI may be under-treated with thrombolytics. However of those receiving thrombolytics 18% of patients with LBBB and 13% of patients with RBBB do not have an AMI and may thus be over-treated. A more accurate tool is needed for identifying patients with AMI and BBB eligible for thrombolytic treatment.

GROWTH FACTORS AND CELL PROLIFERATION

1873 De-differentiated smooth muscle cells in human coronary atherosclerotic lesions express a new mitogen-inducible nuclear orphan receptor gene

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Background: De-differentiation (activation, migration and proliferation) of smooth muscle cells (SMC) in the vascular wall has a key role in the development of spontaneous atherosclerosis and is generally held responsible for restenosis following balloon angioplasty and the failure of coronary bypass grafts. Interest has therefore focused on the regulation of SMC. Quiescent SMC respond to a variety of growth factors by dedifferentiating and re-entering the cell cycle, and these changes in the phenotype are mediated by changes in gene expression. The aim of the project was the identification of genes specifically expressed during differentiation of SMC in response to mitogens.

Methods and Results: Primary cultures of coronary artery SMC were obtained by the explant method and mRNA-differential display of stimulated versus arrested SMC in vitro was performed. An inducible cDNA was cloned, sequenced and characterized. Northern blot and the in situ hybridization technique were used to confirm the inducibility of the cloned cDNA. We have cloned a mitogen-inducible nuclear orphan receptor in porcine SMC (NOR-1), and characterized its inducibility in SMC in vitro and in vivo. The expression of NOR transcripts is induced within 30 min by several mitogens, including PDGF, thrombin and serum, which activate different signal pathways. Moreover, we have directly associated NOR with atherosclerosis. In situ hybridization analysis shows that NOR mRNA is expressed by SMC in immature and growing zones of diet-induced porcine atherosclerotic lesions and human coronary plaques.

Conclusion: We have identified for the first time the expression of NOR-1 gene in mitogen induced SMC in vitro and have found NOR-1 highly expressed in human atherosclerotic plaques. NOR is an immediate early gene, member of a subfamily of the nuclear receptor superfamily, and has typical steroid receptor structure. The role of NOR as a transcription factor regulating the expression of specific secondary genes for SMC may be a key point in the progression of atherosclerosis-restenosis.

1874 Inhibition of restenosis by an orally available cell cycle inhibitor

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Progression of vascular smooth muscle cells (VSMC) through the cell cycle is among the final common signaling events in vasculoproliferative diseases. Thus, targeting the cell cycle is of interest with respect to proliferative events such as restenosis. However, tools combining effectiveness and simple application have not yet entered clinical practice. Flavopiridol is a potent and specific, orally available inhibitor of cyclin-dependent kinases. Flavopiridol (75 nM) significantly inhibited human aortic VSMC proliferation induced by bFGF (10 ng/ml) and thrombin (2 U/ml), ($p < 0.05$). Flavopiridol, at concentrations up to 100 nM, had no effect on the viability of untreated VSMC. Flavopiridol (75 nM) significantly inhibited growth factor-induced activity of cyclin-dependent kinases, as measured by histone H1 phosphorylation ($p < 0.05$). The inhibitor exhibits high substrate specificity, since no effects on MAP kinase activation were noted. Induction of cell cycle-related proteins cyclin D1, proliferating cell nuclear antigen (PCNA) and phosphorylated retinoblastoma protein was blocked by flavopiridol. To test for the growth inhibiting potency of flavopiridol in vivo, a rat carotid artery injury model was employed. Flavopiridol was administered orally (5 mg/kg) and neo-intima formation following balloon injury was monitored. Compared to the controls, treatment with flavopiridol resulted in reduction of neointima size by 35% and 39% at 7 and 14 days, respectively, following balloon injury ($p < 0.05$); PCNA expression was reduced significantly ($p < 0.05$). In summary, flavopiridol effectively inhibits VSMC proliferation in vitro and in vivo by specifically targeting cell cycle regulatory elements. This compound, readily available for oral uptake, might represent a therapeutic tool in prevention and treatment of proliferative vascular diseases.

1875 Platelet-derived microparticles stimulate mitogenesis of coronary artery smooth muscle cells by a PDGF-independent mechanism

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Platelet-derived growth factor (PDGF) is regarded as the most important mitogen secreted from activated platelets. We have previously shown that isolated platelet surface membranes exhibit a very potent mitogenic activity for coronary artery smooth muscle cells (SMC) (Schrör et al., Platelets 1998; 9:424). This study investigates possible mitogenic effects of platelet-derived microparticles.

Methods: Platelet microparticles were prepared from stimulated platelets by differential centrifugation. The effects of microparticles on p42/p44 MAP kinase phosphorylation (Western blot), c-fos expression (Western blot), DNA synthesis ([^{3}H]thymidine incorporation), cell proliferation (increase in cell number), and cell migration (wounded layer migration assay) were studied in cultured bovine coronary artery SMC.

Results: Microparticles concentration-dependently stimulated MAP kinase phosphorylation, c-fos expression and mitogenesis of SMC. These mitogenic effects were significantly higher than maximal effects of PDGF-BB. Microparticle-induced SMC mitogenesis was heat-sensitive (75° C, 15 min), while the effects of PDGF were not. In addition, neutralizing anti-PDGF antibodies prevented PDGF-induced DNA synthesis but did not significantly inhibit the effects of microparticles. In contrast to PDGF, which potently stimulated SMC migration, microparticles had only a minor migratory effect.

Conclusion: These results demonstrate a novel role of platelet-derived microparticles as inducers of SMC proliferation. The mitogenic effects of microparticles are independent of PDGF.

1876 PDGF-BB stimulates nuclear translocation of NFkB in human vascular smooth muscle cells without degradation of IkB: a novel mechanism of NFkB activation?

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The transcription factor NFkB is thought to play a key role in the regulation of proliferation of smooth muscle cells in atherogenesis (Bourcier et al., J Biol Chem, 1997;272;15817). In unstimulated cells, the heterodimer NFkB is located in the cytoplasm bound to the inhibitor protein IkB. In the present concept of NFkB activation the phosphorylation and degradation of IkB is a prerequisite for nuclear translocation of NFkB and its subsequent activity on gene expression.

Methods: This study investigates the mechanism of NFkB activation by platelet-derived growth factor-BB (PDGF-BB, 20 ng/ml) compared to tumor necrosis factor-a (TNFa, 10 ng/ml) in cultured human smooth muscle cells (saphenous vein). IkB phosphorylation and degradation was studied by Western blotting. Translocation of NFkB (p65) was detected by Western blotting using nuclear extracts.

Results: Stimulation with TNFa resulted in a transient phosphorylation of IkBa (maximum after 10 min) and subsequent IkBa degradation and nuclear translocation of NFkB (maximum after 15 min). Stimulation with PDGF-BB also resulted in nuclear translocation of NFkB (maximum after 30–60 min). In contrast to TNFa no phosphorylation and degradation of IkB was detectable. Neither TNFa nor PDGF-BB induced degradation of the IkB-b isoform.

Conclusions: These data demonstrate, that the PDGF-BB-induced NFkB translocation into the cell nucleus is independent of IkBa degradation. PDGF-BB therefore appears to be the first mediator that induces an IkB-independent NFkB activation.

1877 Endothelin-1 markedly potentiates human smooth muscle cell growth to PDGF: effects of ET-A and ET-B receptor blockade

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Endothelin-1 (ET-1) is a well known potent vasoconstrictor peptide via activation of both ET-A and ET-B receptors. While the role of ET-1 in cardiovascular disorders with dysregulation of vascular tone is well documented, its mitogenic effects on vascular smooth muscle cells (SMC) remain controversial. Some studies demonstrated potent mitogenic effects of ET-1 and others showed no proliferative effects. We investigated the role of ET-1 in human SMC growth and its interaction with platelet-derived growth factor (PDGF).

Methods: SMC were cultured from human aorta in medium without any growth factors and cell proliferation was assayed by ^{3}H-thymidine incorporation. PDGF receptor expression, activation of mitogen-activated protein kinase (MAPK), cell cycle regulators such as cyclin-dependent kinase2 (Cdk2), Cdk inhibitor (p27Kip1) and retinoblastoma protein (pRb) were analyzed by immunoblotting.

Results: ET-1 (1 to 100 nmol/L) on its own was unable to stimulate ^{3}H-thymidine incorporation, but dramatically potentiated the effect of PDGF-BB (1 ng/ml) up to 68-fold ($p < 0.001$). Most of the potentiating effects (88%) were blocked by the ET-A receptor antagonist LU135252 (1 to 10 μmol/L) and slightly further by the ET-A/B receptor antagonist bosentan ($p < 0.05$). ET-1 stimulated MAPK, but it neither potentiated PDGF induced MAPK activation nor overexpressed PDGF receptors. While PDGF-BB (10 ng/ml, 24 hours) markedly activated Cdk2, hyperphosphorylated pRb and downregulated p27kip1, ET-1 had no regulatory effects on the cell cycle regulatory proteins.

Conclusion: In human SMC, ET-1 activates MAPK but has no mitogenic effects on its own. However, ET-1 markedly potentiates proliferation to PDGF mainly via ET-A receptors. This may represent an important function of ET-1 for vascular structural changes in patients and provide new therapeutic opportunities for ET-1 receptor antagonists.

1878 Activated coagulation factor VII promotes smooth muscle cell proliferation in vitro

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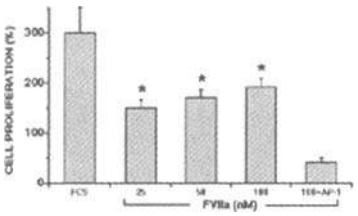
Smooth muscle cell (SMC) proliferation is a key event in the development of atherosclerosis and restenosis following coronary angioplasty. Tissue Factor (TF) is a transmembrane glycoprotein which forms a high affinity complex with factor VII/VIIa (FVIIa) and activates the extrinsic coagulation pathway. We have shown that TF is up-regulated in the media of vessels following vascular injury and thrombus formation. The aim of the present study was to investigate whether binding of FVII/FVIIa to TF promotes SMC proliferation, besides activating the extrinsic coagulation cascade. SMCs isolated from the aortas of New Zealand white rabbits, were grown in DMEM + 10% fetal calf serum (FCS). At 70% confluence, SMCs were made quiescent by removing FCS from the medium. Twenty-four hours later, cells were stimulated for 24 hrs with increasing concentrations of human recombinant FVIIa. SMC proliferation was evaluated by measuring the degree of ^{3}H-Thymidine incorporation. Control experiments included addition of FCS (positive control), and AP-1, a monoclonal antibody against rabbit TF which prevents FVIIa binding to TF. Furthermore, another set of experiments was performed using active site-blocked FVIIa (FVIIai), which binds to TF but has no enzymatic activity. FVIIa induced a dose-dependent increase in SMC proliferation, which was almost completely prevented by AP-1 (figure; *$p < 0.05$).



In contrast, none of the dose of FVIIai employed resulted in a significant stimulation of proliferation. Thus, FVIIa binding to TF induces SMC proliferation in vitro. This effect requires the enzymatic activity of FVIIa, as FVIIai did not stimulate proliferation. This phenomenon might play a role in the pathophysiology of restenosis following vascular injury in vivo.

NITRIC OXIDE: EXPERIMENTAL RESULTS

1879 Nitric oxide prevents hypertension and thromboembolism in transgenic mice with polyglobulia

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Background: Despite being known that nitric oxide (NO) induces vasodilatation and inhibits platelet aggregation and vascular smooth muscle cell proliferation in vitro, a beneficial effect of NO in preventing vascular disease in vivo has not been provided so far. Considering that polyglobulia is associated with an high incidence of cardiovascular complications, such as arterial hypertension and thromboembolism, we sought to assess the function of NO in polyglobulic mice.

Methods: We generated a novel transgenic mice model overexpressing human erythropoietin (Epo) from the platelet derived growth factor B chain (PDGF-B) promoter.NO bioavailability was assessed as endothelium-dependent and -independent function in response to acetylcholine (ACh, 0.01–300 μmol/L) and sodium nitroprusside (SNP, 0.01–300 μmol/L) in isolated aortic rings (n = 7; wildtype siblings served as controls). eNOS protein levels were determined by western blot analysis.

Results: In one transgenic line serum Epo level increased up to 20-fold, and Epo expression was detected in serum, brain, testis and lung. In turn, Epo overexpression induced marked erythrocytosis resulting in an hematocrit value of up to 80%. Notwithstanding very high hematocrit levels, transgenic mice survive 10 to 12 months and do not develop hypertension, stroke or myocardial infarction. Western blot analysis revealed a 10 fold increase of eNOS in aorta of transgenic mice compared to wild-type control animals. In the transgenic aorta, basal NO release as assessed by contraction to NO-synthase inhibitor L-NAME and NO-mediated, endothelium-dependent relaxations in response to ACh were significantly increased, whereas endothelium-independent relaxation to SNP remained unchanged. Similarly, vasorelaxation to thrombin, a potent endogenous stimulus of NO formation and release, was also increased indicating enhanced bioavailability of NO in transgenic animals.

In conclusion, our novel transgenic mouse model of Epo-induced severe polyglobulia provides first evidence that constant NO release by eNOS maintains normotension and prevents vascular disease in vivo.

1880 Transfection of human saphenous vein endothelial cells with the inducible nitric oxide synthase inhibits expression of intercellular adhesion molecule-1 and leukocyte adherence

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Background: Polymorphonuclear leukocytes (PMN) adhere to activated endothelial cells, promote vascular cell damage and disturb their growth regulation mechanisms. Enhanced PMN-adherence might occur due to a diminished basal nitric oxide (NO) release and adhesion molecule upregulation in vascular endothelial cells following ischemia/reperfusion or angioplasty.

Methods: A cDNA fragment with the coding sequence of the iNOS was cloned into a mammalian expression plasmid with a cytomegalovirus promotor sequence. A liposome-mediated transfection into human saphenous vein endothelial cells (HSVEC) was performed and expression of intercellular adhesion molecule-1 (ICAM-1) was measured with a cell surface ELISA following TNF-stimulation (300 U/ml). PMN-adhesion was determined in a cell adhesion assay by epifluorescent microscopy using fluorescent green labeled PMN.

Results: Transfection of HSVEC with the iNOS gene reduced ICAM-1 expression to 37% of maximal ICAM-1 expression compared to non-transfected TNF-stimulated cells. iNOS transfection resulted in reduced PMN-adhesion (31% of maximal PMN-adhesion). Additional treatment of transfected HSVEC with the NO-donors SIN-1 (0.01–1 mM) or SNAP (3–30 μM) did not further diminish ICAM-1 expression and PMN-adhesion. In contrast TNF-stimulated HSVEC which were not transfected showed a significant concentration-dependent reduction in ICAM-1 expression and PMN-adhesion following treatment with SIN-1 and SNAP (SIN-1 1 mM 57 ± 8% of maximal ICAM-1 expression, SNAP 30 μM 35 ± 16% of maximal PMN-adhesion, $p < 0.05$, ± SEM). Inhibition of NO generation with L-NMMA (20 μM) clearly elevated ICAM-1 expression and PMN adhesion.

Conclusion: Transfection of vascular endothelial cells with the iNOS gene is a novel approach to substitute nitric oxide. Substitution of NO by transfection with iNOS effectively substitutes NO diminishing adhesion molecule expression and PMN adherence.

1881 Protection from collar-induced intimal thickening by shear stress: role of nitric oxide

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Nitric oxide (NO) has potent relaxant and antiproliferative effects on vascular smooth muscle cells, which may represent a potent antiatherosclerotic mechanism. Since a major stimulus for NO release is flow-related wall shear stress (WSS), we examined i) the effect of increased WSS on neointima formation (collar model, see below), ii) the role of NO in the antiproliferative effect of increased WSS, and iii) the adaptation of carotid artery (CA) diameter to increased WSS.

Methods: Intimal thickening of the left common CA (LCCA) was produced in New Zealand White rabbits by enclosing the vessel into a non-constrictive silicone collar (group 1). High WSS was induced by further ligating the right internal CA (RICA, group 2). To evaluate the role of NO, nitro-L-arginine methyl ester (L-NAME) was administered at subpressor doses (15 mg kg^{-1} day^{-1}, group 3). At day 14 after surgery, BP, heart rate, CA flow velocities, diameters and WSS were assessed "in vivo". Intimal area and intima/media area ratio were histomorphometrically measured post-mortem.

Results showed that RICA ligation caused WSS to increase and neointima formation to be inhibited; the inhibition was reversed by l-NAME treatment. In group 2, CA diameter was about 20% larger than in groups 1 and 3 ($p < 0.05$).

Groups	n	WSS(dyne cm^{-2})	Intimal area(mm^2)	I/M area ratio (%)
Gr. 1 (LCCA collar)	8	58.8 ± 5.1	0.150 ± 0.030	29.00 ± 3.00
Gr. 2 (collar + RICA lig.)	8	69.1 ± 4.7*	0.040 ± 0.003*	8.00 ± 2.70*
Gr. 3 (collar + lig. + l-NAME)	8	129.2 ± 7.7*°	0.160 ± 0.030°	30.00 ± 3.00°

Means ± SEM; *$p < 0.05$ vs group 1, °$p < 0.05$ vs group 2

In conclusion, we demonstrate that in rabbit carotid arteries with collar-induced intimal thickening, a chronic increase in shear stress i) inhibits intimal thickening via NO production, and ii) produces a significant flow-dependent arterial enlargement that is also due to NO production, and that tends to normalize shear stress.

1882 VEGF receptor-2 (KDR) regulates endothelial function and angiogenesis via strong activation of eNOS-and iNOS-expression and via nitric oxide release in endothelial cells

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Vascular Endothelial Growth Factor-A (VEGF-A) is an endothelial-specific growth factor that induces angiogenesis, i.e. sprouting of capillaries from preexisting vessels *in vivo*. Endothelial nitric oxide synthase (eNOS) is an essential molecule in mediating VEGF-A-induced angiogenesis and endothelial function via production of nitric oxide (NO). It is unclear, however, which of the VEGF-receptors is mediating the signal for induction of eNOS expression and expression of other NOS isoforms and for the generation of NO in endothelial cells.

Human umbilical vein endothelial cells (HUVEC) were stimulated with VEGF-A for 24 hours and the expression of eNOS- and iNOS-protein was evaluated using Western blot analysis. VEGF-A induces expression of both eNOS and iNOS in HUVEC. Using porcine aortic endothelial cells overexpressing either VEGF receptor-2 (PAE/KDR cells) or VEGF receptor-1 (PAE/Flt-1 cells) stimulation of VEGF receptor-2 was found to upregulate both eNOS- and iNOS-protein, while stimulation of VEGF receptor-1 did not influence NOS expression. Moreover, formation of cGMP in endothelial cells as a marker for NO formation is exclusively mediated over VEGF receptor-2 in response to VEGF-A-stimulation.

In summary, only VEGF receptor-2, but not VEGF receptor-1, mediates stimulation of eNOS-and iNOS-expression and formation of NO in endothelial cells. These data further support the functional importance of VEGF receptor-2 in endothelial activation and angiogenesis.

1883 Oxidative stress is a major contributor to age-related endothelial dysfunction

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Aging alters vascular function by exerting functional changes on endothelial cells. However, the nature of age-related endothelial dysfunction is not yet fully understood. We investigated whether increased breakdown of nitric oxide (NO) due to augmented production of free radicals such as superoxide (O_2^-) might be a mechanism involved in biological aging.

Aortas were used from 4–6 months old (Y; n = 8), 19 months old (M; n = 7) and 32–35 months old (O; n = 8) normotensive male rats and cut into rings 0.5 cm long. Rings were mounted in organ chambers connected to a force transducer for recording of isometric tension. For endothelium-dependent relaxations, vessels were contracted with norepinephrine ($2–3 \times 10^{-7}$ mol/L) until a plateau (about 70% of KCl 100 mmol/L) was reached and then relaxed with 10^{-10}–10^{-5} mol/L calcium ionophore A 23187 or acetylcholine (Ach). For endothelium-independent relaxations, deendothelialised rings were relaxed with sodium nitroprusside (SNP). In situ measurements of NO were carried out using a porphyrinic microsensor placed on the endothelial surface of vessels. NO release was induced by A 23187 (10^{-6} mol/L) and amperometric mode was used to detect changes of NO concentration. O_2^- concentration in tissue was determined by a chemiluminescence method using a scintillation counter.

Relaxations to both endothelium-dependent agonists were dramatically reduced in aortas obtained from old rats as compared with ones from young adult and middle-aged rats. Maximal responses to Ach were −95.4 ± 2.2% in young, −88.6 ± 2.5% in middle-aged and −61.5 ± 3% in old rats and to A 23187 −75.4 ± 0.8% in young, −73.9 ± 4.1% in middle-aged and −46.5 ± 3.6% in old rats (for both agonists Y vs O and M vs O: $p < 0.0001$; Y vs M: ns). Endothelium-independent relaxations to SNP were unaffected by age. Maximal NO levels measured by the porphyrinic microsensor were significantly lower in aortas obtained from old and from middle-aged rats compared with aortas from young rats (Y: 1197 ± 76 nmol/L; M: 831 ± 119 nmol/L; O: 340 ± 54 nmol/L; Y vs O: $p < 0.0001$, M vs O: $p = 0.0006$, Y vs M: $p = 0.0064$). Reciprocal changes in O_2^- release were observed. In aortic tissue of old rats there was a nearly threefold increase in O_2^- production (6058 ± 731 cpm/mg) compared with young (2302 ± 617 cpm/mg) and middle-aged (2145 ± 426 cpm/mg) animals (Y vs M: ns; Y vs O and M vs O: $p < 0.0001$).

In conclusion, oxidative stress, as reflected by elevated O_2^- levels, either due to an increased production and/ or to alterations of antioxidant defense systems, plays an important role in age-dependent endothelial dysfunction.

1884 Cardioprotection during ischaemia/reperfusion by an endothelin-A receptor antagonist is dependent on nitric oxide production in the pig

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Background: It has previously been shown that endothelin (ET) receptor antagonists protect the myocardium from ischaemia/reperfusion (I/R) injury. The mechanism behind this effect is unclear. The aim of the study was to elucidate the possible interaction between ET_A receptor antagonism and nitric oxide (NO) during I/R.

Methods: Anesthetised pigs were subjected to 45 min of ischaemia by ligation of the left anterior descendens coronary artery (LAD) followed by 4 h of reperfusion. Vehicle (n = 7), the selective ET_A antagonist LU 135252 (LU; 0.1 mg/kg, n = 7), the combinations of LU and the NO substrate L-arginine (1 mg/kg, n = 7) (LU + L-arg), or LU and the NO synthase inhibitor L-NMMA (0.2 mg/kg, n = 5) (LU + L-NMMA) were given into the LAD during the last 10 min of ischaemia and the first 5 min of reperfusion.

Results: There were no statistically significant differences in coronary flow, pulmonary capillary wedge pressure, mean arterial pressure, heart rate, or rate pressure product between the groups at the end of reperfusion. The area at risk was similar in all four groups. The infarct size of the vehicle group was 79 ± 6% of the area at risk. LU and LU + L-arg reduced the infarct size to 40 ± 6% and 35 ± 8%, respectively ($p < 0.05$ vs. vehicle). There was no significant additional cardioprotective effect of the combination of LU + L-arg compared to LU alone. Administration of L-NMMA completely prevented the infarct limiting effect of LU (infarct size 84 ± 4%; $p < 0.05$ vs. LU alone).

Conclusion: Local administration of LU and LU + L-arg during the last period of ischemia protects the myocardium from I/R injury by similar degrees. Inhibition of NO synthase reversed the cardioprotective effect of ET_A antagonism, suggesting that it is dependent on production of NO.

BASIC MECHANISMS FOR THE DEVELOPMENT OF DILATED CARDIOMYOPATHY

1885 Familial non-X-linked dilated cardiomyopathy: prevalence, inheritance and clinical characteristics

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Prevalences of overall famililal dilated cardiomyopathy (DCM), including X-linked forms, vary depending from different strategies of investigation. Aims of our study were to assess the prevalence of familial non-X-linked DCM, diagnose early asymptomatic cases, identify preclinical markers in relatives of index patients (pts), evaluate inheritance and characterize clinical phenotypes.

An accurate screening was carried out in 402 relatives of 89 consecutive pts diagnosed with DCM by invasive and non invasive methods, including endomyocardial biopsy. In all male index pts, known X-linked DCM were excluded with immunohistochemical and molecular methods. Relatives underwent clinical examination, echocardiographic, electrocardiographic and creatine-phosphokinase (CPK) determination.

Results: 25 out of 89 index pts (28%) had at least one proven affected relative. Juvenile familial rapidly progressive disease affected 4 youths (<20) who underwent emergency transplantation. In one family AV block was the first sign of the disease. Inheritance was autosomal dominant in 11, and not determined in 10. In 4, mitochondrial DNA pathologic mutations were found. In familial group, 21 alive members were diagnosed with DCM; 15 of them were totally unaware of their disease. In index pts of familial DCM transplantation ($p = 0.015$) and atrial fibrillation ($p = 0.03$) were more frequent and left bundle block branch ($p = 0.03$) less frequent. In corresponding relatives, the prevalence of combined instrumental abnormalities was higher in familial DCM ($p = 0.04$).

Conclusions: familial non X-linked DCM was diagnosed in 28% of DCM pts; 4 pts showed a juvenile dramatic phenotype. The immediate benefit of relative screening was the identification of 15 affected, unaware pts, all younger than 30. Relatives with instrumental abnormalities entered a regular follow-up protocol.

1886 Left ventricular enlargement in relatives of dilated cardiomyopathy patients: indication for early angiotensin-converting enzyme inhibition?

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There is increasing awareness of familial nature of dilated cardiomyopathy (DCM) and of the fact that a sizable proportion of DCM relatives has left ventricular enlargement (LVE).

We screened 300 relatives (Rels) (mean age 28.7 years, 154 male, 219 1st degree) of 58 consecutive DCM patients (5.2/family); the diagnosis of DCM was based on WHO criteria. Familial DCM was defined as >1 affected member with DCM. The study protocol included: clinical examination, 12-lead electrocardiogram and two-dimensional echocardiogram. LVE was defined according to method of Henry (%LVEDD > 112). Besides, we measured N-terminal ANP plasma levels by radioimmunoassay in 81 Rels and assessed these values in relation to LVE.

280 Rels had a diagnostic echocardiogram (93.4%); 42 were found to be hypertensive (14%) and were assessed seperately. Familial DCM was defined as >1 affected member with DCM.

Based on the screening we have identified 14 asymptomatic Rels (5.7%) with DCM from 12 families. Thus, we found that familial prevalence of the disease was 20.7% (12/58 families). Of the 246 asymptomatic Rels 80 (32.5%) were found to have LVE. N-terminal ANP plasma levels were higher in Rels with LVE than in those without LVE ($p < 0.05$).

We reassessed with the same protocol 106 Rels after 3.8 ± 1.5 years. Of the 36 Rels with LVE during screening phase (36/106, 33.9%) 9 (25%) progressed to DCM. This was accompanied by a rise in N-terminal ANP plasma level ($p < 0.0001$). Mean percentage fractional shortening in the whole group decreased from 33.1 ± 5.5% to 30.7 ± 4.7%; $p = 0.001$.

Our study demonstrates that: 1) familial DCM is observed in at least 21% of the patients; 2) LVE is common in relatives of patients with the disease and may represent early disease changes; 3) systematic follow-up is necessary to identify relatives who progress to DCM; 4) neurohormonal activation in relatives with LVE indicates that ACE-inhibition may be useful in halting/delaying progression from LVE to DCM.

1887 Mitochondrial DNA mutations and polymorphisms in idiopathic dilated cardiomyopathy

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In the human genome, single nucleotide substitutions are the most common form of sequence variation and disease-causing mutation. In this study, we report the DNA sequence analysis of all the tRNA and structural genes of mitochondrial DNA (mtDNA) derived from cardiac tissues of 27 patients (16 adults, 11 children) with idiopathic dilated cardiomyopathy (IDC). Multiple changes in mtDNA sequence were found relative to control sequences. Novel mutations were found in 12 tRNA genes (including Phe, Ile, Ala, Asn, Cys, Asp, Lys, Arg, His, Leu, Thr) as well as previously reported tRNA changes (MITOMAP) in 6 genes (Ile, Leu, Asp, Gly, Arg, Thr). Novel mtDNA mutations (13) specifying amino acid residue changes were found in COI, COII, COIII, ND3, ND6 and cytb. An additional 26 mtDNA point mutations resulting in amino acid substitutions were found which have been previously reported (MITOMAP). None of the mutations previously found in association with hypertrophic cardiomyopathy were detected In addition, a large number of polymorphic nucleotide changes with no amino acid substitution were present equally distributed throughout the mitochondrial genome. While the majority of these changes represent previously reported polymorphisms, a significant number of new nucleotide substitutions were present in IDC patients. The pathogenicity of these mtDNA mutations and polymorphisms, and their potential contributory role in the severity of cardiomyopathy are currently being studied.

1888 Apoptosis detected by DNA fragmentation and anti-transglutaminase staining in enterovirus-associated dilated cardiomyopathy

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In patients with endstage heart failure a higher rate of apoptosis (Apo-R) of the myoctes has been found as opposed to normal control subjects. However, the relation between Apo-R and cardiac enterovirus infection in idiopathic dilated cardiomyopathy (DCM) is not yet known. Therefore, the purpose of the present study was to investigate the Apo-R of myocytes from right ventricular endomyocardial biopsies in patients (P) with enterovirus-positive and enterovirus-negative DCM.

Methods: The Apo-R was assessed histochemically in 18 consecutive P (13 male, mean age 49 ± 10 years) with idiopathic DCM (LVEF < 55%) on semithin sections (1 μm) using in-situ end labelling with bromodesoxyuridine (BrdU) for demonstrating DNA-fragmentation. Since DNA-fragmentation alone is not specific for apoptosis, an additional staining of the transglutaminase, which represents an essential enzyme in the late phase of apoptosis, was performed. All myocytes showing both DNA-end labelling with BrdU of the nuclei and a positive anti-transglutaminase staining in the cytoplasm were defined as apoptotic. The enterovirus genome was detected by enterovirus-specific polymerase chain reaction (One-Step-RT-PCR).

Pat. with DCM (n = 18)	LVEDD (mm)	LVEF (%)	PCWP (mmHg)	DNA-end labelling + anti-transglutaminase (% positive) = Apo-R
PCR positive (n = 8)	68 ± 10	46 ± 7	17 ± 9	8 ± 3
PCR negative (n = 10)	68 ± 8	38 ± 11	14 ± 7	14 ± 5
	NS	NS	NS	p = 0.01

Conclusion: Enterovirus-positive DCM did not significantly differ from enterovirus-negative DCM with regard to hemodynamic parameters, but showed a significantly lower Apo-R. Our results favour the concept that enteroviruses produce protein inhibitors of apoptosis as has been already shown for other viruses.

1889 Increased expression of tumour necrosis factor-α-converting enzyme and tumour necrosis factor-α in advanced left ventricular dysfunction in human dilated cardiomyopathy

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The expression of tumor necrosis factor-α (TNF-α) has been posited as an important factor in left ventricular (LV) dysfunction associated with dilated cardiomyopathy (DCM). TNF-α-converting enzyme (TACE) has recently been purified and its complementary DNA cloned. The aim of this study was to determine whether TACE expressed with TNF-α in myocardium and whether TACE and TNF-α contribute to LV dysfunction in DCM.

Methods: Myocardial tissues were obtained from DCM patients (n = 51, age 56 ± 14 yrs) and 10 control subjects (CS) using endomyocardial biopsy. TNF-α and TACE mRNA levels were measured by a novel real time quantitative reverse transcriptase-PCR method. The expression of these proteins was also examined immunohistochemically.

Results: TACE mRNA expression increased to a significantly greater extent in the DCM group than in CS (TACE/GAPDH, 7.72 ± 2.40 vs 0.04 ± 0.02, p < 0.05). TNF-α mRNA expressed in the DCM group (TNF-α/GAPDH; 1.40 ± 0.31), while no expression was seen in CS. A positive correlation was found between TNF-α and TACE mRNA levels (r = 0.701, p < 0.001). TACE immunostaining was found in cytoplasm of myocytes in 22 DCM patients. TNF-α immunostaining was positive in myocytes and endocardium in 25 DCM patients. The differences in TNF-α and TACE mRNA levels between the 2 subgroups of DCM divided by LV geometry and LV systolic function are shown in the table.

	LV systolic diameter (mm)		LV ejection fraction (%)	
	<50 (n = 28)	≥50 (n = 23)	<35 (n = 15)	≥35 (n = 36)
TACE/GAPDH	1.81 ± 0.65	6.81 ± 1.11*	7.63 ± 1.59	2.58 ± 0.60*
TNF-α/GAPDH	0.89 ± 0.39	2.02 ± 0.46*	2.40 ± 0.77	0.98 ± 0.27*

Mean ± SD; *p < 0.05

In conclusion: These findings suggest that expression of TACE and TNF-α in myocardium may possibly play an important role in the progression of LV dysfunction in human DCM.

1890 Endothelin receptor density is closely related with cardiomyocyte diameter in dilated cardiomyopathy

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Endothelin-1 have contractile and growth effects on cardiomyocytes both in vitro and in vivo. In the present study the relationship between cardiac function, cardiomyocyte diameter and ET-1 receptor density was investigated in 39 hearts from transplant recipients with heart failure (III or IV NYHA class) due to either idiopathic dilated (DCM, n = 22) or ischemic cardiomyopathy (ICM, n = 17) and from five potential donors excluded from organ donation for non cardiac reasons.

ET-1 receptor density was significantly higher in myocytes from ICM than from DCM (62 ± 4 vs 43 ± 6 fmol/mg, p < 0.01) without differences in Kd. The average diameter of myocytes was larger in ICM (20.1 ± 1.8 μm) than in DCM patients (17.2 ± 0.9 μm, p < 0.001) and controls (15.2 ± 1.5 μm, p < 0.001). At univariate and multivariate stepwise regression analysis the ET receptor density on cardiomyocytes was positively related to the average diameter of myocytes (r = 0.85, p < 0.0001) but not with ejection fraction, fractional shortening and end systolic stress.

In competition studies ETA (PD155080) and ETB (BQ 788) selective antagonists revealed that the ETA subtype represented about 90% of total ET-1 receptors in myocytes from both patient groups as confirmed at the mRNA level by in situ hybridization studies (ETA and ETB cDNA probes from ATCC). Furthermore Northern studies of mRNA ETA and ETB receptors revealed that ETA but not ETB mRNA expression were significantly related with myocyte diameter (r = 0.73, p < 0.001; and r = 0.33, ns respectively).

In conclusion ETA but not ETB receptor density is closely related with cardiomyocyte diameter in dilated cardiomyopathy.

INFECTIVE ENDOCARDITIS – NEW INSIGHTS INTO DIAGNOSIS AND PROGNOSIS

1891 Value of new diagnostic criteria in prosthetic valve endocarditis

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Background: Duke criteria (DC) have been shown to be sensitive in diagnosing native valve infective endocarditis (IE), but their accuracy in pts with prosthetic valve endocarditis (PVE) are not known. We recently proposed modified Duke criteria (MDC) in which serologic diagnosis of Q fever was accepted as a major criterion and IE was considered as "definite" even when only 1 major and 2 minor criteria were present in pts with prior antibiotic therapy and typical echocardiographic findings.

Objectives: To assess the value of DC and MDC in pts with PVE.

Methods. DC and MDC were applied in 131 consecutive pts with proved IE (with pathological confirmation in 93 cases). Blood cultures (BC), serology of Q fever, transthoracic and transoesophageal echocardiography (TOE) were performed in all. Fourty-two pts with PVE (group 1) (16 bioprosthetic, 23 mechanical, 3 homografts) were compared with 89 pts with native IE (group 2).

Results: Using DC, the sensitivity for diagnosis of IE was lower in group 1 than in group 2 (64 vs 84%, p < 0.01), 15 (36%) of 42 pts with proved PVE being misclassified as "possible IE" using DC. The causes for misclassification were negative BC in 8 pts (resulting from prior antibiotic therapy in 6), Q fever IE in 3 pts, and a negative TEE in 3 pts. Application of MDC resulted in a better diagnosis of PVE, with sensitivities of 81 and 92% in groups 1 and 2, respectively.

Conclusion: (1) clinical diagnosis of IE is more difficult in pts with prosthetic than in pts with native IE.

(2) DC have a relatively low sensitivity in these pts.

(3) Use of MDC allows improvement in the clinical diagnosis of PVE

1892 Molecular diagnosis of endocarditis – a new Duke's criterion?

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Infective endocarditis is associated with a high degree of morbidity and mortality. Duke's criteria is now recognized as the most accurate diagnosis and classification of this disease. The aim of this current study was to examine blood culture material from such patients both by cultural and novel molecular techniques. The molecular approach of PCR amplification of genes specific for bacteria (16S rRNA) and fungi/yeast (28S rRNA) and sequencing was used to identify the possible microbial agent(s) responsible for the infection. Blood culture material from six patients were positive by both culture (Staphylococcus aureus, coagulase negative staphylococci [CNS], Streptococcus mitis (2), MRSA, Haemophilus influenzae) and PCR (S. aureus, S. epidermidis, S. gordonni, S. mitis/pneumoniae, MRSA, H. influenzae/aegyptus), respectively. Blood culture material from four patients were negative by culture except for isolated cultures which were classified as environmental contaminants namely Corynebacterium spp., Micrococcus spp., CNS and Propionibacterium spp, which were also identified by PCR. However, blood culture material from one patient revealed the presence of DNA from Propionibacterium acnes in three sets of blood cultures, indicating that it may have been the causative agent. Seven patients' blood culture were culture-negative but PCR-positive for Acinetobacter spp. (1), Nocardiodies spp. (2), Nocardiodes albus (1), Candida-like spp. (1). Bacterial DNA was identified in three other patients but the sequence data was mixed and could not confirm the identity of the organism detected. These findings were analysed along with the patients' clinical background in light of the Duke's criteria.

These results demonstrated that (i) all patients who were classified as definite or possible endocarditis cases by Duke's criteria were positive by PCR, (ii) all patients who were rejected as having endocarditis according to this criteria were negative by PCR except for one patient who had bacteraemia originating from a different source. These findings indicate that a molecular approach may aid in the diagnosis of endocarditis and should therefore be included as an additional criterion in the Duke's classification scheme. In conclusion, molecular identification of the aetiological agents responsible for endocarditis directly from blood culture material will enable specific treatment directed at this agent to be commenced at an earlier stage of the disease and hence reduce the need for valve replacement.

1893 Clinical course of infective endocarditis in the late nineties: preliminary results of the ALKK endocarditis registry

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Recent multicenter clinical data on infective endocarditis (IE) is not available. Therefore, the ALKK conducted a prospective registry on cases of IE diagnosed between January 1996 and December 1998.

Methods: Using a standardized questionaire, more than 70 parameters concerning the patient's demography, predisposing factors, the source of IE, its clinical manifestation, the performed diagnostic and therapeutic procedures as well as the course of the disease were assessed and evaluated in a preliminary descriptive analysis of 327 patients from 51 hospitals.

Results: The patients (59% male) were on average 59 ± 17 years old. Symtoms of IE started on average 43 ± 38 days prior to diagnosis. In 44% of patients IE complicated preexisting heart disease.

At the time of hospitalization the temperature was 39.1 ± 1.2°C, heart murmurs were heard in 56% of patients, the ESR (erythrocyte sedimentation rate) was elevated to 75 ± 4 mm/h, 19% of patients showed enlargement of the spleen and 6% cutaneous lesions. 12% of patients presented with neurological complications and 26% heart failure NYHA III/IV.

The aortic valve was infected in 52% of patients, the mitral valve in 51% and the tricuspid valve in 5%. Infections frequently involved mechanical (13%) or biologic (8%) prosthetic valves, or rarely mitral valves after surgical repair. 73% of all patients had positive blood cultures, Staph. aureus in 31%, Streptoccocus in 24%, Enterococcus in 12%, and Staph. epidermidis in 4%.

Every 4th patient had undergone antibiotic therapy prior to hospitalization and before blood cultures were obtained. Almost every other patient was treated without an antibiogram. 16% of the patients died, 33% suffered NYHA III/IV, 17% had cerebral and 14% peripheral emboli, 4% needed dialysis. 39% received a prosthetic valve.

Thus, even in the late nineties infective endocarditis is often treated without an antibiogram and causes severe morbidity and significant mortality.

1894 Determination of long-term prognostic factors of mortality in infective endocarditis from a consecutive series of 173 patients

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In order to study long-term prognostic factors of infective endocarditis (IE), we prospectively included all the patients who were treated as IE at our university Hospital between November 1990 and December 1997. All initial parameters concerning clinical and bacteriological features were collected. A questionnaire was sent in June 1998 to every patient's general practitioner and cardiologist to collect information about his/her health, and the need for secondary valvular surgery.

Among the 172 pts enrolled, 35 (20.3%) died during the inital hospital stay. As 14 (8%) pts were lost of follow-up, 123 pts were included in our follow-up study (92 M/31 F, 56 ± 16 yrs, 47 pathologically definite, 76 clinically definite IE according to the Duke criteria). Among them, 24 (19.5%) died during the FU period (9 cardiac causes, 7 extra-cardiac causes, 8 unknown reasons), and 11 pts (8.9%) needed secondary valvular surgery. Mean follow-up duration was 3.7 ± 2.1 yrs. Kaplan-Meier survival was 58.2 ± 9.5% at 7 yrs. The effects of the following parameters on long-term mortality were tested by univariate (log-rank) and multivariate (Cox model) analysis: age, previous IE, preexisting heart disease, valvular prostheses, fever, site of IE, causative micro-organisms, extracardiac manifestations, cerebral embolism, significant valvular regurgitation, vegetation at echocardiography, need for valvular surgery during the initial period. Univariate analysis identified age ($p = 0.001$) and lack of initial valvular surgery ($p = 0.05$) as significant factors of mortality. In multivariate analysis, age was the only independant predictor of long-term mortality (RR 1.06, 95% CI 1.02–1.1, $p = 0.002$).

IE still has a high short-term and long-term mortality, probably partly resulting of the high incidence among the elderly. Valvular surgery might be considered more often during the acute phase of IE.

1895 Risks of infective endocarditis in patients with minimal and mild aortic regurgitation

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Background: It is not known, if **minimal or mild** aortic regurgitation (AR) is a predisposing situation for the development of infective endocarditis (IE) of the aortic valve

Methods: Of 17,065 echocardiographic examinations, 1878 fulfilled the inclusion criteria (minimal or mild aortic AR, no aortic stenosis, no prosthetic valve in aortic position and no heart transplantation). Events causing possible bacteremia according to the recommendations of the American Heart Association of 1997 and cases of IE were evaluated by a questionnaire. Cause of death was identified.

Results: Return rate was 99.2%, 12 patients prefered not to answer. Mean age was 65 ± 15 years (range 15–92), male 60.3%, female 39.7%, mean follow-up was 31.9 ± 15.9 months (range 7–67), total follow-up 3794 patient-years. Total bacteremia producing events were 2783 (1.95 per patient, 0.73 per patient-year), 254 patients (18%) hold an antibiotic prophylaxis passport. Two patients have had documented IE of the aortic valve according to Duke's criteria resulting in a calculated incidence of 52 IE/100,000 patient-years. Both had no preventable bacteremia producing event.

Conclusion: The calculated incidence rate of 52 IE/100,000 patient-years in patients with minimal or mild AR was inexpectedly high and is comparable to the risk of patients with mitral valve prolaps and audible systolic murmur. Consequently recommendations for prophylactic use of antibiotics should include minimal and mild AR. However, in both cases no preventable bateremia producing event was present. Large scale studies will be necessary to elucidate the efficacy and cost-effectiveness of antibiotic prophylaxis to prevent IE in patients with moderatly increased risk.

1896 Pacemaker endocarditis. main characteristics

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The objetive of this study was to describe the clinical course, microbiological profile, echocardiographic characteristics, and risk factors of patients (P) with pacemaker endocarditis (PE).

Methods: We analyzed 25 p of PE with definitive Duke criteria that were prospectively recruited (18 male, mean age 63 years)

Results: Main predisposing factors for infection were local: persistance of more than one lead in 17 p and more than one generator or electrode replacement in 11 p. The most common port of entry was skin erosion in 10 p and pouch infection in 6 p. Causal microorganisms were coagulase negative *staphylococci* in 17 p, *S. aureus* in 4 p, polymicrobial in 2 p, and culture negative in 2 p. Lung infiltrates compatible with septic embolism were found in 8 p. Time to diagnosis was 52 days (1–270). Transthoracic echocardiography was negative for PE in 21 p. Transesophageal echocardiography (TEE) was positive in 20 p: vegetation (veg) lead in 14 p, tricuspid veg in 1 p, veg lead plus tricuspid veg in 5 p, mural veg in 1 p, no veg in 5 p. Initial treatment was cardiotomy in 18 p (group I) percutaneous removal in 3 p (group II), and medical treatment without prosthetic removal in 4 p (group III). Lead extraction was incomplete in 1 p from gr I and in other from gr II, both of them relapsed and 1 developed a local thrombosis. There were 2 relapses and 1 local thrombosis in gr III, one of them died when percutaneous lead removal was attempted. Twenty one p become cured (17 p in gr I, 2 p in gr II, and 2 p in gr III). Cardiotomy was performed in 2 p that relapsed: 1 p cured, and 1 p relapsed due to incomplete lead extraction. Two p with retained leads required long term oral supressor antibiotic therapy for an adequate infection control.

Conclusions: Main risk factors for PE were local. The most common port of entry was generator pouch skin erosion. Main pathogens were coagulase negative *staphylococci*. TEE was very sensitive for PE diagnosis. Presence of retained material was an important predisposing factor for recurrence or thrombotic complications. Cardiotomy was the most succesful treatment.

CARDIOPROTECTION: NEW STRATEGIES

1906 Cloning of an AMP-selective cytosolic 5′-nucleotidase-I that produces adenosine inside cells

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In the heart, adenosine increases blood flow and decreases excitatory nerve firing, thereby reducing rate and force of contraction. It also preconditions the heart against injury by prolonged ischaemia. Based on indirect kinetic arguments, an AMP-selective cytosolic 5′-nucleotidase designated cN-I has been implicated in adenosine formation but this has not been cloned or shown directly to produce adenosine during ATP breakdown.

Methods: We purified cN-I from pigeon heart for partial protein sequencing. We then designed degenerate antisense oligonucleotide primers for touchdown PCR to generate a fragment with which to screen a pigeon ventricle cDNA library in λZap II. A full-length cDNA clone was obtained and then subcloned into the eukaryotic expression vector pTargeT. COS-7 cell were transfected using lipofectamine with pSV-β-galactosidase as a control for transfection. Cells were incubated with 10 μM EHNA and 50 μM 5′-amino-5′-deoxyadenosine to inhibit adenosine deaminase and kinase respectively. 10 mM 2-Deoxyglucose and 1 μM FCCP were added to inhibit glycolysis and mitochondrial ATP synthesis. Nucleosides and nucleotides were measured by HPLC and cell viability by LDH release.

Results: The full length clone encoded a novel 40 kDa peptide, unrelated to the IMP/GMP selective cytosolic 5′-nucleotidase (cN-II) or the ecto-5′-nucleotidase (e-N) that have already been cloned. Its mRNA was most abundant in heart, brain and breast muscle. Immunolocalisation in heart showed a striated cytoplasmic location suggesting association with contractile elements. Transient expression in COS-7 cells, generated a 5′-nucleotidase which catalysed adenosine formation from AMP that was increased during ATP breakdown.

In conclusion: We have cloned and expressed cN-I and provided definitive evidence of its ability to produce adenosine during ATP breakdown. Future experiments will address its function in the heart.

1907 Transient activation of adenosine A_1 receptors induces delayed cardioprotection in rats: role of Mn-superoxide dismutase

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We have previously described delayed preconditioning in rabbits 24–72 h after transient adenosine A_1 receptor activation which is associated with enhanced activity of the mitochondrial antioxidant manganese superoxide dismutase (Mn-SOD). In this study we further examined the role of Mn-SOD in mediating delayed cardioprotection. Wistar rats received a single iv bolus of the selective adenosine A_1 agonist 2-chloro-N^6-cyclopentyladenosine 75 μg/kg (CCPA) or saline vehicle (SAL). They were also treated with a 22-mer phosphorothioate oligodeoxynucleotide (ODN) with sequence anti-sense (AS-ODN) to the initiation site of rat Mn-SOD mRNA at a dose of 5 mg/kg by slow iv infusion. The sense (S-ODN) and scrambled ODN (Scr-ODN) were used as controls. 24 h later, rats were anaesthetised, hearts isolated and Langendorff perfused with Krebs-Henseleit buffer at constant pressure. Hearts were subjected to 35 min regional ischaemia and 2 h reperfusion. Risk zone (R) and infarct size (I) were determined with fluorescent microspheres and tetrazolium staining respectively. CCPA treatment significantly reduced the I/R ratio (*$p < 0.0001$) compared to the control group. This protection was completely abolished by prior treatment with AS-ODN which on its own had no effect on infarct size. S-ODN or Scr-ODN did not affect CCPA induced delayed cardioprotection.

	SAL	CCPA	AS-ODN+		S-ODN+	Scr-ODN+
			CCPA	SAL	CCPA	CCPA
n	12	9	8	8	8	7
I/R (%)	42.1 ± 3.8	22.3 ± 3.3*	39.4 ± 2.8	44.5 ± 4.9	24.7 ± 3.9*	29.3 ± 1.8*

Figures are Mean ± S.E.M. *$p < 0.0001$ vs other groups (1-way ANOVA)

This is the first study to show that transient adenosine A_1 receptor activation induces delayed cardioprotection in the rat. These results also strongly suggest an important role for Mn-SOD as a potential end-effector of this protection.

1908 Myocardial infarct size is reduced by post-ischaemic treatment with dipyruvyl-acetyl-glycerol and the associated elevation in pyruvate levels

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The beneficial effects of pyruvate in organ reperfusion injury has been widely documented, nevertheless the therapeutic use of pyruvate has been hindered due to the lack of an appropriate delivery method. Pyruvic acid is unstable for infusion and high rates of sodium pyruvate infusion cause sodium overload. Dipyruvyl acetyl glycerol (DPAG) ester was developed as a novel method for intravenous pyruvate delivery. This approach allows one to deliver pyruvate a high rate without the confounding effect of sodium toxicity. We tested the cardioprotective effect of this novel compound in an anesthetized open chest pig model of myocardial infarction. Ischemia was induced by total occlusion of the distal 2/3 of the left anterior descending coronary artery for one hour. This was followed by two hours of reperfusion. During the two hour reperfusion period animals were either left untreated (n = 7) or treated with an intravenous infusion of DPAG at the rate of 8.0 mg/kg*min. Infarct size was measured on blinded samples by the tetrazolium staining method. Treatment with DPAG resulted in an elevation in arterial pyruvate levels to 0.688 ± 0.132 mM, compared to 0.001 ± 0.001 mM in untreated animals. Treatment with DPAG resulted in a 35% reduction in infarct size, from 30.8 ± 4.6% of the area at risk for infarction in the control group to 20.1 ± 4.2% of the area at risk in the treatment group ($p < 0.05$).

In conclusion peripheral intravenous infusion of DPAG during the post-ischaemic reperfusion period elevates arterial pyruvate levels and reduces myocardial infarct size. Thus DPAG is an effective means to deliver high amounts of pyruvate systemically, and elicit the cardioprotective effects of pyruvate.

1909 Protection of the reperfused ischaemic pig myocardium by selective stimulation of myocardial EP3 receptors

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We have previously identified G protein coupled prostaglandin EP3 receptors in porcine myocardium, which are upregulated during acute myocardial ischemia (Hohlfeld et al., Circ Res 81:765, 1997). Here, we report that EP3 receptor stimulation by a selective agonist improves myocardial tolerance against ischemic myocardial injury. Anesthetised open-chest minipigs (25–35 kg bw.) were subjected to coronary (LAD) occlusion for 1 h and susequent reperfusion for 3 h. The selective EP3 receptor agonist M&B 28.767 (1 nmol/min) or vehicle were infused into the LAD (i.c.), starting 20 min prior to ischemia, until the end of reperfusion. In vehicle-treated pigs, infarct size (tetrazolium staining) was 76 ± 7% of the area at risk. EP3 receptor stimulation by MB significantly reduced infarct size to 36 ± 7% (n = 7–8 per group, $p < 0.01$) and significantly ($p < 0.05$) reduced transcardiac creatine kinase release by 48%. For further analysis, regional myocardial contractile function was recorded (sonomicrometry) during i.c. infusion of M&B 28.767 to non-ischemic hearts (n = 6). While EP3 receptor stimulation did not alter basal left ventricular contractility, the positive inotropic effect of the beta-adrenergic agonist isoprenaline (3 μg/min, i.v.) was almost prevented. This is consistent with additional data from in vitro studies, that demonstrate coupling of transfected porcine EP3 receptors (CHO cell line) to an inhibitory G protein. Similar results were obtained with the nonselective EP receptor agonist PGE1 (1 nmol/min, i.c.). In control experiments, the EP2 selective agonist butaprost was inactive.

It is concluded that myocardial EP3 receptors mediate the protection from ischemic myocardial injury by E-type prostaglandins. This effect may involve the prevention of deleterious actions caused by the ischemia-induced overflow of catecholamines.

1910 Ischaemia/reperfusion-induced myocardial and coronary dysfunction in adult and aged hearts: protective effects of the inhibition of Na-H exchange and of endothelin receptors

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The senescent heart is vulnerable to low-flow ischemia, which induces greater myocardial and coronary tone alterations. Na-H exchange (NHE) is involved in myocardial calcium overload, and endothelin is suspected to induce coronary vasoconstriction during ischemia and reperfusion (I/R). We investigated the effects of the inhibition of NHE with HOE642 (10^{-6} M), and of the endothelin receptors with Bosentan (10^{-5} M) on hearts of 4 (adult) and 24 (senescent) month old rats (mo) subjected to I/R. Isolated hearts were subjected to low-flow ischemia (45 min at 15% of initial coronary flow (CF)) and reperfusion, without (4 mo-I/R; 24 mo-I/R) or with HOE642 (4 mo-HOE; 24 mo-HOE), or with Bosentan (4 mo-BOS; 24 mo-BOS). Active tension (AT) and CF were recorded at baseline and after 5 and 30 min of reperfusion.

Results: mean ± SEM (in % of baseline values).

	AT		CF	
	5 min	30 min	5 min	30 min
4 mo-I/R (n = 9)	83 ± 4	77 ± 4	87 ± 8	73 ± 6
4 mo-HOE (n = 10)	79 ± 5	68 ± 6	73 ± 8	68 ± 10
4 mo-BOS (n = 9)	75 ± 5	73 ± 3	127 ± 11*	121 ± 12*
24 mo-I/R (n = 9)	74 ± 6	50 ± 7†	75 ± 11	52 ± 9†
24 mo-HOE (n = 8)	94 ± 4*	90 ± 6*	99 ± 11	96 ± 17*
24 mo-BOS (n = 7)	90 ± 3	80 ± 4*	111 ± 4*	111 ± 9*

*$p < 0.05$ vs age-matched I/R group. †$p < 0.05$ 24 mo-I/R vs 4 mo-I/R group.

Conclusion: 1) Post-ischemic contractile and coronary dysfunctions are greater in the senescent rat heart 2) Inhibition of endothelin receptors fully restores coronary flow during reperfusion in senescent as in adult hearts, suggesting a predominant role of endothelin on I/R-induced coronary alterations, and improves senescent contractile recovery 3) NHE inhibition markedly improves contractile recovery in the aged heart, suggesting an important role of NHE in I/R alterations of the aged myocardium.

1911 Potential cardioprotective role of insulin at reperfusion by a possible anti-apoptotic mechanism

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Early and complete reperfusion of ischaemic myocardium is essential for tissue salvage, but can paradoxically contribute to cell death (reperfusion injury). Although the majority of cell death during myocardial ischaemia-reperfusion results from cellular necrosis, we hypothesise that programmed cell death (apoptosis) may contribute to overall myocyte death during the reperfusion period. We investigated the potential cardioprotective role of insulin (0.3 mU/ml) given at the moment of reperfusion in isolated rat hearts subjected to 35 min regional ischaemia and 120 min reperfusion. We also describe experiments in isolated rat cardiomyocytes undergoing 6 h of lethal hypoxia and 2 h of reoxygenation, investigating the possible contribution of an anti-apoptotic effect of insulin to its cardioprotective action. The effect of inhibiting the signalling pathways with respect to protein tyrosine kinase and phosphatidylinositol 3-kinase (PI3-kinase) was assessed using 0.1 μM Lavendustin A (Lav) and 1 μM Wortmannin (Wort), respectively. Reperfusion/reoxygenation treatment with insulin significantly reduced infarct size and the percentage of apoptotic cells, and this protective effect was abolished by either Lav or Wort.

	Isolated Hearts		Isolated myocytes	
Group	n	% I/R	% apoptosis (TUNEL)	% apoptosis (Annexin V)
Control	7	46.2 ± 2.5	49.2 ± 3.1	65.0 ± 2.9
Ins at reperfusion	9	23.3 ± 2.8*	28.5 ± 1.8*	34.5 ± 2.4*
Lav alone	6	50.3 ± 3.1	58.5 ± 3.0	67.8 ± 4.3
Ins + Lav	6	50.3 ± 6.5	61.0 ± 4.2	54.2 ± 7.1
Wort alone	5	51.1 ± 5.5	65.2 ± 3.1	60.5 ± 1.5
Ins + Wort	6	50.9 ± 4.6	54.8 ± 2.0	52.5 ± 2.5

Mean ± s.e.m. *$P < 0.001$ vs. control group; (1-way ANOVA). Ins = insulin.

These data strongly suggest that the cardioprotective effect of insulin during reperfusion may be due to attenuation of ischaemia/reperfusion-induced apoptosis, and may be mediated via tyrosine kinase and/or PI-3-kinase activated signalling pathways.

STENTING PERIPHERAL ARTERIES

1912 Renal artery stenting with intravascular ultrasound guidance

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Background. Renal artery stenting is becoming the preferred revascularization strategy for atherosclerotic renal artery disease.

Methods. We used IVUS to understand the pathology of renal artery atherosclerotic disease and evaluated the value of IVUS guidance on renal artery stenting in 109 consecutive patients (age 70 ± 8, 45% men, 45% diabetics) in 136 renal arteries (71% ostial). The lesion cross-sectional area (CSA) was compared to the reference CSA; negative remodeling was defined as lesion CSA < reference CSA.

Results. Negative remodeling was the main feature in 96% of ostial vs. 69% of non-ostial lesions ($p = 0.04$). EEM CSA was 34.4 ± 13.3 mm^2 at the reference site vs. 25.4 ± 11.0 mm^2 at the lesion ($p = 0.01$). Procedural success was 100%. IVUS determined the need for further stent expansion in 38%, and additional stenting in 2.5%. Mean contrast volume used was 74 ± 25 ml. Although baseline creatinine was >1.8 mg/dl in 50%, only 7% developed post-stent renal failure (1.8% dialysis), which was transient in 90%. Quantitative results and correlation of IVUS and QCA:

	QCA	IVUS	r
Pre-reference diameter, mm	5.3 ± 1.2	4.9 ± 1.0	0.71
Pre-lesion min diameter, mm	1.9 ± 0.8	1.9 ± 0.6	0.51
Final lesion min diameter, mm	5.1 ± 0.7	4.9 ± 1.0	0.63

$P < 0.0001$ for all.

Significant decreases in arterial pressure were noted during long-term follow-up: both systolic (145 ± 21 vs. 170 ± 25, $p < 0.001$) and diastolic (74 ± 12 vs. 84 ± 16 baseline, $p < 0.001$) measurements decreased.

Conclusions. 1) Negative remodeling is common in renal arteries. 2) IVUS measurements are reliable and may therefore limit angiographic imaging and lower the contrast volume used 3) IVUS derived further dilatation/stenting was required in greater than one third of cases despite optimal angiographic result 4) Renal artery stenting is a safe and effective technique with favorable long-term outcome.

1913 Femoropopliteal stenting: results, indications – choice of the stent

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Purpose: To retrospectively study safety, efficacy, mid/long-term results of femoro-popliteal stenting. To try to select the best suited stent depending on location and characteristics of lesion and access site.

Methods: 700 lesions in 669 symptomatic pts (M: 66%, F: 34%, mean age: 65.9 ± 10.3 years) with femoro-pop. occlusive diseases (stenoses: 373, occlusions: 312, aneurysms: 15) treated with 3 types of stents: balloon expandable (Palmaz: 126, Long Medium Spiral: 68), self-expandable nitinol (Sinus: 150, Instent: 143, Medicorp Expander: 94), covered (Cragg: 93, Corvita: 26). Indications: post-PTA residual stenosis: 78%, dissection: 13%, restenosis: 9%. Mean lesion length: Palmaz: 3.8 cm, Long Medium: 6.8 cm, nitinol: 5.9 cm, covered stent: 9.5 cm.

Results: Immediate technical success: 98%, clinical: 97%. Acute thrombosis more frequent with covered stents (9% vs 2.5%). In the lower part of superficial femoral artery (SFA) and in popliteal artery, balloon expandable stents can be compressed and lead to higher restenosis rate than nitinol stents (50% vs 15%). Primary (PI) and secondary patency (PII): Palmaz stents at 4 years: PI: fem.: 65%, pop.: 50%, PII respectively: 95%, 69%. Long Medium Spiral at 3 years: femoropop: (upper part of pop. artery): PI: 77.5%, PII: 90%. Nitinol stents at 4 years: PI: femoral: 82%, popliteal: 84%, PII respectively: 91 and 94% (no difference for lesions < or >8 cm). With covered stents at 27 months at fem.-pop. level: PI: 64%, PII: 76%.

Conclusion: Femoro-popliteal stenting seems safe, efficient. Balloon-expandable stents seem particularly indicated for the 2 upper thirds of SFA (to be avoided for lower part and for popliteal artery). Self-expandable nitinol stents may be implanted in any artery, particularly in popliteal artery and flexion sites. Covered stents are rather indicated for aneurysms. Their results are not better than nitinol stents for the treatment of long lesions.

1914 Continous stenting after recanalization of long superficial femoral artery occlusions improves one-year results

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Implantation of endovascular stents in case of relevant dissections or residual stenoses improves acute interventional results after recanalization of long chronic SFA-occlusions. However, due to rapid progression of obstructive disease restenoses are observed frequently both proximally or distally of the stented segment. The objective of this study was to assess whether continous stenting of the entire recanalized vessel may improve the results after Excimer laser assisted recanalization (ELA) of SFA -occlusions.

In 110 patients a total of 367 stents (Wallstent n = 312, Palmaz n = 55) were implanted to stabilize recanalized SFA-occlusions, which evidentiated relevant dissections of the vessel wall. Patients were subgrouped according to the length and the continuity of the stented segment. Group A (n = 62): only partial stenting of the former occlusion, mean occlusion length (MOL) 21.4 cm, mean length of stented segment (MSL) 10.4 cm; Group B (n = 48): continous stenting of the SFA, MOL 22.1 cm, MSL 25.6 cm, no gaps between the stents. Technical success and primary patency rates after 6 and 12 months are given in the table.

Group	Technical Success <30% stenosis	Primary Patency 6 months	Primary Patency 12 months
A	60/62 (96.8%)	46/62 (74.2%)	30/62 (48.4%)
B	47/48 (97.9%)	43/48 (89.6%)	33/48 (68.8%)
Significance	p = n.s.	p < 0.01	p < 0.001

In conclusion, continous stenting of the entire recanalized vessel segment in case of relevant dissections after ELA of SFA-occlusions may improve the patency rate after 1 year. These results need to be validated prospectively.

1915 New approach to treatment of pseudobifurcational lesions

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Objective: To assess the angiographic and clinical result of a new method to treat pseudobifurcational lesions (stenosis involving only the parent vessel proximal to bifurcation, with ostia of the daughter branches preserved).

Patients and lesions: Fifteen pseudobifurcational lesions were consecutively treated in the last nine months with the technique described below. All lesions were type B2 or C. Lesion distribution was LCX/OM in 4 cases, LAD/DIAG in 2 cases, crux cordis (RCA) in 5 cases, and LMCA in 4 cases (2 of them unprotected). Mean reference vessel diameter was 3.1 ± 0.6 mm for the main vessel and 2.73 ± 0.4 mm for the daughter branch. All patients were treated with ASA and Ticlopidine. Clinical follow-up was available for all patients.

Technique: Both branches were predilated using a double wire technique. Subsequently a stent was hand-crimped on two appropriately sized balloons; this stent "sandwiched" the balloons leaving their distal portion uncovered. The balloons were then advanced on the two wires until the stent hit the carina of the bifurcation. The simultaneous balloon inflation flared the distal part of the stent towards both branches creating a funnel just proximal to the bifurcation.

Results: The stent crimped on 2 balloons could successfully be delivered in 14 cases (93.3%). Residual stenosis was 7.4 ± 6% in the main vessel. In 11 cases (79%) patency of daughter branches was completely preserved and in 3 (21%) the implantation of an additional stent was required. In these cases residual stenosis was 12 ± 4.8%. We had no in-hospital major events. At a mean four-month clinical follow-up, the frequency of composite end points of death, AMI, and target vessel revascularization was 0%.

Conclusions: The technique is relatively easy to perform and does not commit the operator to side branch stenting if not needed. The main advantage is that the access to both branches is maintained throughout the procedure and stenting either one or both of them, if required, is easy to perform.

1916 Six-month follow-up results of the Femoral Artery Stent Study (FASTEST)

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In a prospective randomized trial patients were randomized after successful conventional balloon angioplasty of a femoral artery lesion to no further interventional treatment (PTA), implantation of conventional stents (Stent) or implantation of a Dacron covered stent (Endo).

Follow-up (FU) angiogram was performed after 6 months or earlier, if indicated for clinical reasons.

	PTA	Stent	Endo	P
n	40	41	25	
Proc. Success	100%	100%	96%	N.S.
Thromboembolic compl.	0	10%*	16%*	<0.05*
MLD pre (mm)	0.7 ± 0.9	0.8 ± 0.9	0.8 ± 0.9	N.S.
MLD post (mm)	3.7 ± 0.7	5.2 ± 1.0*	4.2 ± 1.0*	<0.01*
MLD FU (mm)	2.0 ± 1.5	2.8 ± 1.5	2.1 ± 1.7	N.S.
Re-Stenosis (>50%) FU	65%	35%*	59%	<0.05*
Total occlusion FU	14%	11%	23%	N.S.

In conclusion, conventional stents as well as Dacron covered stents led to improved acute results compared to conventional balloon angioplasty alone. However, there is an increased risk of acute and subacute thromboembolic complications. After 6 months the restenosis rate was lower after implantation of conventional stents but not after implantation of Dacron covered stents compared to conventional balloon angioplasty.

1917 Long-term follow-up after stenting for iliac stenoses and occlusions

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Implantation of endovascular stents is a commonly used technique for percutaneous treatment of iliac stenoses. In contrast, the long-term efficiency of stents after recanalization of long iliac occlusions (LIO) remains uncertain. The objective of this study was to compare the results after stent-supported recanalization of iliac artery stenoses and occlusions.

In 458 patients a total number of 960 stents were implanted to stabilize suboptimal results after recanalization of high grade iliac stenoses (mean 87.2 ± 8.3%) (group A: n = 296) or total occlusions (group B: n = 211). The target lesion was localized in the common iliac artery (A: n = 133, B: n = 67), the external iliac artery (A: n = 96, B: n = 74) or both vessel segments (A: n = 68, B: n = 71). Length of the stented segment was significantly larger in group B (10.2 cm vs. 5.62 cm, $p < 0.01$).

Accordingly, more stents were needed after recanalization of LIO (3.1 vs. 1.46, $p < 0.01$). Comparing the clinical situation, we found a shorter walking capacity in group B as well as a reduced Ankle-Brachial-Index (ABI), measured after standarized treadmill test (0.55 ± 0.27 vs. 0.41 ± 0.18).

Results: A primary technical success (residual stenosis < 30%) could be achieved in 98.1% (group A) and 89.6% (group B) of patients, respectively. Clinically, a marked improvement of +2 or +3 grades according to the AHA-criteria was found in 144 pts. (69.9%, group A) and 179 pts. (84.4%, group B). During the mean follow-up of 19.5 months the primary patency rates were 87.0% in group A and 81.2% in group B. In the majority of cases reobstruction could be successfully treated by PTA, leading to secondary patency rates of 93.1% (group A) and 89.1% (group B).

In conclusion, endovascular stenting provides an effective treatment option for iliac stenoses as well as LIO. A high long-term patency has been proven in both groups.

LOCAL DRUG DELIVERY AND COMPOUND ELUTION USING STENTS: CLINICAL AND EXPERIMENTAL RESULTS

1927 Local delivery of low-molecular-weight heparin decreases restenosis rate after coronary stenting: final results of the POLONIA randomized study

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Intimal hyperplasia has been observed to be the primary cause of restenosis after stenting. Furthermore, recent findings suggest that low molecular weight heparin, at high concentration, inhibits smooth muscle cell (SMC) proliferation. We investigated whether intramural delivery of Enoxaparin prior to stenting decreases in-stent restenosis rate in patients receiving reduced systemic anti-coagulation. We randomly assigned 100 patients from 4 centers, who presented with single lesion, single vessel disease to local administration of Enoxaparin via drug delivery/balloon angioplasty catheter (Transport) prior to stenting (LDD) versus systemic heparinization (SH). All patients were treated with balloon expandable stents (NIR). The primary study endpoints included late luminal loss and in-stent restenosis, using a binary definition at 6 months. The secondary endpoints included activated clotting time at the end of the procedure, subacute stent closure, MI, emergent CABG, death, and target lesion revascularization.

Clinical follow up was available in all patients, and angiographic follow up at 6 month was completed in 99% of patients. At six months, late loss and in-stent restenosis in the LDD and SH groups were, respectively, 0.76 ± 0.42 mm (30.5 ± 13.0%) and 1.07 ± 0.49 mm (43.6 ± 18.2%). The activated clotting time was 146.9 ± 39.8 sec in the LDD group and 381.9 ± 182.2 sec in the SH group. There was one subacute closure and one MI in the SH group. There were no deaths or emergent CABG. Target vessel revascularization was 6% in the LDD group and 22% in the SH group ($p = 0.05$).

Conclusions: Intramural delivery of Enoxaparin prior to stenting significantly reduces late luminal loss, in-stent restenosis and target lesion revascularization rates. No subacute closure was observed despite reduced systemic heparinization.

1928 Local delivery of nadroparin for the prevention of neointimal hyperplasia following stent implantation: final results of the IMPRESS trial

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Purpose: The IMPRESS trial is a prospective randomized multicentre trial, designed to assess immediate and long term results of local low molecular weight heparin delivery (nadroparin) following coronary stenting.

Methods: 250 patients, submitted to balloon angioplasty followed by successful stent implantation were randomized into control group (none local drug delivery) or local delivery of nadroparin (5,000 IU anti-Xa in 3 ml of saline with the Crescendo catheter a microporous infusion catheter). Inclusion criteria were: age <75 years and >20 years, de novo type a or b lesions, lesion length < 15 mm, native coronary arteries with a reference diameter ^{3} 3 mm, implantation of only 15 mm Palmaz-Schatz stent as primary choice or justified either by unsatisfactory result, elastic recoil or dissection. The primary endpoint was the late loss in MLD at 6 month follow-up angiography. Secondary endpoints included% restenosis (>50% DS), acute procedural results, and major adverse cardiac events (MACE: death, myocardial infarction, repeat angioplasty, bypass surgery) at 8 weeks and 6 months follow-up.

Results: In total 250 patients were enrolled into the study. Local delivery of nadroparin was successful in 124 patients (99.2% success rate) and was not associated with an increase in coronary artery dissections, distal embolization or abrupt arterial closure. There were no differences in MACE at any time point (88.8% vs 89.6% of event free survival at 6 months in the control and nadroparin groups, respectively).

Angiographic data

	Control (n = 125)	Nadroparin (n = 125)	p value
Acute gain (mm)	1.86 ± 0.46	1.82 ± 0.5	0.39
Late loss (mm)	0.84 ± 0.62	0.88 ± 0.63	0.48
Net gain (mm)	1.01 ± 0.75	0.94 ± 0.74	0.56
Restenosis (%)	20	24	0.50

Conclusion: Intramural delivery of nadroparin (5,000 IU in 3 ml of normal saline) via the Crescendo catheter after stent deployment: (1) has no effect in reducing restenosis, (2) is technically feasible as successful delivery was achieved within the lesion site in 99% of cases, (3) is safe as intramural delivery was not associated with an increase in peri-procedure clinical or angiographic complications.

1929 Local angipeptin delivery from coronary stents in porcine coronary arteries

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Background: Local drug delivery from polymer coated stents is a novel concept to prevent restenosis. Angiopeptin has previously been shown to reduce intimal hyperplasia. We aimed to characterise the release kinetics and distribution of [^{125}I]angiopeptin loaded onto phosphorylcholine-(PC) coated BiodyvYsio stents *in vivo*.

Methods: PC-coated stents were loaded with 8.3 μg (± 0.8) [^{125}I]angiopeptin. The stents were deployed into porcine LADs, with the RCA and Cx as non-stented controls. Surface radioactivity was measured over the first 30 mins, and also immediately before sacrifice. The pigs (n = 8) were killed at 1 and 24 hrs, & 7 and 28 days. [^{125}I]angiopeptin in blood, urine and tissue samples was quantified.

Results: 99% of the time zero post-deployment radioactivity (Geiger surface count) persisted at 30 min and 43% at 7 days. The mean level of [^{125}I]angiopeptin present in blood 5 min following stenting was 0.40 ng/ml and 0.49 ng/ml after 1 hr, and fell to zero by 7 days. Maximum levels of [^{125}I]angiopeptin were detected in the arterial wall around the stent at all time-points; 506 pg/mg wet weight at 1 hr (artery alone), 419 pg/mg at 24 hrs (artery alone), 387 pg/mg at 7 days (artery alone) and 209 pg/mg at 28 days (artery and stent). [^{125}I]Angiopeptin was also detected in proximal and distal regions of the LAD. Less than 1 pg/mg was detected in the Cx and RCA. The maximum level of [^{125}I]angiopeptin in tissue other than the heart was detected in kidney at 24 hrs post-stenting (2.09 pg/mg). After 7 days 1.25% of the [^{125}I]angiopeptin initially loaded onto the stent remained.

Conclusion: Efficient, sustained and truly local delivery of [125I]angiopeptin into coronary artery wall can be achieved by loading onto a PC-coated stent. These data provide sufficient evidence to justify performing an efficacy study.

1930 Activated protein C-eluting stent inhibits platelet deposition in an in vivo model

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In previous experiments, we have shown that Activated Protein C (APC) is an extremely potent endogenous antithrombotic. It could be loaded onto polymer-coated stents to produce a biexponential elution profile and significantly reduced fibrin thrombus in vitro. We now aim to determine the in vivo efficacy of these stents in reducing platelet thrombosis in a balloon injury rabbit iliac artery model.

Method: Male NZ white rabbits were used. Rabbits received Aspirin and Ticlopidine for 5 days before operation. ^{111}In-labelled autologous platelets was given to the rabbit 1 h before operation. At operation, balloon injury was performed to both iliac arteries via arteriotomy. After injury, stents were deployed at the injury site under visual guidance. Flow through the stented arteries was monitored using perivascular flowprobes. After 2 h, rabbits were sacrificed and stented arteries removed and gamma-counted for platelets deposition. Systemic clotting time was measured during operation. APC-loaded, albumin (alb)-loaded and plain polymer-coated stents (p-s) were deployed with the operator blinded to the stent type.

Results: None of the APC stents occluded (0/14) as compared to more than half of the plain stents (9/15). Alb-stents and plain stents that did not occlude sustained only non-biphasic flow at extremely low flowrates (0.2–0.56 mL/min). Percentage of remaining flowrate was higher in APC-stent as compared to plain stent ($p < 0.001$) and higher in APC-stent as compared to alb-stent ($p < 0.001$). APC-stent had significantly less platelet deposition as compared to both plain and alb-stents ($p < 0.005$). No change in systemic clotting time was noted throughout operation.

Conclusion: APC-eluting stents significantly inhibit platelet thrombosis in vivo and may be useful for intervention in high risk situations.

1931 Successful gene transfer to swine coronary arteries using a polymer-coated DNA-eluting stent

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Background: Catheter-based gene delivery to the arterial wall is limited by both the need for prolonged incubation times to achieve efficient transgene expression and the absence of a sustained DNA release mechanism. A DNA-eluting stent may overcome these limitations. The objectives of this study were to engineer a biodegradable polymer-coated DNA-eluting stent, to characterize its in vitro release kinetics, and to determine the in vivo transfection efficiency in nonatherosclerotic porcine coronary arteries.

Methods: DNA emulsions were prepared by mixing reporter plasmid DNA encoding beta-galactosidase or green fluorescent protein with a volatile polymer solution. Rat aortic smooth muscle cells (SMC) in culture were exposed to samples of dessicated emulsion to assess in vitro transfection. The emulsions were applied to the surface of Crown stents (Cordis, Warren, NJ), and the kinetics of DNA release into saline were measured. Coated stents were hand-crimped on 3.0 or 3.5 mm angioplasty balloons and deployed in swine left anterior descending or left circumflex coronary arteries (n = 6). Coronary arteries were harvested at 5–7 days for analysis. Nuclear counterstaining was used to estimate transfection efficiency. DNA extraction followed by PCR was performed to assess site specificity of transgene expression.

Results: Optimal transfection in vitro was observed using an intermediate DNA concentration (14 μg/mL) and polylysine condensation. DNA release profiles from the coated stents in vitro were characterized by a rapid burst phase followed by exponential slowing. Reporter transgene expression was observed in all arteries in the DNA treated group, but in none of the control arteries. Transfection efficiency was 1.14 ± 0.08% (mean ± SEM, range 0.21–1.65%). Systemic transgene expression was excluded using PCR.

Conclusions: Successful gene transfer to the arterial wall was demonstrated using a biodegradable polymer-coated DNA-eluting stent, with a consistent transfection efficiency. This technique may prove useful for the treatment of pathologic vascular processes, such as atherosclerosis or in-stent restenosis.

1932 E2F1 and cyclin E directed ribozymes as a tool to inhibit smooth muscle cell proliferation after percutaneous transluminal angioplasty

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A major problem following coronary interventional procedures such as percutaneous transluminal angioplasty (PTA) is the re-narrowing of the vessel lumen (restenosis) at the site of dilatation that occurs in a high percentage of cases. Although restenosis is a complex process, one of the most crucial events is the induction of proliferation of the vascular smooth muscle cells and their migration into the intimal space. Therefore, we based our gene therapy project on the inhibition of vascular smooth muscle cell growth by hammerhead ribozymes. Hammerhead ribozymes are short catalytic RNA molecules capable of inducing the site-specific cleavage of a phosphodiester bond within a RNA molecule. As ribozyme targets we have chosen the mRNA species coding the proteins E2F1 and cyclin E which play a key role in the transition from G1 to S phase during the cell cycle.

Methods: ribozyme accessible cleavage sites were mapped on the two full length mRNAs species by the RNase H digestion technique. On the basis of these results four ribozymes targeted against E2F1 mRNA and six ribozymes targeted against cyclin E mRNA were generated with 8 nucleotides per binding arm and tested in vitro under single turnover conditions. Cleavage reactions were performed under physiological conditions of temperature and pH. The most active ribozymes had kreact/Km ratios in the range of 50–80 × 10,000/M min which are among the best published kreact/Km ratios for ribozymes targeted against long structured mRNAs. For the best ribozymes the effect, on the cleavage efficiency, of the binding arm length variations was also tested generating ribozyme either with 5 or 12 nucleotides per side. As a result of these experiments, we found that the optimal binding arm length was in the range of 8–12 nucleotides. The in vivo effectiveness of the most active ribozymes was then tested in human smooth muscle cells grown either in the presence or in the absence of the specific active ribozyme. To check the possible ribozyme antisense effect, cells were also grown in the presence of the inactive ribozymes bearing a mutation in the active core which abolishes the catalytic activity but not the possibility to bind to the target. Cell cycle progression was evaluated by facs analysis.

In conclusion our data represent the first example of in vitro highly active ribozymes targeted against cyclin E and E2F1 mRNAs. In addition, preliminary in vivo studies indicate that our ribozymes can significantly reduce smooth muscle cells proliferation.

VASCULAR REMODELLING: CLINICAL ASPECTS

1936 MMP inhibition following balloon angioplasty inhibits constrictive remodelling in favour of expansive enlargement: an intravascular ultrasound study in pigs

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Background: Constrictive remodeling is the major determinant of restenosis following balloon angioplasty. Previously, we demonstrated that inhibition of Matrix Metalloproteinases (MMPs) significantly reduces late lumen loss after balloon angioplasty by inhibition of constrictive arterial remodeling. It is unknown whether inhibition of constrictive remodeling occurs in favour of expansive remodeling (enlargement) or whether expansive remodeling is blocked by inhibition of MMPs as well.

Methods: Balloon angioplasty was performed in 33 femoral and internal iliac arteries in 11 pigs. Pigs were randomly divided into 4 groups: 1 control group (n = 6 vessels) and 3 groups in which Marimastat, a MMP- inhibitor which can be administered orally, was administered for 2 weeks (n = 10 vessels), 4 weeks (n = 7 vessels) and 6 weeks (n = 10 vessels) respectively. Marimastat treatment was started one day prior to the intervention. Pigs were terminated 42 days after intervention. 30 MHz intravascular ultrasound was performed at all time-points. At regular sites, intravascular ultrasound images of each balloon dilated area were matched pre-, post interventional and at follow-up. For each matched segment the mode of remodeling (shrinkage/enlargement) was determined by the difference in the vessel area (VA) between post intervention and at follow up (control group: n = 23, pooled Marimastat group: n = 94). The segments were divided in 3 groups: compensatory enlargement (VA change > +5%), no remodeling (VA change −5 to +5%), and shrinkage (VA change > −5%). Data of the different Marimastat groups were pooled since no significant differences were observed among groups.

Results: see table (*$p < 0.01$).

Remodeling and marimastat

	Shrinkage	No remodeling	Enlargement
Control (n = 23)	22 (= 96%)	0	1 (= 4%)
Marimastat (n = 94) *	24 (= 25.5%)	24 (= 25.5%)	46 (49%)

Influence of marimastat on the remodeling mode following balloon angioplasty.

Conclusion: MMP inhibition following balloon angioplasty inhibits constrictive remodeling in favour of expansive enlargement. Whether MMP inhibition does actively affect expansive enlargement remains to be investigated.

1937 The "Glagov effect" is a rare event in native coronary arteries in vivo

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In the majority of patients with coronary artery disease a compensatory enlargement of the left main stem and the left anterior descending coronary artery was observed post mortemand this was described as the "Glagov effect". This current in vivo study was performed to determine the occurrence and incidence of compensatory vessel enlargement in arteries with hemodynamically relevant lesions before coronary intervention with intravascular ultrasound.

Methods: In 308 patients intracoronary ultrasound (CVIS, 3.2 F) was used to analyze the vessel dimensions prior to coronary intervention. The target vessel was the left anterior descending coronary artery in 172 patients, the circumflex artery in 25, and the right coronary artery in 111 patients.

Results: The prestenotic vessel area (EEM CSA) was 20.2 ± 9.0 mm^2, the intrastenotic EEM CSA 18.1 ± 5.7 mm^2, and the poststenotic area 16.7 ± 5.4 mm^2 in the total group. In 74 patients an intrastenotic vessel enlargement was found whereas in the majority of patients (n = 234) a significant reduction of the intrastenotic vessel area by 2.3 mm^2 was present.

In conclusion, these results indicate that in-vivo and in the presence of hemodynamically relevant lesions compensatory vessel enlargement is a rather rare event. The data indicate that in the majority of patients remodelling will result in a decrease of the vessel area (shrinkage). Thus, the "Glagov effect" cannot be postulated as a predominant pheonomenon in native coronary arteries in-vivo.

1938 Differential results after coronary intervention due to pre-existing vessel enlargement

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We have previously shown that adaptive remodeling is associated with a significantly higher degree of restenosis severity, and that pre-existing AR is a significant independent predictor for occurrence of major adverse cardiac events (MACE). The aim of this study was to examine, which factors (clinical, angiographic or procedural) may be responsible for the paradoxical worse clinical outcome of the patients with pre-existing adaptive remodeling of the target lesion.

Method Clinical (age, gender, coronary risk factors), quantitative angiographic (minimal lumen diameter, reference diameter and %diameter stenosis), qualitative (soft/hard plaque, plaque eccentricity, presence of calcification, thrombus and rupture) and quantitative IVUS (minimal lumen cross-sectional are /CSA/, external elastic membrane /EEM/ CSA, plaque CSA and plaque burden) data on 81 patients were compared. Adaptive vs constrictive remodeling was defined if the EEM CSA of the target lesion was greater/smaller than that of the proximal/distal reference EEM CSA.

Results 31 patients exhibited adaptive remodeling (57 ± 14 y, 81% men, Group AR), while constrictive remodeling was found by 20 patients (64 ± 8 y, 70% men, Group CR), and no remodeling in 30 patients (61 ± 10 y, 77% men, Group NR). MACE at six months follow-up was significantly more frequent in patients in Group AR than in Group CR and NR (43% vs 15% and 23%, $p < 0.05$). Clinical data, pre- and postinterventional quantitative angiographic and qualitative IVUS data did not differ significantly between the three groups. The preangioplastic EEM CSA, plaque CSA and postinterventional plaque CSA were significantly greater in Group AR (table)

	Before intervention			After intervention		
	EEM CSA [mm^2]	Plaque CSA [mm^2]	Plaque burden [%]	EEM CSA [mm^2]	Plaque CSA [mm^2]	Plaque burden [%]
Group AR	17.2 ± 4.8*	12.8 ± 4.3*	75.1 ± 10.9	17.5 ± 4.8	8.5 ± 3.1*	49.6 ± 12.4*
Group CR	12.5 ± 4.8	8.8 ± 4.0	67.8 ± 8.0	15.1 ± 6.6	6.3 ± 4.1	44.1 ± 11.7
Group NR	15.6 ± 3.8	10.6 ± 4.5	72.5 ± 14.3	16.9 ± 4.6	6.9 ± 3.1	40.9 ± 10.5

*$p < 0.05$ between Group AR vs CR and NR

Conclusions Patients with adaptive remodeling have a higher plaque burden after intervention due to the significant greater amount of residual plaque, this factor may be responsible for the higher rate of restenosis and MACE in patients with pre-existing adaptive remodeling.

1939 Regional vascular remodelling: assessment of distribution and contribution to the lumen narrowing by intravascular ultrasound

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The purpose of this study was to evaluate the distribution of regional vascular remodeling and its influence on the lumen dimensions in vivo. Sixty-three patients with 68 coronary lesions were imaged by intravascular ultrasound (IVUS) before transcatheter therapy. Quantitative measurements of lumen area (LA), total arterial area (TAA) and plaque area (PA = TAA − LA) were performed at the lesion site and at the proximal and distal reference site. Three different groups of vascular remodeling were determined based on IVUS measurements: 1) positive remodeling = stenosis TAA > maximal reference TAA; 2) intermediate remodeling = maximal reference TAA ≥ stenosis TAA ≥ minimal reference TAA; 3) negative remodeling = stenosis TAA < minimal reference TAA.

In 57% of lesions TAA in the stenosis was not between the proximal and distal reference TAA: 29% of lesions (20/68) had positive, 28% (19/68) negative and 43% (29/68) intermediate remodeling. In the negative remodeling group, reduction of TAA contributed to 40% of lumen narrowing, in the positive remodeling group TAA was 21% enlarged ($p < 0.001$). Lesions with negative remodeling exhibit a lesser PA, lesions with positive remodeling a larger PA than other vessels (8.2 ± 2.4 mm^2, 13.8 ± 3.7 mm^2; 10.8 ± 3.7 mm^2; $p < 0.001$).

Distinct vascular remodeling occurred in the majority of atherosclerotic lesions and appeared to be a bidirectional process. Overall the frequency of positive and negative remodeling was almost balanced. In lesions with negative remodeling PA was less than expected, reduction of TAA contributed to 40% of lumen narrowing. In lesions with positive remodeling vessel enlargement compensated for 21% of plaque accumulation.

1940 Baseline remodelling of native denovo coronary lesions is predictive of target lesion revascularisation after stent implantation

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Coronary artery stenting eliminates late lumen loss due to arterial constriction, and instent restenosis is due to neointimal hyperplasia. To study the impact of baseline arterial remodeling (REM) on target lesion revascularsation (TLR) after stenting in native coronary arteries, we used pre-interventional intravascular ultrasound (IVUS) in 701 patients with 813 denovo coronary lesions. REM was determined by comparing the lesion external elastic membrane area (EEM) to the mean reference (Ref) EEM. REM was defined as positive (+REM: lesion/Ref EEM ≥ 1.0, n = 352) or negative (−REM: lesion/Ref EEM < 1.0, n = 461). Target lesion revascularisation (TLR) rate was compared between two groups at 12 months follow-up.

	−REM	+REM	P
Diabetes (%)	24.0	29.9	0.08
Ref luminal area (%)	8.4 ± 0.1	8.1 ± 0.2	0.1
Final stent area (%)	7.7 ± 0.1	7.6 ± 0.1	0.6
Final luminal area (%)	7.6 ± 0.1	7.5 ± 0.1	0.3
TLR (%)	9.5	11.3	0.03

We therefore **conclude** that denovo lesions with +REM, as defined by pre-intervention IVUS, have a higher TLR after stenting compared to lesion with −REM. The probability of TLR after stenting increases with increasing +REM. Documentation of baseline −REM may indicate that the lesion is less prone to develop exaggerted neointimal hyperplasia.

1941 Vessel remodelling before directionary coronary atherectomy effects on chronic vessel response

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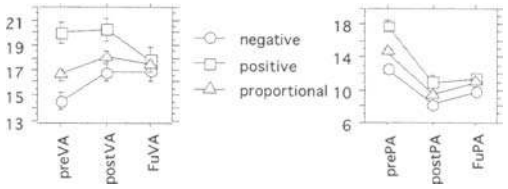
Recent studies have been reported that vessel remodeling before intervention is one of factors of restenosis. However, the effects of remodeling on chronic vessel response after angioplasty have been unknown. We examined the relation between vessel remodeling before directionary coronary atherectomy (DCA) and chronic vessel response at follow-up (Fu) by serial intravascular ultrasound (IVUS) study. In 152 lesions, which was de novo and underwent IVUS guided DCA, serial IVUS study was performed at pre, post and at Fu (mean duration 194 days). Vessel area (VA) and lumen area (LA) was measured and plaque area (PA) was calculated. Vessel remodeling was defined as following. Negative remodeling group (n = 39): proximal reference (Rp) VA > distal reference (Rd) VA > lesion (L) VA, Proportional remodeling group (n = 87): RpVA > LVA > RdVA, Positive remodeling group (n = 26): LVA > RpVA > RdVA.

Results: Serial changes in VA and PA are shown as follows.



Chronic vessel shrinkage was significantly largest in the positive remodeling group. However, the change of plaque was not significantly difference among these three groups. We concluded that positive remodeling before DCA accelerates vessel shrinkage.

CLINICAL RESULTS OF ENDOVASCULAR IRRADIATION

1942 Dosing comparison of radiation sources of intracoronary brachytherapy

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Background: Recently both β and γ radiation have been effectively used to reduce post PTCA restenosis. It has been assumed, due to its greater penetration that γ sources result in a more homogeneous dose to the vessel wall (VW). The object of this analysis was to determine the influence of source selection (Sr/Y^{90}-β and Ir^{192}-γ) on VW and normal tissue.

Methods: IVUS was performed in all 30 patients in the Canadian arm of the BERT study. Inclusion criteria included angioplasty in native coronary arteries 2.5–3.5 mm diameter. Retrospective analysis of dosing was performed on 22 patients using the iplan (Atlanta GA) treatment planning system. Images were captured every 2.5 mm over the treated segment. Two non-centered sources were modeled. The first a γ source train comprising eight 3 mm long seeds with 1 mm interseed spacing, as used in the SCRIPPS trial and secondly a β source train comprising twelve 2.5 mm long seeds with no interseed gaps. Dose volume histograms were constructed for the vessel wall volume as well as for the normal tissue as represented by the volume of tissue extending 3 mm beyond the EEM. D10, D90 and means were then extracted from the DVH for each source.

Results:

Dose (Gy)	Gamma	Beta*
Mean	**11.9**	**12.3**
D90	**7.4**	**6.6**
D10	**18.5**	**19.9**

*p = ns γ vs. β

Conclusions: In this group of patients, there was no statistical difference between the doses that would have been delivered to the vessel wall had the source been a γ source rather than the β-emitter used. The dose delivered to the perivascular normal tissue however would have doubled with the use of γ radiation. In mid sized native coronary arteries γ radiation appears to offer no dosimetric advantage over a β-emitter.

1943 Regional analysis of dosimetry and volumetric morphological changes in coronary segments treated with β-radiation following successful balloon angioplasty

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Beta-radiation therapy (β-rad) appears to be feasible and safe in the treatment of "de novo" coronary stenoses. Inhomogeneity of dose distribution and anatomical aspects of the treated atherosclerotic plaque, such as, type of tissue or presence of dissection after balloon angioplasty (BA), may influence the outcome of irradiated lesions. We evaluated the influence of dose distribution and morphological characteristics of coronary stenoses treated with β-rad following successful BA in 18 consecutive patients treated according to the BERT-1.5 Trial.

Methods: The site of angioplasty was irradiated using a β-emitting Sr-90 source. Using the sidebranches as anatomical landmarks, the irradiated area was identified and volumetric assessment was performed by 3-dimensional (3-D) intracoronary ultrasound imaging after treatment and at 6-months. Image acquisition was performed by ECG-triggered pullback and 3-D reconstruction of the image by the contour detection system. The type of tissue, the presence of dissection and the luminal, plaque and total vessel volumes were assessed every 2 mm within the irradiated area. The minimal dose absorbed by 90% of the adventitial volume (D90adv) was calculated in each 2 mm-segment. Segments with > 180° arc of calcium and sidebranches occupying > 90° of circumferential arc were excluded.

Results: 206 coronary segments were included. Fifty-five segments were defined as soft tissue, 129 hard tissue and 22 normal or intimal thickening. Dissection was observed in 32 segments. Plaque volume showed a higher increase in normal segments as compared to soft and hard segments (+9.9 ± 10 mm^3 vs. +3.8 ± 6.4 mm^3 vs. +1.4 ± 4.4 mm^3, respectively; $p < 0.01$). However, D90adv was lower in normal segments (4.2 ± 2.6 Gy vs. 5.8 ± 2.0 Gy in soft tissue vs. 5.5 ± 2.5 Gy in hard tissue; $p < 0.01$). Dissected coronary segments showed a lower increase in plaque volume than non-dissected (+1.2 ± 3.7 mm^3 vs. +3.3 ± 6.8 mm^3, respectively, p = 0.01). D90adv was significantly higher in dissected segments (6.5 ± 2.4 Gy vs. 5.4 ± 2.6 Gy in non-dissected; p = 0.01). The multiple linear regression analysis identified the independent predictors of the plaque volume at follow-up: plaque volume post-treatment (p = 0.0001), type of plaque (soft p = 0.21 and hard p = 0.03 as compared to normal), D90adv (p = 0.0001).

Conclusion: Differences in tissue composition and dose distribution play a fundamental role in the volumetric changes after β-rad therapy following BA.

1944 Maintained efficacy of intracoronary β-radiation for restenosis prevention at one year

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The effectiveness of beta radiation in reducing post angioplasty restenosis at six months has recently been reported. The durability of this treatment has not been demonstrated and this intervention may potentially alter the natural history of restenosis. This, coupled with the possibility of late side effects makes more prolonged follow up essential.

Methods: A total of 30 patients (pts) underwent PTCA and beta radiation therapy with a closed end 5F non centered catheter in doses of 12–16 Gy for restenosis prevention in the Canadian arm of the Beta Energy Restenosis Trial. All 30 pts underwent 6 month angiographic and IVUS follow up. One year clinical follow up including provocative nuclear perfusion imaging was also performed. Beyond 6 months, angiography and PTCA were symptom driven. Two year angiographic follow-up has recently commenced.

Results: Between 6 months and one year, one patient developed angiographic restenosis. Target lesion revascularization was therefore performed in 4 patients and target vessel revascularization in 7 patients by one year. There have been no deaths during the first year of follow up.

Conclusion: The clinical efficacy of post PTCA beta radiation achieved at 6 months is predominantly maintained at one year. No late side effects or complications were identified in this group of patients. Although close follow up of this patient group is essential, these results are most encouraging for the long term effects of catheter based beta radiation for restenosis prevention.

1945 β-Energy to prevent restenosis: the Rotterdam contribution to the BERT 1.5 trial – 1 year follow-up

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Introduction BERT 1.5 is a multicenter trial at Emory University Hospital, Rhode Island Hospital-Providence, the Montreal Heart Institute and the Thoraxcenter Rotterdam to evaluate safety and efficacy of β-irradiation following PTCA to prevent restenosis in pts with de novo single lesions in coronary arteries.

Methods After successful balloondilatation a 30 mm train of 12 Strontium-90 β-emitting seeds was hydraulically railed to the lesion through a 5 F radiation deliverycatheter. Pts were randomized to a dose of 12, 14 or 16 Gy After a dwelling time of at maximum 3.33 min. (16Gy) the elements were returned into a transfer device and the catheter was removed. In 26% additional stenting was performed for recoil or dissection.

Results From Apr to Dec 1997 we enrolled 21 male and 10 female pts in the BERT 1.5 trial. Pts had stable angina CCS 2 (n = 7), 3 (n = 14), 4 (n = 4) or unstable angina pectoris Braunwald class 1C (n = 2) or 2B (n = 2). Lesions treated were in LAD (n = 16), LCX (n = 7) and RCA (n = 8). In 1 pt the Beta-catheter could not cross a proximal calcified plaque. No major adverse cardiac events occurred in hospital. At 1-month follow up all pts but 2 had a reduction in anginal class. At 6-months, 18 pts had no angina, 11 pts had stable angina and 2 pts had unstable angina. Angiographic restenosis (DS > 50% in irradiated segment) was seen in pts (26%). (4 refusals) Quantitative Coronary Analysis of these 27 angiograms showed a median late loss index of 0.25 (range −0.81 to 3.43). At 1 year follow up 4 pts had angina pectoris, 22 pts (71%) were eventfree, 1 pt underwent CABG, 7 pts underwent repeat PTCA, 2 pts had MI and 1 pt had CVA.

Conclusion. Our experience with 31 pts indicates that the technique is feasible and safe. A restenosis rate of 26% at 6 months was observed and at 1 year follow up clinical results were well preserved.

1946 Radioactive ^{32}P β-particle emitting stents in patients with coronary artery disease reduce in-stent neointimal hyperplasia in a dose-related manner: a serial volumetric IVUS study

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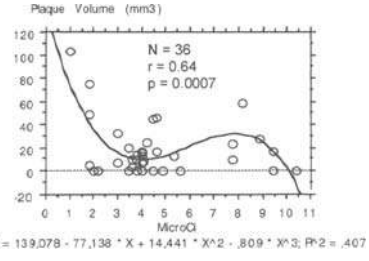
Restenosis after stenting is mainly due to intimal hyperplasia. We have previously reported that in patients with CAD, ^{32}P radioactive β-emitting stents (Isostent) with an initial activity level of 0.75–6.0 μCi reduce in-stent late loss at 4–6 month follow-up in a dose related manner. Aim of this study was to analyze the relationship between the stent radioactivity level at the time of implantation and the subsequent in-stent plaque volume increase measured by IVUS at 4–6 month FU.

Methods: We analyzed 36 lesions in which a single 15 mm long radioactive ^{32}P β-particle-emitting stent was implanted and in which a serial IVUS study (post-stenting and at 4–6 month FU) was performed. Two types of slotted tubular stents were implanted: initially the Palmaz-Schatz (0.75–3.0 μCi) and later the BX Isostent (3–12 μCi). IVUS imaging was performed using a motorized transducer pullback. In-stent plaque area was measured on 15 slices analyzed 1 mm apart and the plaque volume computed using the Simpson's rule. The graph below summarizes the results.



Conclusions: In-stent intimal hyperplasia decreses with increasing initial stent radioactivity levels. The points were best fitted by a sigmoidal curve obtained by regression with a polynomial model of 3rd order. A complete analysis including other stents already implanted with higher initial activity levels (12–20 μCi) will be available at the time of presentation.

1947 Acute results of the Vienna P-32 Dose Response study: radioactive BX stents at high activity for reduction of restenosis after coronary interventions

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Beta-particle emitting stents have been found to have an activity dependant antiproliferative effect on vascular smooth muscle cells in animal models of restenosis. However, an efficient activity to reduce restenosis in humans has not been clearly determined yet.

Methods: The Vienna P-32 Dose Response Study is designed to test the safety and efficacy of beta-emitting stents with a higher initial activity (up to 24 μCi) in up to 60 consecutive patients with either de novo lesions, in-stent restenosis, or restenosis after PTCA. Optimal stent deployment is guided by intravascular ultrasound (IVUS), and angiographic and IVUS data are evaluated in two independent Core labs. Patients are treated with aspirin (100 mg) for at least one year and ticlopidine (500 mg) for 90 days after stenting. They will undergo clinical follow up at 30 days, and angiographic and IVUS follow up at 6 and 12 months. In the first six weeks of the study, 13 radioactive BX IsoStents (3.0 and 3.5 mm diameter, 15 mm length) containing P-32 were implanted in ten lesions (6 LAD, 1 RCX, 3 RCA) in ten patients. Seven lesions were de novo, and three were in-stent restenoses.

Results: In the first ten patients there were no adverse procedural or in-hospital events, and all stents could be successfully implanted. Mean activity at the time of implantation was 15.16 ± 5.56 μCi (range 7.2–19.8 μCi). Mean lumen area as measured in on-line IVUS increased from 2.64 ± 1.32 mm^2 at baseline to 7.55 ± 1.26 mm^2 ($p < 0.001$) after stent implantation.

Conclusion: Preliminary data suggest, that P-32 coated BX stents at high activity can be safely implanted in both de novo and in-stent restenotic coronary lesions with no acute major adverse cardiac events. 30 day and 6 month follow up data will be presented.

GUIDANCE FOR PERCUTANEOUS INTERVENTIONS (PART I)

1954 Vessel response in ICUS versus angiographically guided stent placement: a substudy analysis from the Optimization with ICUS to reduce stent restenosis (OPTICUS) trial

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Background: The application of predefined ICUS criteria of optimized stent expansion may reduce traumatic vessel response. We prospectively compared neointimal formation as well as reference vessel response between ICUS and angiographically guided stent optimization strategies.

Methods: A 6 months follow up ICUS-substudy of the multicenter OPTICUS trial was prospectively designed in 150 patients. Patients were randomized to ICUS-guided stent placement (ICUS) to reach primarily the ICUS-criteria of optimized stent-expansion or to angiographically guided (ANGIO) stent deployment. Recordings from motorized mechanical catheter pullbacks (0.5 mm/sec) were digitized and analyzed with the aid of a three-dimensional analysis software package using minimal cost contour detection algorithms. Using volumetric ICUS measurements, reference segment plaque burden (mean plaque volume/mean vessel volume) as well as neointima burden (neointima volume/mean stent volume) were calculated.

Results: In both groups, preinterventional angiographically determined reference diameter (RD) and diameter stenosis (DS) were similar (ANGIO: RD 2.99 mm, DS 65.2%; ICUS: RD 3.02 mm, DS 66.6%). Interim substudy results in 50 single stent implantation procedures at a mean of 6 ± 1 months follow-up:

	ICUS (n = 23)	ANGIO (n = 27)	p
Maximal stent area (mm^2)	11.55	9.63	0.056
Neointima burden (%)	13 ± 16	22 ± 18	0.041
Proximal reference plaque burden (%)	43 ± 17	53 ± 19	0.043
Distal reference plaque burden (%)	40 ± 24	46 ± 13	0.330

Conclusion: These preliminary results show a trend towards larger stent area and reduced neointima proliferation in ICUS versus ANGIO guided stent placement. There is no evidence of excessive vessel response within the reference segments in patients with ICUS guided balloon sizing for optimized stent expansion.

1955 Clinical outcome after stent implantation with versus without intravascular ultrasound guidance: eighteen month follow-up of the "restenosis after intravascular ultrasound stenting" (RESIST) study

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Background: One hundred and fifty five patients were randomized to routine stent deployment with versus without IVUS guidance. At 6 months, a 20% larger lumen cross sectional area (L-CSA) was found in the IVUS group, but differences in restenosis rate and in minimal lumen diameter (MLD) were non significant. The clinical translation of a 20% larger L-CSA remains unclear.

Methods: Clinical event was defined as death, myocardial infarction, or the need for ischemia/symptom-driven target lesion revascularization. The clinical follow-up was performed over 18 months. Follow-up-information was obtained from hospital records and telephone contact with the patient to determine the occurrence of major clinical events and the symptoms level.

Results: Clinical follow-up was completed for all 155 patients. Two patients died (one in each group), repeat angioplasty was performed in 26/76 patients in the group without IVUS and in 19/79 in the group with IVUS. During the follow-up, a second restenosis was observed in six patients and treated by surgery (2 patients from the non IVUS group) and by repeat angioplasty (2 in each group), using balloon in 2 cases and rotational atherectomy plus balloon in 2. A total of 52 revascularization procedures were performed, 31 in the non IVUS group and 21 in the IVUS group ($p = 0.03$). Event free survival was 48/76 (63%) versus 59/79 (75%), non-IVUS vs IVUS, $p = 0.059$. The only independent predictor of clinical event, according to multivariate logistic regression analysis, was stent L-CSA at stent implantation, odds ratio 0.56 per additional mm^2,(95% CI = [0.40; 0.76], $p < 0.001$).

Conclusions: A significantly larger L-CSA was observed at stent implantation and at 6 months. We thus conclude that the larger L-CSA resulting from IVUS guidance led to a trend towards better clinical outcome, but which was only of borderline significance ($p = 0.059$). The number of revascularization procedures was lower in the IVUS group ($p = 0.03$).

1956 Guiding balloon dilatation by IVUS measurements: the Upsize pilot trial

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Background: Recent trials report a reduction of restenosis using intracoronary stents and suggest that this is a result of the high immediate luminal gain. The present study was based on the assumption that optimising balloon dilatation may result in equivalent acute and longterm outcome.

Methods: Preinterventional intravascular ultrasound was performed in 252 patients (pts) with 271 lesions. Quantitative assessment of the vascular dimensions was performed online. The balloon diameter was adapted to the diameter of the external elastic membrane, regardless of dimensions assessed by quantitative coronary angiography. The mean balloon diameter was 4.1 ± 0.5 mm.

Results: Acute events occurred in 5 patients (two repeat-PTCA, one CABG, two CABG with death). Angiographic dissection occurred in 157 pts (58%). Stent implantation for flow limiting dissection was necessary in 3 pts. A GPIIb/IIIa antagonist was administered in 5 pts. The one year clincal event rate was 15%: 5 pts experienced a myocardial infarction, 15 repeat PTCA of the target vessel, 8 pts underwent elective CABG. Control angiography was performed in 178 patients (71%). The angiographic restenosis rate was 19%.

Conclusion: Despite the use of larger balloons, the strategy of balloon dilatation guided by preinterventional intravascular ultrasound appears to be safe in the acute setting. The longterm outcome in this initial series seems to be favourable and is comparable to the results achieved with stent implantation. These results warrant verification in a randomised trial.

1957 Deferral versus performance of PTCA based on coronary pressure derived fractional flow reserve: the DEFER study

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Many patients undergo PTCA, without prior documented evidence of inducible ischemia. In such patients it is unknown whether performance of PTCA improves clinical outcome. This prospective randomized study compared clinical outcome in those patients after deferral versus performance of PTCA, based on fractional flow reserve (FFR), which is an accurate invasive index of inducible ischemia.

Methods: Included were patients with chestpain, admitted for PTCA of 1 stenosis (>50% by visual estimation) without documented evidence of inducible ischemia (absent, negative, or in-conclusive non-invasive testing). Just prior to PTCA, FFR of the target lesion was calculated by the ratio of adenosine induced hyperemic distal coronary pressure to aortic pressure. If FFR < 0.75 (equivalence of inducible ischemia) PTCA was performed as scheduled. If FFR ≥ 0.75 (making inducible ischemia unlikely) patients were randomized to deferral or performance of PTCA.

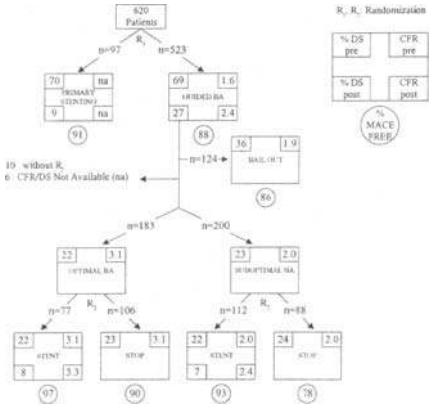
Results: A total of 326 patients were included. In 185 patients FFR was ≥ 0.75. These patients were randomly assigned to deferral (n = 89, group A) or performance of PTCA (n = 96, group B). In the remaining 141 patients (group C) FFR was <0.75 and PTCA was performed anyway. Baseline and QCA characteristics were identical in all 3 groups. At follow-up of 9 ± 3 months event-rates were 3%, 9%, and 16% in group A, B, and C, respectively. Kaplan-Meier event-free survival at 1-year in group A, B, and C was 93%, 87%, and 84%, respectively. Improvement in average functional class during follow-up occurred in all groups and was similar in group A and B, but was significantly higher in group C.

Conclusions: In 43% of all patients, admitted for PTCA without documented proof of inducible ischemia (stress test negative, in-conclusive, or just not performed) inducible ischemia could still be proven by coronary pressure derived FFR < 0.75. These patients improved by PTCA. In the patients without ischemia, as concluded by FFR ≥ 0.75, performance as compared to deferral of PTCA did not improve event-free survival nor functional class.

1958 DEBATE II:fFinal results of the 6-month follow-up

P.W. Serruys[1], B. de Bruyne[2], E. Sousa[3], J.J. Piek[4], T. Muramatsu[5], C. Vrints[6], P. Probst[7], R. Seabra-Gomes[8], I. Simpson[9], V. Voudris[10]. *[1]Thoraxcenter Rotterdam; [4]Academisch Medisch Centrum, Amsterdam, Netherlands; [2]Cardiovascular Center, OLV Hospital, Aalst; [6]University Hospital Antwerp, Edegem-Antwerp, Belgium; [3]Instituto Dante Pazzanese, Sao Paulo, Brazil; [5]Kawasaki Central Hospital, Kawaka-Shi Kan, Japan; [7]Allgemeines Krankenhaus der Stadt Wien, Vienna, Austria; [8]Hospital Santa Cruz, Linda-A-Velha, Portugal; [10]Onassis Cardiac Surgery Center, Athens, Greece*

Abstract: The primary objective of the DEBATE II was to evaluate whether we can identify by QCA on-line (DS, Diameter Stenosis) and intracoronary flow velocity reserve (CFR) a population in which after optimal balloon angioplasty (OBA: DS < 35%, CFR > 2.5) stenting will not further improve the clinical outcome (MACE) and conversely a subgroup of pts in whom stenting should be preferred to balloon.



Conclusions: Stenting further improves the clinical outcome (97% vs 90%, Log Rank test, $p = 0.046$) of pts having undergone an optimal balloon angioplasty, raising the legitimate question as to whether all pts fulfilling the inclusion criteria in this trial should have been stented.

1959 DEBATE II: analysis of the flow velocity profile in the stented and non-stented, optimal and suboptimal groups

M. Albertal, G. Van Langenhove, P. Serrano, S.G. Carlier, M.A. Costa, J.L. Guermonprez, P.M. Schoefield, E. Verna, J.A. Belardi, P.W. Serruys. *On behalf of the Debate II investigators; Thoraxcenter and Cardialysis, Rotterdam, Netherlands; Hospital Broussais, Paris, France; Papworth Hospital, Cambridge, UK; Ospedale di Circolo, Varese, Italy; Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina*

Coronary flow reserve (CFR) has been shown to have a clinical predictive value after balloon angioplasty (BA). The aim of this study was to further analyze the flow velocity profile in various subsets of patients in the Debate II trial, in which the concept of provisional stenting is investigated.

Methods: 620 patients were randomized to guided balloon angioplasty or direct stenting (n = 97). Optimalization (DS% < 35% and a CFR > 2.5) of BA (OBA) was attempted in 84% (n = 523), successful in 38% (n = 200), generating 23% (n = 124) of bail-outs stenting and 34% (n = 183) of suboptimal results (SOBA). A second randomization further assigned the patients to additional stenting or no further treatment. We compared the resting (b) hyperemic (h) average peak velocities (APV) and CFRs in target and normal reference vessels (REF) of the 4 subrandomized patient groups: SO BA, OBA, without and with additional stenting (SOBA + S, OBA + S).

Results:

	SOBA N = 88	OBA N = 106	SOBA + S N = 112	OBA + S N = 77
DS (%)	22^{+}	23^{+}	7	8
Pts DS < 35%	87%	100%	93%	100%
Pts CFR < 2.5	94%	0%	99%	0%
b-APV (cm/s)	23*	17	22*	16
h-APV (cm/s)	43	45*	49^{+}	52^{+}
CFR	1.9	3*	2	3.2*
CFR REF	2.6	3*	2.5	3.2*
RelCFR (CFR/CFRREF)	0.8	1*	0.8	1.1
MACE 180 days	21.6%$^{*+}$	10.4%$^{+}$	7.1%	2.6%

* optimal vs suboptimal ($p < 0.05$). $^{+}$ stent vs balloon ($p < 0.05$)

Conclusion: 1) CFR is confirmed to be of prognostic value. 2) CFR of the target vessel following intervention seems to be related to the vasoregulatory function of the non-treated normal vessel. 3) The failure to normalize the CFR (<2.5) in the suboptimal group appears to be explained by a high b-APV, a finding which should be further elucidated.

ELECTROPHYSIOLOGICAL MODULATION BY CARDIOVASCULAR DRUGS

1973 Effects of metoprolol and atenolol on short-term resting heart rate variability in patients with unstable angina

Yu. A. Zuikov, I.S. Yavelov, O.V. Averkov, N.A. Vaulin, N.A. Gratsiansky. *Institute of Physico-Chemical Medicine, Moscow, Russian Federation*

It was previously suggested what lipophilic β-blockers (BB) due to their centrally-mediated action could enhance vagal activity to a greater degree than hydrophilic ones. In order to test this hypothesis an open comparative randomised trial was conducted on 75 patients (45 men) aged 35–69 years (mean 57.3 ± 8.4) with acute unstable angina (n = 65) and non-Q-wave myocardial infarction (n = 10). Mean of normal RR intervals (RRNN), very low (VLF; 0.003–0.04 Hz), low (LF; 0.04–0.15 Hz) and high (HF; 0.15–0.40 Hz) frequency powers together with LF/HF ratio were assessed on short ECG strips (512 RR intervals) at supine rest on admission and after 1 week of hydrophilic atenolol (n = 40) or lipophilic metoprolol (n = 35) use. Dose of BB was titrated to suppress symptoms of myocardial ischemia and to decrease heart rate below 60 bpm. Average daily dose of atenolol was 148 ± 70 mg, of metoprolol – 282 ± 137 mg. HRV parameters were compared with t-test after logarithmic transformation because of skewed data distribution.

		Atenolol (n = 40)	Metoprolol (n = 35)	p
Baseline	RRNN, ms	837 ± 143	837 ± 142	0.98
	ln (VLF, ms^2)	5.9 ± 1.1	5.9 ± 0.7	0.77
	ln (LF, ms^2)	5.5 ± 1.0	5.6 ± 0.8	0.84
	ln (HF, ms^2)	5.1 ± 1.0	5.1 ± 0.9	0.99
	LF/HF	1.7 ± 0.9	1.8 ± 0.9	0.65
1 week of BB therapy	RRNN, ms	1086 ± 145**	1036 ± 153**	0.13
	ln (VLF, ms^2)	6.1 ± 0.7	6.1 ± 0.8	0.96
	ln (LF, ms^2)	6.2 ± 0.7**	6.0 ± 0.6*	0.15
	ln (HF, ms^2)	6.2 ± 0.7**	5.9 ± 0.7**	0.08
	LF/HF	1.1 ± 0.5**	1.2 ± 0.5*	0.39

$^{*}p < 0.01$; $^{**}p < 0.001$ compared to baseline

Results are shown in the table (mean ± SD). Administration of both BB was associated with increase of RRNN, HRV and relative augmentation of vagal activity (decrease of LF/HF ratio). RRNN and HRV parameters did not differ between atenolol and metoprolol groups at admission and after 1 week of BB treatment. Thus in patients with acute unstable angina and non-Q-wave myocardial infarction atenolol and metoprolol exerted similar action on HRV obtained in standardised conditions.

1974 The comparative value of low-dose sotalol vs. metoprolol in the prevention of postoperative supraventricular arrhythmias

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Background: Supraventricular arrhythmias occur commonly following open heart surgery and can significantly prolong hospital stay or prompt thromboembolism. Although beta-blockers have been used successfully, sotalol with its beta-blocking and class III antiarrhythmic properties may be better suited for prevention of such arrhythmias. To test this hypothesis, we compared the efficacy and safety of low-dose sotalol with those of metoprolol.

Methods: In a prospective and double-blind fashion, 191 eligible, consecutive patients (mean age 64 years; 142 men) undergoing open heart surgery were randomly assigned to receive sotalol or metoprolol within 24 hours following extubation. Of these patients, 93 were treated orally with sotalol 40 mg, q 12 hours for one day and 80 mg b.i.d. for 5 days thereafter, while 98 patients received metoprolol 25 mg, q 12 hours for one day and 50 mg b.i.d. for the ensuing 5 days.

Results: Demographics and clinical characteristics did not differ between the two groups. Supraventricular arrhythmias occurred in 16% of all patients while atrial fibrillation was the commonest type. Length of hospital stay was longer among patients who developed supraventricular arrhythmias [9.2 ± 3.5 vs. 7 ± 4, P = 0.01]. A smaller number of patients developed supraventricular arrhythmias in the sotalol group [9 (10%) vs. 22 (22%); P = 0.028, chi square]. Non-sustained ventricular tachycardia was recorded in 2 patients in each group. There were no episodes of torsade de pointes and no deaths in either group. Bradyarrhythmias necessitating cessation of treatment occurred in 3 patients receiving sotalol (3.2%) and in 7 patients receiving metoprolol (7.1%); P = NS

Conclusions: Low-dose oral sotalol was used for short intervals following cardiac surgery without mortality or significant morbidity. Our data indicate that sotalol is well tolerated compared to metoprolol and is more efficacious in the prevention of supraventricular arrhythmias following open-heart surgery.

1975 Chronic amiodarone therapy does not increase epicardial dispersion of repolarization in the isolated porcine heart

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Drug-induced Torsades de Pointes are thought to propagate through reentry due to non-uniform prolongation of repolarization. The low arrhythmogenic potential of amiodarone has been related to a lack of increase in repolarization dispersion on the body surface but the effects at the epicardial level are not documented. Activation-to-recovery intervals (ARI) were mapped epicardially from 128 unipolar electrograms in isolated-perfused intact porcine hearts with an interelectrode distance of 2.5 mm. Group I consisted of 7 controls, Group II animals (n = 7) were fed with amiodarone 20 mg/kg/day over 30 days while Group III animals (n = 7) received 50 mg/kg/day. Myocardial concentrations of amiodarone and n-desethyl-amiodarone in Group II and III encompassed the values found in clinical studies.

Results: In control hearts, mean ARI was frequency dependent (from CL = 500 to 1500 ms) and peaked at 288 ± 14 ms at CL = 1000 ms. ARI dispersion (computed as ARIs SD) was frequency independent peaking at 8.9 ± 4.6 ms and generated smooth gradients that were mainly dipolar. In Group II, mean ARIs were longer than controls at all pacing CLs ($p < 0.05$) peaking at 325 ± 30 ms at CL = 1000 ms, ARI dispersion peaked at 11.3 ± 2.9 ms and was not statistically different from controls. In Group III, mean ARI were further prolonged mainly at long CLs and peaked at 390 ± 27 ms at CL = 1500 ms. Again, ARI dispersion was not different from controls peaking at 9.3 ± 2.7 ms.

In conclusion, Chronic Amiodarone induces Class III effects in ventricular porcine epicardium that are concentration dependent and reverse frequency dependent but does not affect dispersion of repolarization, this may explain in part its low arrhythmogenic potential.

1976 HERG potassium channels are a pharmacological target of the class III antiarrhythmic drug amiodarone

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The class III antiarrhythmic drug amiodarone is a potent therapeutic agent in the clinical management of ventricular tachycardias. Experimental data have shown that amiodarone inhibits the rapid component of the delayed rectifier potassium current (I_{Kr}) in native cardiomyocytes. In this study, we used the two-microelectrode voltage-clamp technique and the Xenopus-oocyte expression system to study the effects of amiodarone on cloned potassium channels encoded by the human ether-a-go-go related gene (HERG), which is the genetic basis of I_{Kr}.

Results: Amiodarone blocked HERG channels with an IC_{50} of 9.8 μM and a maximum outward tail current reduction of 62.8%. The block consisted of two main components; a closed channel block that could not be reversed within the time of experiments and an open channel block with a slow unblock, having a recovery time constant of 73 seconds at −80 mV. Inactivation of the HERG channels during strong inward rectification at very positive potentials could not prevent amiodarone block. The block of open channels was cumulative, voltage-dependent and use-dependent with stronger block at higher stimulation rates.

Conclusions: This study provides the first analysis about amiodarone effects on the cloned HERG potassium channel, which is an important target for the pharmacological therapy of arrhythmias. With respect to the desired antiarrhythmic effect of amiodarone, our results indicate that the drug is a potent blocker of closed, open and inactivated HERG channels. The profile of action of amiodarone on HERG, with a use-dependent block of open channels at high stimulation rates may explain the positive outcome of the clinical amiodarone trials regarding ventricular tachycardias.

1977 Lengthening of cardiac repolarization and block of the rapid component of the delayed rectifier potassium current by the phosphodiesterase V inhibitor, sildenafil (Viagra®)

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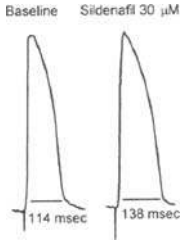
Several cases of unexpected death have been reported following use of sildenafil in patients predisposed to cardiac ischemic events due to their underlying pathology (coronary artery disease, diabetes). Although acute episodes of coronary ischemia could account for some of these deaths, we hypothesized that patients treated with sildenafil may also be at risk for pro-arrhythmia due to unsuspected cardiac electrophysiological effects of the drug. Studies were undertaken in 12 isolated, buffer-perfused guinea pig hearts which demonstrated prolongation of cardiac repolarization by sildenafil 30 μM (figure).



In addition, experiments using isolated guinea pig ventricular myocytes (n = 5) and HERG transfected human embryonic kidney 293 cells (n = 30) demonstrated block of the rapid component of the delayed rectifier K^+ current (I_{Kr}): activating current was 50% decreased at 100 μM.

Conclusions: Sildenafil possesses direct cardiac electrophysiological effects similar to class III antiarrhythmic drugs. These effects are observed at concentrations that can be found in conditions of impaired drug metabolism (e.g. during co-administration of another CYP3A4 substrate) or after drug overdose and form the basis of a new hypothesis to explain sudden death during sildenafil treatment.

1978 Electrophysiologic properties of endothelin receptor: a blockade in patients with coronary artery disease

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Endothelin-1 (ET-1) is a coronary vasoconstrictor, produced by endothelial cells. Animal studies have indicated that ET-1 may have significant electrophysiologic (EP) actions, independent of myocardial ischemia. We investigated the EP properties of ET_A blockade in patients (pts) with 1-vessel coronary artery disease.

Methods: Immediately after coronary angiography, a basic electrophysiologic study was performed before and after an intracoronary (ic) infusion of normal saline (NSAL) or BQ-123, a selective endothelin receptor-A antagonist (Clinalfa, CH) at a rate of 300 nmol/min for 20 min. BQ-123 or NSAL were administered randomly, in the non-diseased coronary artery. Statistical analysis was performed using t-test for dependent variables.

Results: 25 pts were studied. 14 pts (10 male, mean age 59 ± 9, mean EF: 56 ± 12%) received BQ-123 [left coronary artery (LCA): 8 pts, right coronary artery (RCA): 6 pts]. 11 pts (7 male, mean age 60 ± 9%) received NSAL [LCA: 7 pts, RCA 4 pts]. No complications were observed. No changes were found in heart rate, arterial blood pressure, or in basic conduction intervals.

	QT	QTc	CSNRT	ERP-AVN	ERP-RV
Baseline	373 ± 30	394 ± 36	258 ± 135	309 ± 87	226 ± 20
BQ-123	395 ± 20	421 ± 28	308 ± 96	300 ± 82	227 ± 18
p	0.0008	0.001	NS	NS	NS
Baseline	367 ± 16	401 ± 27	326 ± 109	286 ± 36	230 ± 18
NSAL	374 ± 23	406 ± 35	384 ± 47	283 ± 34	245 ± 16
p	NS	NS	NS	NS	NS

cSNRT: max corrected sinus node recovery time, ERP: effective refractory period, AVN: AV node, RV: right ventricle

Conclusions: In patients with 1-vessel coronary artery disease, high-dose ic ET-A receptor blockade causes QT interval prolongation, without affecting sinus or AV nodal function.

EMERGING THERAPIES FOR CARDIAC DISEASES: FROM BENCH TO BEDSIDE

1983 Adenovirus-based phospholamban antisense RNA expression as potential gene therapy approach for the improvement of diastolic dysfunction

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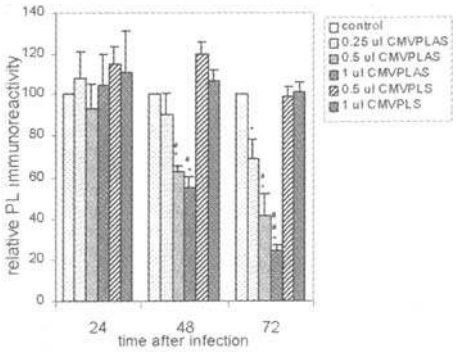
Background: Downregulation of the genes encoding the sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2) and the beta-adrenergic receptors is thought to be causally related to the disturbed myocardial Ca^{2+} homeostasis and beta-adrenergic signal transduction in heart failure. SERCA2 is inhibited by phospholamban (PL) so that SERCA pump activity should be enhanced by either SERCA gene transfer or by inhibition of PL expression. We have investigated the influence of adenovirus-mediated PL-antisense-mRNA expression in cardiac myocytes (CMC) on cellular Ca^{2+} homeostasis.

Methods: A set of CMV promotor-controlled recombinant adenovectors was developed expressing either a partial PL-sense-mRNA (Ad5CMVPLs) or an otherwise identical PL-antisense-mRNA (Ad5CMVPLas). A second set of vectors carried an endothelin-inducible ANF-promotor instead. Neonatal rat CMC were used as target cells, Ca^{2+} homeostasis was analyzed using published methods.

Results: (1) The PL-antisense vector Ad5CMVPLas suppressed endogenous PL-mRNA expression strongly starting on day 2. The control vector Ad5CMVPLs had no influence showing that the antisense vector effect is PL-specific. (2) The effect of the vector Ad5CMVPLas on endogenous PL-protein expression is summarized in fig. 1. There was a strong, time-dependent suppression of PL-protein content of the target CMC down to 20% of baseline on day 3. (3) High dose Ad5CMVPLas vector resulted in a significant stimulation of maximal Ca^{2+} uptake of the CMC at pCa 6.5.



Antisense phospholamban suppression.

Conclusions: Adenovirus-mediated transfer and expression of PL-antisense-mRNA results in a strong and specific suppression of the SERCA-inhibitor phospholamban in cardiac myocytes. This antisense strategy is a new potential gene therapy approach towards improvement of diastolic cardiac dysfunction.

1984 Increased heart function by S100A1 gene therapy

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The Ca^{2+} binding protein S100A1 is significantly downregulated in human end stage heart failure. Since this protein has been shown to enhance the caffeine induced Ca^{2+} release, we hypothesized that this finding might causally be related to altered Ca^{2+} transients in human cardiomyopathy. In order to better understand the intracellular function of S100A1, we established a model of S100A1 gene therapy in rabbit myocardium. S100A1 cDNA was cloned into an adenoviral shuttle behind a CMV-promotor, while green fluorescent protein (GFP) was introduced into the shuttle as reporter gene. S100A1 adenoviral infection of myocardium was performed with 2×10^{11} virus particles (n = 6 animals). Rabbits infected with empty virus (2×10^{11} virus particles; n = 6) and rabbits injected with saline (n = 11) served as controls. Efficacy of infection was controlled by GFP detection. Overexpression of S100A1 was confirmed by northern and western blotting. Hemodynamic data were gained on day 7 under basal conditions and isoproterenol stimulation (0.1, 0.5, 1 μg/kg/min iv). *Empty-virus* rabbits showed a reduced contractility +dP/dt (−10%; $p < 0.01$) and a decreased systolic ejection pressure SEP (−9%; $p < 0.02$) as compared to saline controls. This loss of contractility caused by the *empty virus* induced T-cell myocarditis was overcompensated by S100A1 adenoviral infection leading to an increase of +dP/dt by +18% ($p < 0.03$) and SEP by +11% ($p < 0.06$). Compared to saline controls S100A1 transgenic rabbits showed an increase of +dP/dt and SEP by 5% (n.s.). These data demonstrate for the first time that the S100A1 adenoviral gene transfer leads to an improvement of contractility and might thus be of great interest for gene therapy of heart failure.

1985 Cardiomyoblast-mediated ex vivo gene transfer into the infarcted myocardium

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Gene transfer to the heart for investigation and therapy of diseases is a rapidly expanding field with a potential clinical application. Introduction of therapeutic genes, such as those encoding for growth factors, into the ischemic myocardium may improve collateral circulation, enhance healing, function and viability. However, introduction of therapeutic genes into the infarcted myocardium is seriously limited because of the intense inflammatory response. We examined the possibility that cardiomyocytes could be genetically marked or modified before being grafted to the infarcted heart under conditions applicable to the clinical setting. In addition, we tested the hypothesis that this approach may be superior to direct injection of adenoviral vector. Rats were subjected to extensive myocardial infarction by permanent LAD coronary artery occlusion. We delivered a replication-defective recombinant adenovirus carrying the beta-galactosidase reporter gene (4x10E11 OD/ml) to cultured rat fetal cardiac myocytes. Almost all fetal cardiomyocytes in the primary culture expressed beta-galactosidase 24 hours after recombinant adenovirus transfection. These cells (1x10E6) were transplanted into the infarcted rat hearts 7 days after induced myocardial infarction (n = 3). Another group of infarcted rats (n = 3) was subjected to direct injection of adenovirus carrying the same reporter gene. Expression of the beta-galactosidase gene in the grafted cells was demonstrated by staining with X-gal, resulting in a blue color. Transgene expression was recognized 7 days after transplantation and was significantly greater than expression achieved by direct injection of adenovirus into myocardial infarction.

Conclusions: Our findings demonstrate that ex vivo gene transfer to the infarcted myocardium is feasible and significantly more efficient than direct adenoviral vector mediated gene delivery. Our results suggest that the ex vivo approach may eliminate one of the major hurdles facing the application of gene therapy to myocardial infarction.

1986 Growth hormone attenuates pathologic remodelling and decreases myocardial noradrenaline content in the rats with postinfarct heart failure

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Background: Increasing experimental evidence suggests that growth hormone (GH) may have beneficial effects in the treatment of heart failure. However, the mechanisms behind these positive effects are poorly understood. The aims of this study were: 1) to investigate the effects of GH on cardiac function, remodeling and energy metabolism in the postinfarct phase 2) to evaluate the effect of GH on myocardial noradrenaline content.

Methods: Myocardial infarction (MI) of left ventricular (LV) anterolateral wall was induced by ligation of the left coronary artery in male Sprague-Dawley rats (200–250 g). Three different groups were studied: MI rats treated with GH (GH, n = 11) (3 mg/kg/day), MI rats placebo treated (P, n = 10), and sham operated rats (S, n = 7). All rats were investigated with transthoracic echocardiography and ^{31}P magnetic resonance spectroscopy (for estimation of myocardial energy status) at 3 days and 3 weeks after MI. Myocardial catecholamines content was analyzed by high performance liquid chromatography with electrochemical detection.

Results: The results are summarized in the table. Treatment with GH attenuated increase in LV volumes and improved LV systolic function. Myocardial content of noradrenaline was markedly decreased (42%) in the GH group compared to P.

	ΔEF %	ΔEDV ml	ΔESV ml	LV/BW mg/g	NA ng/g
GH	$6.6 \pm 5.2^{*}$	$15.1 \pm 2.1^{*}$	$9.3 \pm 1.5^{*\#}$	2.5 ± 0.05	$385 \pm 37^{*\#}$
P	-15.6 ± 6.6	$24.3 \pm 2.5^{\#}$	$17.6 \pm 2.3^{\#}$	2.4 ± 0.06	661 ± 86
S	1.6 ± 5.2	8.7 ± 2.2	3.1 ± 1.5	2.8 ± 0.09	583 ± 67

EF = ejection fraction, EDV = end distolic volume, ESV = end systolic volume, LV/BW = left ventricular index, NA = noradrenaline, * = $p < 0.05$ v. Placebo; # = $p < 0.05$ v. sham

Conclusion: GH attenuates pathological remodeling and improves systolic function of LV without induction of LV hypertrophy. The marked decrease in myocardial content of NA after GH treatment may protect myocardium from adverse effect of catecholamines during postinfarct remodeling phase.

1987 Pharmacokinetics of recombinant fibroblast growth factor-2 after intracoronary administration in patients with severe coronary artery disease in a phase I study

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Background: FGF-2, a powerful mitogen capable of inducing angiogenesis in animal models, has undergone Phase I testing in patients with severe coronary artery disease (CAD) who remain symptomatic despite optimal medical management and are suboptimal candidates for standard revascularization procedures.

Methods: In a dose-escalation protocol, rFGF-2 was delivered as a single 20 minute infusion divided between two major sources of coronary blood supply. Doses (ug/kg) studied were 0.33 (n = 4), 0.65 (n = 4), 2 (n = 8), 6 (n = 4), 12 (n = 4), 24 (n = 8), 36 (n = 10), 48 (n = 10). Patients were pretreated with 40 U/kg heparin 1–95 min before the start of the rFGF2 infusion. Concentrations of rFGF-2 in the EDTA plasma samples were measured by a commercially available ELISA.

Results: The rFGF-2 plasma concentrations followed a bi-exponential curve with an initial (first hour) steep decline over several log scales (distribution phase), followed by a more moderate decline (elimination phase). Peak rFGF-2 plasma levels increased proportionally with dose from approximately 1 to 1000 ng/mL, and areas under the plasma concentration-time curves (AUC) increased linearly with dose. The mean (±SD) value for the terminal elimination half-life ($T_{1/2}$) was 1.9 ± 2.2 hr; for the elimination clearance (CL) was 264 ± 150 mL/hr/kg; and for the volume of distribution (V_{ss}) was 184 ± 74 mL/kg. Across patients, greater systemic rFGF-2 exposure (AUC) was observed when heparin pretreatment was given closer to the start of the rFGF-2 infusion. This is consistent with slower clearance of circulating heparin/FGF-2 complexes.

Conclusions: The pharmacokinetics of rFGF-2 after a single intracoronary dose of rFGF-2 in patients with CAD were linear and predictable.

NEW ASPECTS OF ENDOTHELIAL DYSFUNCTION IN HEART FAILURE

1993 Improvement of endothelial dysfunction in patients with congestive heart failure during treatment with carvedilol

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Congestive heart failure (CHF) is a condition with endothelial dysfunction, where antioxidants has been shown to improve forearm blood flow via endothelium dependent mechanisms. Carvedilol, a non-selective, vasodilating beta-blocker, with antioxidant properties, might therefore be beneficial on endothelium-dependent regulation of vasomotion. The thesis was tested in a randomized, double-blinded, placebo-controlled study.

Methods: We randomised 60 patients with CHF (EF 31 ± 8,NYHA II-III) to receive either carvedilol (C), n = 40, 25 mg b.i.d. or placebo (P), n = 20 additional to standard therapy. Measurements of brachial artery diameter were done utilizing 7.0 MHz vascular probe, and were performed at rest, during reactive hyperemia (an endothelium-dependent stimulus to vasodilaion = Flow Mediated Dilation (FMD)), after 10 minutes resting, and finally after administration of sublingual nitroglycerin (an endothelium-independent vasodilation = Nitroglycerin Induced Dilation (NID)). FMD and NID were calculated in relation to resting diameters (mean of 16 measurements) before (Pre) and after (Post) 23 weeks therapy. Seven patients (5 C, 2 P) dropped out of the study, and tapes from 3 patients (2 C, 1 P) were not readable. The groups were comparable by age, blood pressure, cholesterol, blood glucose and HbA1C (see table).

	Carvedilol (n = 33)	Placebo (n = 17)
FMD% Pre	2.06	2.41
FMD% Post	6.28*	2.32
NID% Pre	13.9	13.5
NID% Post	15.0	13.3

*P = 0.003 vs placebo, values are mean.

Conclusion: Carvedilol appears to improve endothelial function in patients with CHF. A general improvement in endothelial function during treatment with carvedilol, could contribute to the decrease in mortality, which has been shown earlier. However, further prospective studies should be performed to clarify the importance of reversing endothelial dysfunction.

1994 Improvement in vascular endothelial function in patients with heart failure treated with β-blockers

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In patients with chronic heart failure long term administration of beta-blockers induces clinical and haemodynamic improvements. Even if the beneficial effect of ACE inhibitors (ACEI) on the endothelial function was proved, little is known about the effect of beta-blockers on the vascular endothelial function in patients with heart failure.

We hypothesized that chronic beta-blockade in heart failure could have a beneficial effect on the peripheral vascular endothelial function as manifested by the improvement of percent increase of brachial artery diameter following 5 min. of upper arm arterial occlusion.

Methods: We included 45 patients with chronic heart failure (NYHA class more than II, EF 27% ± 7.5). They were randomized in 2 groups of treatment: group A treated with ACEI and group B treated with ACEI + Metoprolol in progressively increasing doses. The two groups had similar baseline characteristics. At inclusion and after 16 months of treatment the percent change in brachial artery (%BA) diameter after 5 min. of upper arm blood pressure cuff occlusion was measured using a 7.5 MHz echographic transducer.

Results: At baseline both groups had similar%BA (6.45% ± 5.5 vs. 6.37% ± 5.7; p: NS). After 16 months follow-up%BA in group A was 10.3% ± 4.7 ($p < 0.01$ vs. baseline) and in group B was 13.7% ± 5.2 ($p < 0.01$ vs. baseline and $p < 0.05$ vs. group A).

Conclusion: Chronic administration of beta-blockers (Metoprolol) could enhance the improvement of endothelial-dependent vasodilatation obtained in patients with heart failure treated with ACEI.

1995 Antioxidative treatment reduces endothelial cell apoptosis induced by congestive heart failure serum

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Congestive heart failure (CHF) is associated with increased serum levels of proinflammatory cytokines. Apoptosis of endothelial cells induced by proapoptotic cytokines could contribute to endothelial dysfunction observed in patients with heart failure. We measured apoptosis rates of endothelial cells exposed to serum of CHF patients and determined the effect of antioxidative treatment.

Results: In endothelial cell culture, application of serum of patients with CHF induced apoptosis ($p < 0.05$ vs. healthy volunteers). Endothelial cell apoptosis was significantly correlated with clinical NYHA staging of patients ($p < 0.05$) and with TNFα serum levels as a marker of proinflammatory activity ($p < 0.001$). Coincubation with either vitamine C (100 μM) or the antioxidative β-blocker carvedilol (5 μM), which improves the clinical performance of patients with CHF, suppressed the proapototic activity of CHF serum ($p < 0.005$ and $p < 0.001$, respectively), whereas the β-blocker propranolol had no effect. Apoptosis induction in endothelial cells by TNFα (50 ng/ml) was as well antagonized by vitamine C or carvedilol. To demonstrate the *in vivo* relevance of antioxidants as mediators of endothelial cell survival in CHF, we treated heart failure patients with vitamine C. Serum drawn from patients following a 3 day treatment with 2.5 g oral vitamine C per day lead to significantly lower proapoptotic activity in cultured endothelial cells compared to serum of the same patients before treatment ($p < 0.05$).

In conclusion, these data suggest that endothelial cell apoptosis induced by activation of the proinflammatory cytokine cascade could be involved in the pathophysiology of endothelial dysfunction in CHF. The antiapoptotic activity of antioxidants such as carvedilol or vitamine C on the endothelium could contribute to their beneficial effect in heart failure.

1996 Endothelial dysfunction secondary to oxidative stress impairs left ventricular relaxation in pressure-overload hypertrophy

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Endothelium-derived NO enhances LV relaxation via direct effects on cardiac myocytes. We have previously shown that the NO-mediated LV relaxant effect of bradykinin (BK) and substance P (sub P), is blunted in guinea pigs with compensated pressure-overload LVH, 3 weeks after aortic banding. In this study, we investigated potential underlying mechanisms. The expression of eNOS protein in whole LV homogenate (Western blot) was similar in banded (n = 6) and sham-operated (n = 5) animals (7.6 ± 0.5 vs 7.8 ± 1.0 densitometric units respectively; P = NS). Isolated ejecting hearts of banded animals were studied at varying pre-load, constant afterload and constant, paced heart rate. LV pressure was measured by a 2F Millar catheter. Changes in the timing of onset of LV relaxation, assessed by the time to dP/dt_{min} (TdP/dt_{min}, ms), after addition of sub P (100 nM) or BK (10 nM) were measured with and without pre-treatment with the anti-oxidants vitamin C (vit C, 10 μM) or deferroxamine (Def, 0.5 mM).

Results are shown below.

$\Delta TdP/dt_{min}$ (ms)		+Vit C	+Def
Sub P	0.9 ± 1.9	−5.9 ± 1.5*	−8.9 ± 2.2*
BK	−3.4 ± 1.8	−8.8 ± 1.5*	−8.3 ± 1.3*

$n \geq 6$ in each group. All values ± SEM. *P ≤ 0.05 vs sub P/BK alone

Neither vit C nor Def had an effect on LV pressure, dP/dt_{max} or coronary flow. Thus, acute administration of anti-oxidants restored the ability of sub P and BK to enhance LV relaxation in LVH.

Conclusions: 1) cardiac endothelial dysfunction associated with pressure-overload LVH may be secondary to increased oxidative stress and decreased bioavailability of NO; 2) endothelial dysfunction impairs NO-mediated enhancement of LV relaxation.

1997 Asymmetrical-dimethyl-arginine, an inhibitor of the nitric oxide synthase: relation to endothelium-mediated vasodilation and peak oxygen consumption in patients with chronic heart failure

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Flow-dependent, endothelium-mediated vasodilation (FDD) is reduced in patients with chronic heart failure (CHF) possibly due to reduced formation of nitric oxide (NO) from ist precursor L-arginine. We hypothesized that plasma levels of asymmetrical-dimethyl-arginine (ADMA), a competitive antagonist of L-arginine, are increased in CHF leading to reduced availability of NO. Accordingly, FDD of the radial artery was determined in 37 patients with CHF (NYHA III) and 27 healthy controls (N). Diameter (high resolution ultrasound; precision 2 μm) and blood flow (BF; ml/min) were measured at rest and after wrist occlusion (8 min). Plasma levels of L-arginine and ADMA were measured using HPLC, L-arginine/ADMA ratio was calculated. Peak oxygen consumption was determined by spiroergometry.

	FDD (%)	ADMA (μmol/l)	L-arginine/ ADMA-ratio	peak oxygen consumption (ml/kg/min)
Normals	15.3 ± 0.6	0.99 ± 0.1	106 ± 7	40.1 ± 2.2
CHF	7.1 ± 0.7*	4.16 ± 0.6*	24 ± 6*	14.7 ± 0.6*

(all data mean ± SEM; *p < 0.01 vs. N).

There was an inverse correlation between ADMA plasma levels and FDD ($r = -0.79$; $p < 0.01$) and between ADMA plasma levels and peak oxygen consumption ($r = -0.72$; $p < 0.01$) and a positive correlation between L-arginine/ADMA-ratio and FDD ($r = 0.85$; $p < 0.01$) respectivly peak oxygen consumption ($r = 0.75$; $p < 0.01$).

Conclusion: In patients with chronic heart failure plasma levels of the NO-synthase inhibitor ADMA are increased up to 400%. There is an inverse correlation to endothelium-mediated vasodilation and peak oxygen consumption.

1998 Spironolactone suppresses vascular ACE and improves endothelial dysfunction in patients with chronic heart failure

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Background: The RALES study has shown that spironolactone, when added to conventional therapy for chronic heart failure, has an added beneficial effect on cardiovascular mortality. We wished to test the hypothesis that this benefit was in part due to improvement in endothelial dysfunction and/or increased suppression of the vascular renin-angiotensin axis.

Methods: A randomised, placebo controlled, double-blind cross-over study was performed on 10 patients with NYHA Class II–III chronic heart failure taking standard diuretic/ACEI therapy, comparing 50 mg spironolactone daily (1 month) vs placebo. Brachial artery endothelial function was assessed by bilateral forearm venous occlusion plethysmography using *acetylcholine* and *N-monomethyl-L-arginine*, with *sodium nitroprusside* as a control vasodilator. In addition, vascular ACE activity was assessed using *angiotensin I*, with *angiotensin II* as a control vasoconstrictor.

Results: Spironolactone significantly increased the forearm blood flow response to acetylcholine (percentage change in forearm blood flow (mean ± SEM): 177 ± 29% vs 95 ± 20% spironolactone vs placebo; $p < 0.001$), with an associated increase in vasoconstriction observed with L-NMMA (−18 ± 4% vs −35 ± 6% placebo vs spironolactone; $p < 0.05$). There was no significant difference in blood flow between treatments with regards to nitroprusside (290 ± 98% vs 281 ± 47% placebo vs spironolactone; p = NS). The angiotensin I response between treatments was also significantly reduced with spironolactone (−42 ± 8% vs −35 ± 8% placebo vs spironolactone; $p < 0.05$), with no statistical differences observed with the control vasoconstrictor angiotensin II.

Conclusion: Spironolactone improves endothelial dysfunction and inhibits vascular ACE in patients with chronic heart failure. This provides a novel mechanism for its beneficial effect on cardiovascular mortality.

NEW ANTIPLATELET TREATMENTS IN UNSTABLE ANGINA AND ACUTE MYOCARDIAL INFARCTION

2012 Evaluation of combination therapy with tirofiban and enoxaparin in patients with unstable angina and non-Q-wave myocardial infarction

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Tirofiban (T) (AGGRASTAT®) an intravenous platelet GP IIb/IIIa antagonist, and enoxaparin (E) (LOVENOX®, CLEXANE®), a low molecular weight heparin, have been shown to be effective at reducing cardiac ischemic events in separate trials of unstable angina and non-Q wave MI (UA/NQMI). The combination of these agents may offer further therapeutic benefit. The present study randomized patients with UA/NQMI to double-blind treatment with T (0.1 μg/kg/min iv) for 48–108 hours coadministered with either E (1 mg/kg sc q 12 h) (n = 26) or unfractionated heparin (UH) (iv adjusted to aPTT) (n = 27) to evaluate pharmacodynamics and safety. Coadministration of T and E was generally well tolerated. No patient discontinued T and E treatment due to adverse events. Administration of T with E vs UH resulted in lesser variability and a trend towards greater inhibition of platelet aggregation (IPA) using 5 μM ADP agonist.

Median IPA%	T and E (N = 25)	T and UH (N = 24)	p-value
Hour 24	88.0	83.9	0.06
Hour 30	88.8	86.4	0.10
Hour 48	87.6	83.5	0.05
Average	87.1	85.4	0.08

More patients achieved target IPA > 70% in the T + E group (88% vs 62%, p = 0.05). Median bleeding time (BT) was 21 minutes for T + E vs ≥30 minutes for T + UH (p = NS). For a given level of IPA, BT was less prolonged with T + E than T + UH (adjusted mean BT 19.9 vs 24.6 minutes, p = 0.03). There was an increase in nuisance cutaneous bleeding in the T + E group (46% vs 18%). However, there were no major or minor bleeding events in either group by the TIMI criteria.

Conclusions: The lower adjusted BT and more consistent IPA of T + E vs T + UH support the therapeutic potential of combining these two agents. These data are consistent with prior data which show differential pharmacodynamic effects of E and UH on platelet aggregation.

2013 First report of an intravenous and oral glycoprotein IIb/IIIa inhibitor administered in patients: results of TIMI 15B

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Background: Intravenous platelet glycoprotein IIb/IIIa receptor blockade is beneficial in high-risk unstable angina and angioplasty. RPR 109891 is a unique competitive inhibitor because it is available in both IV and oral formulations.

Methods: We performed a phase II double-blind placebo- controlled dose-ranging trial in patients with acute coronary syndromes who were randomized to 24–96 hrs of IV RPR 109891 followed by 1 of 6 different doses of oral RPR 109891 for 1 mth vs IV placebo followed by oral placebo. Inhibition of platelet aggregation (IPA) to ADP-20 uM and receptor occupancy (RO) were measured in 110 pts; plasma drug levels and safety information were collected in all patients.

Results: 192 patients (median age 60 years, 75% men, 49% with UA) were enrolled in 4 countries. Preliminary results (aggregate data for all patients including those receiving placebo) were as follows: at end of IV infusion the median IPA was 83%, while median IPA 4 hours post oral drug was 43%. Median RO was 86% at end IV infusion and 82% 4 hours post oral drug. Major hemorrhage occurred in 9 patients (4.7%) during the IV phase and in 7 patients (4.2%) during the oral phase. Thrombocytopenia (<90 K) occurred in 23 pts (11.9%), of which 9 pts had associated bleeding. Unblinded data by dose group will be available after March 1999 and will be presented.

Conclusions: A strategy of IV followed by oral GP IIb/IIIa inhibition with RPR 109891 can achieve moderate-high degrees of platelet inhibition, although poor bioavailability and thrombocytopenia represent challenges to its oral administration.

2014 Which patients should receive abciximab in the contemporary stent era?

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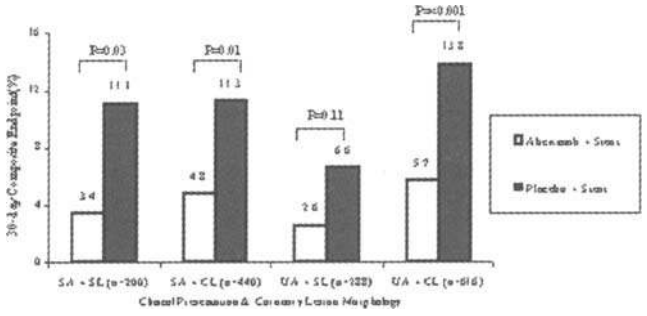
Background and Objective: While abciximab, a potent IIb/IIIa inhibitor, is effective at reducing ischemic events during PCI, its use in the contemporary stent era has been limited by cost issues. With this in mind, we reviewed the largest prospective stent trial (EPISTENT) to discern which stent patients derive greatest benefit from adjunctive IIb/IIIa therapy. To simplify patient selection during stenting, we categorized patient as having stable angina (SA) or unstable angina (UA) and as having a simple [type A,B1] lesion (SL) or complex [type B2,C] coronary lesion (CL).

Methods and Results: Of the 2305 EPISTENT patients with stable or unstable angina, 760 were randomized to stent plus abciximab and 784 to stent plus placebo. The addition of abciximab provided a marked reduction in clinical events (30-day death, MI, urgent revasc) in both stable and unstable angina patients (Figure). Abciximab therapy provided the highest risk group (UA+CL) a 59% relative and 8.1% absolute risk reduction (13.8% vs 5.7%, p = 0.001) and the lowest risk group (SA+SL) a 69% relative and 7.7% absolute risk reduction (11.1% vs 3.4%, p = 0.03). Importantly, these absolute and relative benefits persisted at 6 months.



Outcomes by angina and lesion definition.

Conclusion: The use of abciximab in conjunction with stents substantially improves clinical outcome in a wide spectrum of patients with a large relative (~50%) and absolute (~8%) reduction in adverse clinical events. Though cost remains an important issue, the strikingly similar benefit in high-risk and low-risk patients makes it difficult to preferentially recommend abciximab therapy for a specific group of stent patients.

2015 Bailout use of abciximab in complicated PTCA: results from the Italian registry RICORDA (Registro Italiano sulle COndizioni d'uso di Reopro Durante Angioplastica)

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Aim: The R.I.CO.R.D.A. registry was created with the aim of monitoring the early Italian experience on the clinical use of abciximab (ReoPro) in the setting of high risk coronary angioplasty (PTCA). Indications for enrollement included clinical presentation (acute myocardial infarction (MI), unstable angina), complex coronary anatomy (type C lesions, diffuse coronary disease, intracoronary thrombosis), or procedural factors, such as deployment of long or multiple stents, coronary dissection, acute coronary occlusion, etc. Abciximab administration was either elective (i.e. pre-PTCA) or in the course of a complicated precedure (bailout administration).

Results: From June 1996 to January 1998, 359 patients undergoing PTCA on 443 lesions were enrolled in 24 catheterization laboratories. In 91/359 patients (25%), abciximab was administred as bailout, and in the remaining cases as a pre-treatment before PTCA. The incidence of death, coronary artery bypass grafting (CABG), Q wave and large non-Q wave MI, small non-Q wave MI and recurrent ischemia in the elective group were 1.9%, 1.9%, 2.6%, 6.7% and 3.4%, respectively. In the bailout group, corresponding figures were 4.4% (ns), 3.3% (ns), 16.5% ($p < 0.01$), 16.5% ($p < 0.01$), and 12.1% ($p < 0.01$). Heparin dose during PTCA was quite variable. Overall, 46% of patients were administered a dose of heparin 5,000 U or less, while the remaining received a higher dose, more often 10,000 U. As expected, the latter group showed a significantly higher incidence of bleeding complications (25% vs 10%; $p < 0.01$). The incidence of bleeding was almost double in patients treated with abciximab in bailout (29% vs 15%; $p < 0.01$), due to the higher heparin dose used in this group (mean ± SD: 9,253 ± 3,341 U vs 6,649 ± 3,156 U; $p < 0.01$).

Conclusions: Bailout use of abciximab occurred in a quarter of patients enrolled in this registry. The incidence of adverse cardiac events and bleeding complications in the elective abciximab group was comparable with that reported in the major large scale international trials. The bailout group showed a higher incidence of both cardiac events and bleeding complications.

2016 Remarkable consistency of benefit of ADP receptor blockade compared with aspirin across a variety of endpoints, including avoidance of rehospitalization

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In a large, international trial of 19,185 patients with atherosclerotic vascular disease, the ADP receptor antagonist, clopidogrel, was compared with aspirin for the primary outcome cluster of vascular death, ischemic stroke, or myocardial infarction (MI). Although an 8.7% relative-risk reduction (RRR) was noted for the overall trial primary endpoint, important secondary endpoints had not been ascertained. This is especially true in the case of repeat hospitalizations in such patients, which represent a considerable economic burden and may further reflect efficacy in an active-control comparison of antiplatelet agents.

Results: RRRs and the 3-year event rates for clopidogrel vs. aspirin are shown below (on-treatment analysis) (see table).

Endpoint	3-year event rates	RRR (p-value)
Stroke (all causes, fatal/non-fatal), MI (fatal/non-fatal)	Clopidogrel 10.32% Aspirin 12.14%	12.2 (0.017)
Death (all causes), non-fatal stroke (all causes), MI	Clopidogrel 14.35% Aspirin 15.71%	7.2 (0.113)
Vascular death, non-fatal stroke (all causes), MI, hospitalization for angina, TIA or limb ischemia	Clopldogrel 26.24% Aspirin 27.72%	7.4 (0.022)

There was a significant reduction of 9.3% in the incidence of rehospitalization for clopidogrel compared with aspirin (13.9% vs 15.3%; p = 0.032), and this was consistent across individual outcomes of unstable angina, transient ischemic attack (TIA), or limb ischemia. By multivariate analysis for reduction of vascular death, stroke, MI, or hospitalization, clopidogrel therapy was an independent predictor (p = 0.015).

Conclusions: The use of clopidogrel led to a highly consistent demonstration of superiority over aspirin, and both confirmation and extension of this benefit is reflected in the avoidance of hospitalizations related to atherosclerotic disease.

2017 A whole blood assay for ex vivo monitoring of glycoprotein IIb/IIIa antagonists

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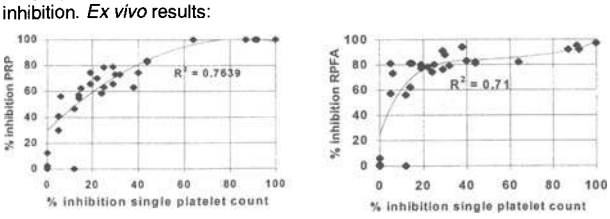
Background: Platelet rich plasma (PRP) turbidimetry, the standard method for monitoring GPIIb/IIIa antagonists, has many limitations and only measures inhibition of platelet macroaggregation. We have used a whole blood (WB) assay for monitoring inhibition of microaggregation, comparing this with PRP turbidimetry, WB impedance aggregometry and Accumetrics Rapid Platelet Function Assay (RPFA).

Methods: *In vitro* studies were performed to assess the effects of fradafiban, an intravenous GPIIb/IIIa antagonist, on platelet aggregation in WB and PRP using ADP 30 μM as agonist, in order to validate a WB assay based on single-platelet counting. *Ex vivo* studies were performed on blood from patients with unstable angina (n = 8) randomised to receive either oral lefradafiban (the prodrug of fradafiban) or placebo. Blood samples were taken before and during treatment and analysed by 4 methods: (1) PRP turbidimetry (2) WB impedance aggregometry (3) RPFA, Accumetrics (4) WB single-platelet counting assay.

Results: There was good correlation between PRP turbidimetry, RPFA and single-platelet counting assay inhibition values ($R^2 > 0.7$). Impedance aggregometry showed complete inhibition at low levels of GPIIb/IIIa blockade. Single-platelet counting and RPFA were most discriminating at high levels of inhibition. *Ex vivo* results:



Conclusion: The whole-blood single-platelet counting assay is an ideal tool for monitoring GPIIb/IIIa antagonists in the predicted therapeutic range, providing information on inhibition of microaggregation.

ECHO DOPPLER INSIGHTS INTO LEFT VENTRICULAR FILLING

2018 Evaluation of left ventricular diastolic function by the ratio of maximal flow velocity of the early filling wave to its propagation velocity

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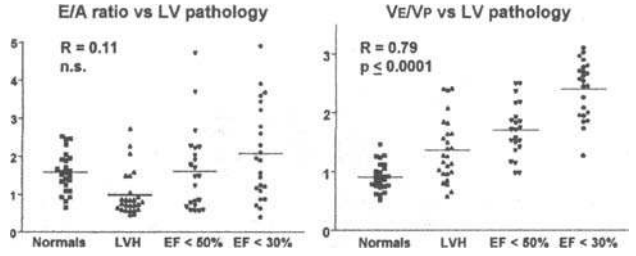
Active left ventricular relaxation creates a small intraventricular gradient which determines the propagation velocity of the early filling wave from the base of the left ventricle to the apex (V_P), which can be assessed by color M-Mode echocardiography. Impaired relaxation will reduce V_P and cause vortex formation as blood flow entering the ventricle interacts with stagnant blood within the cavity. In this case maximal particle velocity during early filling (V_E), assessed by pulsed wave Doppler, will significantly exceed V_P. We therefore hypothesized that the ratio of V_E to V_P will be directly correlated to the severity of left ventricular pathology and examined 96 consecutive subjects: 25 normals, 26 patients with LVH, and 45 patients with reduced EF. While the E/A ratio showed an expected U-shaped relation to the severity of LV pathology, V_E/V_P showed a direct linear correlation. Out of 24 patients with a $V_E/V_P > 1.85$ 19 patients (79%) had either a history of pulmonary congestion or developed it within 6 months.



Conclusion: V_E/V_P is a parameter of diastolic function which increases directly with the severity of left ventricular pathology and potentially predicts outcome.

2019 Different effect of inotropic stimuli and preload changes on intraventricular pressure gradients during rapid early left ventricular filling

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Objectives: This study investigates mechanisms of LV intracavitary early diastolic flow.

Methods: In twelve anaesthetised dogs we measured LV pressures at the mitral tip and in the apex, intraventricular velocities by color M-mode Doppler, and LV volume by sonomicrometry. We investigated responses to isoprenaline, to ischaemic LV failure by coronary microembolization, and to changes in preload by volume loading.

Results: Modulation of LV inotropy caused marked changes of the early diastolic mitral-to-apical pressure gradient, from 1.4 ± 0.6 to 3.2 ± 1.8 ($p < 0.05$) after isoprenaline and to 0.6 ± 0.5 mmHg ($p < 0.05$) after coronary micro-embolization, and inflow tract peak velocity increased from 0.51 ± 0.03 to 0.71 ± 0.13 m/s ($p < 0.05$) and decreased to 0.35 ± 0.10 m/s ($p < 0.05$), respectively. Volume loading, however, did not change the mitral-to-apical pressure gradient, although inflow tract velocity increased moderately from 0.56 ± 0.08 to 0.65 ± 0.09 m/s ($p < 0.05$). The different responses to increased inotropy and increased preload were associated with opposite effects on LV end-systolic volume and time constant of isovolumic relaxation (tau), which both decreased ($p < 0.05$) with isoprenaline and increased ($p < 0.05$) with volume loading.

Conclusions: Inotropic stimuli modified intraventricular flow and the mitral-to-apical driving pressure by changing the rate of LV relaxation, and appeared to enhance apical suction. Elevation of preload did not change the mitral-to-apical pressure gradient, and the increased flow velocities were attributed to increased left atrial pressure. These findings have implications for how to interpret intraventricular filling patterns in a clinical context.

2020 Changes in filling dynamics and stroke volume due to atrial relaxation during early diastolic transmitral flow acceleration

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Atrial relaxation (AR) during early diastolic transmitral flow acceleration (ED-Facc) may change filling dynamics and stroke volume (SV).

Methods: To analyse these changes micromanometric transmitral pressure gradient (TMPG), pulsed wave Doppler transmitral flow velocity profile and SV were measured and compared in EDFacc with and without AR in AV blocked, AV paced (80 bpm) dogs (N: 17).

Results: The duration and time integral of positive early diastolic TMPG decreased (37.6 ± 15.2 ms vs. 65.3 ± 17.0 ms, $p < 0.001$; 4.5 ± 59.9 mmHg*ms vs. 90.9 ± 58.1 mmHg*ms, $p < 0.05$; mean ± SD), but the reversed early diastolic TMPG did not change significantly (113.5 ± 35.0 ms vs. 108.2 ± 38.9 ms, NS; 89.1 ± 62.7 mmHg*ms vs. 85.2 ± 59.6 mmHg*ms, NS), EDFacc time shortened (41.9 ± 12.8 ms vs. 55.6 ± 12.6 ms, $p < 0.05$), EDFacc increased (996.1 ± 471.8 cm/s^2 vs. 823.6 ± 227.8 cm/s^2, $p < 0.05$), peak velocity fell (36.9 ± 8.5 cm/s vs. 43.9 ± 8.0 cm/s, $p < 0.05$), deceleration time did not change significantly (128.8 ± 33.4 ms vs. 131.2 ± 36.6 ms, NS), deceleration decreased (306.7 ± 120.3 cm/s^2) vs. 362.4 ± 128.8 cm/s^2, $p < 0.05$) and SV was smaller (67.8 ± 10.0% vs. 100%, $p < 0.001$) in EDFacc influenced by AR.

Conclusion: AR during EDFacc has unfavourable effect on filling dynamics and on SV explaining the hemodynamic background in some severe pacemaker syndrome.

2021 Propagation velocity of mitral inflow by colour M-mode is not independent of loading conditions in congestive heart failure

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Background: Interpretation of LV diastolic function is confounded by load-dependence of parameters used to asses it. The propagation velocity (PV) of mitral inflow into the LV has been proposed as a load-independent descriptor of LV diastolic function. Accurate assessment of diastolic function is especially advantageous in systolic dysfunction.

Methods: We examined changes in PV induced by sublingual nitroglycerin (NTG) 1.2 mg, an intervention known to decrease LA pressures. Twenty-one patients with LVEF < 40% by 2-D echo were included, while non-sinus rhythm, significant aortic valve disease, mitral stenosis or prosthesis were excluded.

Results: Age was 63 ± 14 (38–90) yrs, 5 were women, and 11 had an ischemic etiology. Mean LVEF was 32 ± 6 (21–40)%. At baseline, there was a significant correlation between E-velocity and PV (r = 0.69). Changes induced by NTG are shown in the Table. A significant decrease in E/A velocity ratio and an increase of E-wave deceleration time demonstrated that NTG succesfully lowered LA pressure. Similarly, pulmonary venous peak systolic-to-diastolic flow velocity ratio (S/D) increased. Heart rate was unchanged. Propagation velocity significantly decreased after NTG. No differences in response of PV to NTG was observed between ischemic and idiopathic etiology.

	E/A	E dec.time	S/D	PV (cm/s)	heart rate
Basal	1.9 ± 0.3	171 ± 10	0.9 ± 0.1	26 ± 2	66 ± 2
NTG	1.4 ± 0.2	203 ± 14	1.3 ± 0.1	22 ± 2	67 ± 3
% change	27	18	40	13	
P	0.005	0.002	0.004	0.03	NS

Changes induced by 1.2 mg NTG sublingually (mean ± SEM)

Conclusion: We found a decrease of PV after an intervention known to decrease LA pressure. This suggests that PV and LA pressure are positively correlated. It may be speculated that decreased PV after NTG is related to decreased atrio-ventricular pressure gradients.

Our findings indicate that PV may be subject to similar drawbacks as are the conventional parameters of LV diastolic function in congestive heart failure.

2022 Ratio of left ventricular peak E-wave velocity and flow propagation velocity assessed by colour M-mode Doppler echocardiography in first myocardial infarction: prognostic and clinical implications

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Objective: To determine the ability of the ratio of peak E-wave velocity and flow propagation velocity (E/FPV) measured with color M-mode echocardiography to predict in-hospital heart failure, and cardiac mortality in an unselected consecutive population with first myocardial infarction (MI).

Background: Several experimental studies indicate color M-mode echocardiography to be a valuable tool in the evaluation of diastolic function, but data regarding the clinical value are lacking.

Methods: Doppler echocardiography was performed within 24 hours of arrival at CCU. Highest Killip class was determined during hospitalization. Patients were divided in groups according to E/FPV < 1.5 and ≥1.5.

Results: 70 of 72 (97%) eligible patients were enrolled in the study. During hospitalization 35 patients were in Killip class II. In patients with E/FPV ≥ 1.5 Killip class was significantly higher compared to patients with E/FPV < 1.5 ($p < 0.0001$). Multivariate logistic regression analysis identified E/FPV ≥ 1.5 to be the single best predictor of in-hospital heart failure when compared with age, heart rate, E-wave deceleration time < 140 msec(Dt), ejection fraction, wall motion index (WMI) and enzymatic infarct size. At day 35 survival in patients with E/FPV < 1.5 was 97%, and in patients with E/FPV ≥ 1.5, 58% ($p = 0.0002$). Univariate Cox analysis identified Dt, E/FPV, age, WMI, Killip class II, heart rate, and enzymatic infarct size to be predictors of cardiac death. Cox proportional hazards model identified Dt, E/FPV ≥ 1.5 and age to be independent predictors of cardiac death, in the model Dt was superior to age and E/FPV.

Conclusions: E/FPV ≥ 1.5 measured with color M-mode echocardiography in the acute phase of MI was a strong predictor of in-hospital heart failure. In the prediction of cardiac death E/FPV was superior to systolic measurements, however E-wave deceleration time < 140 msec. was the most powerful predictor of cardiac death.

2023 Pulsed doppler-color M-mode E/Vp ratio for estimating mean left atrial pressure: an early postoperative coronary artery bypass grafting study

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Purpose: to evaluate the utility of the information obtained by combining the Doppler peak early transmitral velocity (E) with the color M-mode Doppler flow propagation velocity (Vp) for estimating mean left atrial (LA) pressure in early postoperative of coronary artery bypass grafting (CABG).

Methods: we studied 62 consecutive patients (pts) (48 males, 60 ± 14 years, sinus rhythm), 5.1 ± 2.3 hours after CABG, under mechanical ventilatory support. From the analysis of pulsed Doppler transmitral flow we obtained peak E and late (A) velocities (cm/s), E/A ratio and E wave decceleration time (EDcT – ms). We also measured the color M-mode Doppler Vp (cm/s) as the slope of the first aliasing velocity during early filling, from mitral valve plane to 4 cm distally into the left ventricle (LV) cavity, and we calculated E/Vp ratio. Simultaneously, LA pressure (LAp – mmHg) was obtained using LA line placed during surgery. All measurements were done at end-expiration.

Results: 10 pts (16%) were not considered due to inadequate echocardiographic images. In the remaining 52 pts: E = 57 ± 17 (23 to 111), A = 52 ± 19 (20 to 113), E/A = 1.3 ± 0.7 (0.3 to 3.5), EDcT = 149 ± 44 (50 to 240), Vp = 49 ± 19 (19 to 86), E/Vp = 1.36 ± 0.74 (0.43 to 3.64) and LAp = 10 ± 6 (2 to 25). We found a significant correlation between LAp and E ($r = 0.51$), E/A ($r = 0.68$), Vp ($r = -0.73$) and E/Vp ($r = 0.95$). The E/Vp provided the best correlation ($Z > 4.47$ – $p < 0.0001$) and best estimated LAp (LAp = 7.48xE/Vp-0.06, SEE = 1.8 mmHg). Using this equation to calculate LAp, the mean difference between the measured and estimated LAp from E/Vp (Bland-Altman analysis of agreement) was 0.04 ± 1.69 mmHg (mean − 2 SD = −3.34, mean + 2 SD = 3.42).

Conclusions: the ratio of peak E wave over the color M-mode propagation velocity during early LV filling can be assessed in the majority of pts in the first hours after CABG and compared to standard measurements of transmitral Doppler flow provides a better estimate of mean left atrial pressure.

RIGHT VENTRICULAR PERFORMANCE

2024 Three-dimensional echocardiographic paraplane and omniplane analysis for accurate right ventricular volume calculation: a comparison with magnetic resonance imaging

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Our aim was to study the measurements accuracy of three-dimensional echocardiography (3DE) using three different methods of analysis for right ventricular volume (RVV) calculation, using magnetic resonance imaging (MRI) as the reference standard. Precordial 3DE acquisition was performed in 12 patients at 2-degree rotational intervals with ECG and respiratory gating. MRI was performed at 0.5 T. End-diastolic (ED) and end-systolic (ES) RVV and ejection fraction (EF) were derived using Simpson's rule at 9-mm slices for MRI. While for 3DE RVV and EF were calculated by paraplane analysis (3DS) with 8 equidistant parallel RV short axis slices, omniplane analysis (OMN) with 8 RV long axis views obtained at 22.5° of rotation and by biplane modified Simpson's method with two orthogonal RV long axis views. Endocardial borders were traced manually in all methods.

Results. The mean ± SD of ED- and ES-RVV (ml) and EF (%) from MRI were (143 ± 70 and 85 ± 40 and 40 ± 11), from 3DS were (141 ± 72 and 86 ± 44 and 40 ± 12), for OMN were (141 ± 74 and 87 ± 46 and 38 ± 11) and those from BMS were (140 ± 74, 84 ± 45 and 41 ± 12) respectively. There were no significant differences between measurements of RVV and EF obtained from MRI and 3DE methods (p = NS). There were closer limit of agreements between measurements obtained by both 3DS and OMN methods with MRI (± 16, ± 16 and ± 6.6) and (± 18, ± 18 and ± 6.6) than that between BMS and MRI (± 24, ± 21 and ± 11.8) for calculating ED- and ES RVV and EF respectively. There was smaller interobserver variability for 3DS and OMN than that for BMS.

Conclusions. Precordial 3DE rotational acquisition for RV reconstruction is feasible. 3DE using both paraplane and omniplane analysis produce more accurate and reproducible measurements of RVV than that from BMS as compared to MRI.

2025 Doppler-derived acceleration rate of right ventricular early filling reliably predicts right atrial pressure at baseline and after loading manipulations in patients with chronic heart failure

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Although it has been recently suggested that the analysis of Doppler diastolic tricuspid flow (DTF) may be useful in estimating right atrial pressure (RAP) in patients (pts) with chronic heart failure (CHF), its value has not been fully elucidated.

Methods: 136 CHF pts (57 ± 8 yrs), 23 in atrial fibrillation, underwent simultaneous echo-Doppler and hemodynamic monitoring (Swan-Ganz cath.). The effects of different loading conditions were also investigated in 18 pts, during nitroprusside infusion (unloading) and in 13 other pts during a 2' active legs elevation (overloading). The following Doppler parameters were considered: peak flow velocity E, acceleration rate (Ac), acceleration time (Ac-T) and deceleration time (DT) of early DTF (in all study pts), peak flow velocity during atrial contraction A and peak E/A velocity ratio (only in sinus rhythm pts).

Results: RAP ranged from 0 to 20 mm Hg (5.5 ± 4.5 mm Hg). At univariate regression analysis all Doppler variables, but A velocity ($r = 0.16$), were well correlated with RAP both in the total population (E: $r = 0.70$; DT: $r = -0.72$; Ac-T: $r = -0.75$; Ac: $r = 0.98$) and when pts with atrial fibrillation (E: $r = -0.82$; DT: $r = -0.83$; Ac-T: $r = -0.75$; Ac: $r = 0.98$) and sinus rhythm (E: $r = 0.68$; E/A: $r = 0.46$; DT: $r = -0.70$; Ac-T: $r = -0.75$; Ac: $r = 0.98$) were separately considered. The best correlation was between Ac and RAP. At multivariate analysis Ac was the strongest and sole independent predictor of mean RAP ($r = 0.98$). In unloading condition (RAP ranging from 10 ± 4 to 3 ± 3 mm Hg), E velocity ($p < 0.05$), E/A velocity ratio ($p < 0.01$) and Ac ($p < 0.0005$) decreased, while DT and Ac-T increased ($p < 0.01$). In overloading condition (RAP ranging from 2 ± 1 to 7 ± 3 mm Hg) the opposite changes were observed: Ac increased ($p < 0.05$) while DT and Ac-T decreased ($p < 0.05$). In both loading conditions, at multivariate analysis, Ac was again the best and sole independent predictor of RAP, with $r = 0.98$.

In conclusion: acceleration of early diastolic tricuspid flow, easy to obtain in all pts with heart failure, represents a highly reliable and accurate tool for predicting and monitoring RAP.

2026 Evaluation of right ventricular ischaemic dysfunction with dobutamine stress echocardiography

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Ischemic dysfunction of the right ventricle (RV) is often ignored during stress testing whereas it is important in patients with multivessel coronary artery disease undergoing myocardial revascularization and affects prognosis.

Objective: To assess feasibility and diagnostic value of dobutamine stress-echocardiography (DSE) in identification of RV dysfunction in patients with coronary artery disease.

Patients and Methods: Study group consisted of 88 male consecutive patients (38–74 years, mean 53 ± 4.7) with the history of at least one MI. Posterior MI was present in 31 case. All patients underwent complete clinical investigation including coronary angiography that revealed multivessel disease in 77 cases. DSE was performed according to the standard protocol with dobutamine (DOB) infusion of 5, 10, 15, 20, 30, 40 mcg/kg/min and analysis of RV wall motion in 7 segments.

Results: Patients were divided into 3 groups: group 1 – with normal resting RV function (32 pts, WMSI = 1.0), group 2 – with dysfunction of interventricular septum, but normal RV (19 pts, WMSI = 1.5) and group 3 – with baseline RV wall motion abnormalities (37 pts, WMSI = 2.0). In group 1 – abnormalities of RV wall motion developed in 25 (81.3%) pts with high doses of DOB (WMSI = 1.6, $p < 0.01$). In group 2 – RV function improved with low doses of DOB (WMSI = 1.2, $p < 0.05$) and deteriorated with high doses (WMSI = 1.5, $p < 0.05$). In group 3 – WMSI decreased with low doses of DOB (1.1, $p < 0.01$), but with high doses of DOB, 26 (70.3%) pts developed asynergy in previously abnormal, but improved, or normal segments (WMSI = 1.7, $p < 0.01$). RV wall motion abnormalities were always accompanied by LV asynergy of various degree.

Conclusion: 1) DSE can detect RV dysfunction in patients with CAD; 2) Impairment of RV wall motion is reversible with low doses of DOB in the majority of segments; 3) Abnormality of RV systolic function in patients with normal RV wall motion is due to the extensive involvement of interventricular septum.

2027 The excursion of the tricuspid annular plane can help to find patients with right ventricular infarction

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Right ventricular (RV) infarction is important to identify for adequate treatment of patients having acute myocardial infarction. We hypothesized that echocardiographic measurement of the systolic excursion of the tricuspid annular plane (TAPSE) could be a useful tool to distinguish patients with RV infarction in a group of patients with acute myocardial infarction.

Methods: Forty-eight patients with acute myocardial infarction and fifteen healthy volunteers were investigated. Fourteen of the patients had electrocardiographical signs of RV infarction (Group A). The other thirty-four patients formed group B and the healthy volunteers constituted group C. The mean age was 74, 75 and 73 years, respectively. There was no difference between group A and B regarding left ventricular ejection fraction and RV systolic pressure. TAPSE of the RV free wall and of the septal segment were measured using the apical four-chamber view.

Results: TAPSE measurements of the RV free wall was in group A: 13 mm, in group B: 20 mm and 25 mm in group C (group A vs. group B and group A vs. group C, $p < 0.001$, respectively). In order to diminish influence of body size TAPSE measurements were corrected for body length, Group A: 8 mm/m, group B: 12 mm/m, group C: 15 mm/m. (Group A vs. B and group A vs. C, $p < 0.001$, respectively). The septal TAPSE measurements did not differ significantly between the groups.

Conclusion: TAPSE of the RV free wall was easily measured. In the setting of acute myocardial infarction it could distinguish patients having RV infarction. TAPSE can be a useful echocardiographic measure of right ventricular function in the coronary care unit.

2028 Combining assessment of right ventricular systolic and diastolic function: a new approach in patients with advanced lung disease

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Aim: Right ventricular performance (RVP) is an important prognostic factor in patients with pulmonary vascular disease and a quantitative non-invasive method of assessment remains a major challenge. We studied the use of an echocardiographic index of global myocardial performance (IMP) which is based on Doppler-determined time intervals and represents the sum of the right ventricular isovolumic contraction and relaxation times divided by the right ventricular ejection time.

Methods and Results: Doppler studies were performed to assess RVP in 70 patients with idiopathic pulmonary fibrosis (IPF), 27 matched normals and 5 patients with primary pulmonary hypertension (PPH). IMP was correlated with pO_2 and right heart catheter data (n = 25). Measurement of the IMP was possible in all study subjects. Non-invasive estimation of pulmonary artery pressure by Doppler evaluation of tricuspid regurgitation was possible in 56% of IPF patients. The mean IMP was 0.35 ± 0.10 in normals, 0.52 ± 0.23 in IPF patients ($p < 0.001$ vs normals) and 1.11 ± 0.42 in PPH patients ($p = 0.04$ vs IPF patients). There was a significant correlation between the IMP and pO_2 and mean pulmonary artery pressure ($r = -0.49$, $p = 0.001$ and $r = 0.59$, $p = 0.005$ respectively). In the IPF group mean IMP was 0.62 in patients with $pO_2 < 60$ mmHg (room air) compared to 0.38 in patients with $pO_2 \geq 60$ mmHg ($p < 0.001$). Mean IMP for IPF patients with significant pulmonary hypertension (mean PA pressure ≥ 30 mmHg) was 0.71 compared to 0.46 in those without pulmonary hypertension ($p = 0.02$). An IMP value of >0.55 (mean + 2SD in normals) identified those IPF patients with significant pulmonary hypertension with a sensitivity of 78% and specificity of 71%.

Conclusion: The IMP provides a simple, non-invasive assessment of global RVP in IPF patients with secondary pulmonary hypertension and relates closely to clinically important physiological variables.

2029 Right ventricular function by Doppler tissue imaging in patients with chronic obstructive lung disease and pulmonary hypertension

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Aim of the study was to assess right ventricular function in patients affected by chronic obstructive lung disease (COLD) with or without pulmonary hypertension (PH) by pulsed Doppler Tissue Imaging (DTI).

Methods: Standard Doppler-echo and right ventricular DTI was performed to 20 patients with COLD without PH (mean age = 63 years), 10 patients with both COLD and PH, i.e. with pulmonary artery systolic pressure (PASP) > 36 mm Hg (mean age = 61 years) and 10 healthy subjects, comparable for age and sex prevalence to the other 2 groups. PAPS was estimated by continuous-wave Doppler as the peak regurgitation velocity + estimated right atrial pressure. By standard Doppler, transtricuspid peak velocities E and A and their ratio were determined. DTI sample-volume was placed at the level of tricuspid annulus, measuring both myocardial systolic indexes (peak and time-velocity integral of S wave) and diastolic indexes as peaks and time-velocity integrals of E_m, A_m E_m/A_m ratio, relaxation time (RT_m).

Results: Transtricuspid E/A ratio was not significant among the 3 groups. Despite no difference of myocardial systolic indexes, patients with COLD and PH showed in comparison with patients without HP and controls lower E_m/A_m ratio ($p < 0.001$ and $p < 0.01$ respectively) and longer RT_m ($p < 0.0001$ and $p < 0.001$) In the overall population including subjects with at least minimal trucuspid regurgitation, a significant direct relation was found between PASP and DTI RT_m ($r = 0.80$, $p < 0.00001$).

In conclusion, pulsed DTI tricuspid pattern distinguishes patients with COLD having or not PH. The relation found between the degree of RTm lengthening and PASP underscores the ability of DTI to identify patients with different levels of PH. These findings suggest potential clinical use of DTI to assess PH also in subsets of patients with COLD and high transthoracic acoustic impedance, where adequate tricuspid flow is not measurable.

COMPUTER DEMONSTRATIONS

D2044 Injection catheter for computer guided intramyocardial drug delivery: precision assessment in the animal model

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Agents provoking angiogenesis have recently been introduced for surgical management of ischemic myocardium. The availability of an injection catheter for intramyocardial delivery of such agents would have the potential to overcome the drawbacks of a surgical approach. Precise application with regard to the ischemic region is indispensable for angiogenetic response.

Methods: The NOGA™ technology allows a 3-dimensional (3D) reconstruction of the endocardial contour of the left ventricle, using ultralow magnetic fields. Location and orientation of the tip of a special catheter is visualized relative to the endocardium in real time, allowing accurate navigation to the ischemic region. The catheter is provided with a needle which can be advanced from its tip. Intramyocardial dye injection (pig model, toluidine, 0.5 ml) was performed at 52 sites. Each injection site was marked on the 3D reconstruction of the endocardial contour. Distances were measured between these virtual sites and compared to the distances of identified injection locations in the sacrificed hearts.

Results: 46/52 injection could be identified macroscopically. Mean depth of stained tissue was 8 mm, mean width was 9 mm. The mean deviation of the distances measured on the virtual contour from the distances assessed in the sacrificed heart was 3.2 mm.

Conclusion: The computer-aided injection catheter is a precise instrument for local delivery of substances into the myocardium. This may be of particular importance for non-surgical treatment of ischemic myocardium with agents provoking angiogenesis.

D2045 A new computer method for analyzing contractile movement of myofibril under cardiotonic drugs

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The purposes in this study are to report a newly developed computer method for analyzing contractile movement of myofibrils in a single cardiac myocyte, and to evaluate the kinetic changes of that under cardiotonic drugs.

Methods: the cultured beating myocytes stimulated at 0.5 Hz were prepared from the rat heart. The microscopic views of the cells were stored in video tapes. After recording the myocyte images under normal perfusate (N; 1.0 mM/l Ca^{2+}), digoxin (Dig; $10^{-6, -7, -8}$ M) or pimobendan (Pim; $10^{-6, -7, -8}$ M) was added to the perfusate. The beating myocyte images were repeatedly recorded. Then consecutive video pictures in each experiment were taken into the computer for analysis. In order to analyze the movement of myofibrils, trajectories of markers characterizing it were selected on a single cell image. Those are traced by means of the maximum correlation method. When a marker M is specified in a frame, a square region M′ which has maximum correlation of the gray scales with M is searched in the next frame, and then M is considered to move to M′. If a marker at a point (r) in a frame moves to a point (R) in the next frame, the cell movement is specified by the correspondence between 2D vectors **r** and **R: R = f (r).** In a small region, the function (f) can be correspondence well by a linear function **R = Ar + v,** where **v** is a 2D vector representing translation and **A** is a 2 × 2 matrix representing rotation and transformation. The **v** and **A** can be determined by means of least square method from several pairs {r, R} obtained from the above method.

Results: the maximum displacement of the markers under Dig. (10^{-6} M) were 7.2 ± 1.5 μ m (n = 50) that was larger than N (5.3 ± 1.2 μ m; n = 50), the same dose of Pim. (5.2 ± 0.6 μ m; n = 50). The maximum velocity of contraction (mV_C) to relaxation (mV_R) ratio was dose-dependently increased under Dig., but decreased under Pim. Average mV_C/mV_R were 0.48 ± 0.05 (n = 50) in N, 0.99 ± 0.21 (n = 50) under of Dig. (10^{-6} M), 0.28 ± 0.05 (n = 50) under Pim. (10^{-6} M). The magitudes of rotations and transformations of the small square region under Dig. were dose-dependently increased in both contraction and relaxation phases, and under Pim. the magnitude of transformation were only increased in the earlier phase of contraction.

In conclusions: this computer methods can supply the new knowledge on the kinetics of myofibrils in a single myocyte. The exaggerated contractile movement induced by Dig. was essentially different from the contractile movement under Pim. The contractile movement induced by Pim. may require less energy because Pim. influenced only transformation in the contraction phase. Accordingly it is suggested that Pim. might be clinically beneficial to long term treatment for severe cardiac failure.

STENTING IN SPECIFIC SUBGROUPS

P2046 Coronary interventions: is being a woman a risk factor?

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Increased awareness to women's health issues has prompted considerable interest in assesing the outcome of coronary artery disease in the female population. Our purpose was to evaluate whether outcome in coronary interventions can be a gender related phenomenon.

Methods: We analyzed the results of percutaneous revascularization in 247 consecutive women (374 lesions) and 2113 men (3468 lesions) treated between 1995–98. All patients were treated with antiplatelet therapy. 6 month angiographic follow-up was obtained in 75% of patients.

Results:

	Female	Male		Female	Male
Mean age*	64 ± 10	59 ± 10	Ref diam, mm*	2.8 ± 0.5	2.9 ± 0.6
EF, %	62 ± 11	61 ± 11	Pr MLD, mm*	0.7 ± 0.5	0.8 ± 0.6
Unst ang, %*	38	28	Fin MLD, mm*	2.7 ± 0.8	2.8 ± 0.8
Asymp. pt, %*	11.7	17.9	B/A ratio	1.2 ± 0.2	1.2 ± 0.2
Hyperten, %*	61.5	49.3	Pro success%*	94.8	98.3
Elev. cholest, %	64.3	58.6	Fin CSA, mm*	7.7 ± 2.6	9.5 ± 3.3
Diabetes, %*	14.9	8.3	St thromb, %*	2.0	0.8
Smoker,*	34.4	60.5	TLR, %	27.2	27.7
MVD, %*	53.3	63.7	Restenosis, %	37.2	34.6
Compl. les, %	66.2	63.3	MACE, %, Hospital*	3.6	0.9
Ost and prox location, %*	56.7	48.6	1 month*	4.8	1.3
Les leng, mm	12.7 ± 9	13 ± 8	6 month*	9.8	4.7

*$p < 0.05$; MLD minimal lumen diameter; MIP maximal inflation pressure; MVD multivessel disease; TLR target lesion revascularization; 6 month MACE = post procedure MI, CABG, death.

Sub-analysis shows that differences in clinical outcome became insignificant (p = NS) when vessel size in the two groups is matched.

Conclusion: Female patients have a significally lower procedural success and higher incidence of acute, intermediate and long-term MACE, most probably, because of the differences in clinical and lesion characteristics with smaller vessel size playing a major role.

P2047 Validity of appropriateness criteria for indication of coronary artery by pass surgery and angioplasty in predicting outcome of patients suffering from coronary artery diseases

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Objective: To assess whether appropriateness criteria set by a multispecialties panel of experts for cardiac re-vascularization procedures in Italy predicted for patient outcomes.

Design: Prospective cohort study using information obtained from: 1) revascularization laboratories; 2) patients' hospital medical records; 3) death certificates from administrative sources.

Setting: Sixteen Northern Italian hospitals belonging to the National Health Services (NHS).

Participants: Out of 2718 consecutive patients undergoing a coronary angiogram during the recruitment period (February – May 1995), a total of 1213 (44%) had an indication deemed appropriate by the expert panel to receive a re-vascularization procedure (either coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA).

Main Outcome: For the entire patient cohort (n = 1213) total (both unadjusted and adjusted) mortality (with a minimum follow-up of 9 months) was assessed according to receipt of a re-vascularization procedure.

Results: Patients who received re-vascularization within 9 months since the index angiogram had lower mortality than those who did not (4.8% vs 10.6%, P = 0.001). This association held true after adjustment for relevant risk factors such as extent of coronary artery disease, clinical symptoms, and cardiac surgical risk index (adjusted OR = 0.46; 95% confidence intervals (CIs) = 0.28–0.77) and was confirmed when outcome was assessed using survival analysis (adjusted hazard ratio = 0.29; 95% CIs = 0.18–0.48).

Conclusions: Appropriateness criteria set by a multispecialty expert panel in Italy appeared to validly predict patients outcomes. These results strongly urge the need of monitoring the possibility that underuse of effective procedures may jeopardize patients outcome and provide some further evidence of validity of the RAND/UCLA appropriateness methodology in the area of interventional cardiology.

P2048 In-hospital and 6-month outcomes of coronary angioplasty and non-elective stenting in dialysis patients

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Outcome of coronary angioplasty (PTCA) in dialysis patients is reported to be poor in small series.

Methods: We studied immediate angiographic results, in-hospital complications and 6 month outcome of PTCA, with or without stenting, performed in 119 patients with long-term dialysis. The results were compared to those of 1328 non-dialysis patients undergoing PTCA during the same period [12/93–12/97]. Indications for stenting were post-PTCA diameter stenosis ≥ 35%, threatening dissection and bail-out after balloon PTCA. All patients were followed-up ≥6 months.

Results:

	Dialysis n = 119	Non-dialysis n = 1328
Stenting (%)	38*	26
Angiographic success (%)	91	91
In-hospital:		
Death (%)	2.5	1
MI (%)	3.9*	1.5
Follow-up:		
Angina (%)	58†	35
Death (%)	2.5†	0.2
TLR (%)	41*	28
MACE (%)	52†	37

*p < 0.05, †p < 0.01, MACE: death/MI/CABG/PTCA

Outcomes were comparable between dialysis patients with optimal result after balloon PTCA and those with stent implantation.

Conclusions: Compared to non-dialysis patients, balloon PTCA provides more sub-optimal angiographic results in dialysis patients, requiring higher rates of stenting. Despite comparable final angiographic results, in-hospital and 6 month outcomes are poorer in dialysis patients.

P2049 Angiographic outcome of different coronary interventions in patients with chronic renal failure with or without haemodialysis

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Coronary balloon angioplasty (PTCA) in patients (pts) with chronic renal failure is reported to be limited by a high incidence of restenosis and target lesion revascularization. The role of newer interventional techniques such as stents or rotablation (Rota) is unclear. In a retrospective analysis, we evaluated the angiographic outcome of coronary interventions in 125 pts with chronic renal failure (creatinine ≥ 2.0 mg/dl, no hemodialysis, group 1) and in 75 pts with chronic hemodialysis (0.5 to 7 years; group 2). The rate of angiographic restenosis defined as a more than 50% diameter stenosis at six month by quantitative coronary angiography (CMS, Medis, Leiden, the Netherlands) and ischemia driven target lesion revascularization were identified in each group.

Results:

	Group 1		Group 2		p
	Restenosis	TLR	Restenosis	TLR	
PTCA	6 of 8 (75%)	4 of 8 (50%)	6 of 8 (75%)	5 of 8 (63%)	1.0
PTCA+ Stent	10 of 32 (32%)	9 of 32 (28%)	3 of 10 (30%)	3 of 10 (30%)	0.756
Rota+ PTCA	8 of 18 (44%)	7 of 18 (40%)	6 of 12 (50%)	5 of 12 (42%)	0.943
Rota + PTCA + Stent	19 of 67 (28%)	17 of 67 (26%)	12 of 45 (26%)	11 of 45 (24%)	0.986
P	0.049	0.031	0.043	0.041	

In conclusion, rotablation plus stenting provides significantly better results on restenosis and TLR in pts with chronic renal failure with no impact of hemodialysis on these findings.

P2050 Prediction of long-term survival and improvement of LV function after PTCA in patients with ischaemic heart failure

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The aim of this prospective observational study was to assess the value of simple clinical data for prediction of the long term outcome after PTCA in patients with ischaemic heart failure.

Material and Methods: Eighty-five patients with symptomatic coronary artery disease (CCS angina class≫2), impaired left ventricle function (EF < 35%) and suitable for total or incomplete percutaenous revascularisation were enrolled into the study. The mean period of observation after PTCA was 21.4 ± 10.6 months. Basic demographic, clinical and angiographic data were analysed to find simple predictors of long-term survival and improvement of LV function. Additionally, a new EKG index (EKG-Ix) was developed to show the value of routine EKG in a such prediction. Kaplan-Meier (product-limit) survival analysis and multivariate regression were performed to reach statistical conclusions.

Results: Demographic and clinical data are shown in the table below. The Kaplan-Meier one year survival was 90 ± 3%. All deaths could be observed in a high risk group (27 patients) with three vessel disease, LV-EF < 25% and disqualified from CABG (one year survival 69.1%, conf. interval 50.5–87.7%). In this group a value of EKG-Ix < 5 discriminated a subgroup of patients with extremely poor prognosis (85.6 vs 15% mortality, Fischer test: p = 0.002). Multivariate regression analysis showed that EKG-Ix was the only good predictor of LV function improvement (p < 0.0001).

Demographic and clinical data

Age	56.4±10.2	Hypertension	39 (49%)	Previous CABG	8 (94%)
Male	67 (79%)	Smoking	54 (63%)	Disqualification	
NYHA class II/III/IV	3/49/33	Diabetes	15 (18%)	from CABG	54 (66%)
CCS class II/III/IV	4/34/47	Hyperlipidemia	50 (59%)	Risk (Cleveland score)	12±9%
				Total revascularisation	42 (45%)

Conclusions: The results suggest that simple clinical parameters may be helpful in prediction of good long term outcome in patients with ischaemic LV dysfunction suitable for percutaneous revascularisation.

P2051 In-hospital outcome and long-term follow-up after coronary stenting in patients with severe left ventricular dysfunction

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Though conventional PTCA can be performed in patients with poor LV function, it carries an increased risk of in-hospital complications and whether it can improve survival remains uncertain. Intracoronary stenting with combined antiplatelet therapy has increased the safety of coronary angioplasty procedures. The aim of this study was to assess the in-hospital and long-term outcome in pts with poor LV function treated with intracoronary stents. A consecutive series of 78 pts (65 men; mean age 65 ± 11 years) with LVEF ≤ 35% (mean LVEF 29 ± 6%) treated with intra-coronary stenting from 1995 through 1997 was followed-up for an average of 15 months. Pts with PTCA ≤ 24 hours of AMI were excluded. Most pts had 2-vessel (47%) or 3-vessel disease (37%). PTCA was performed on 1 vessel in 66 pts; 104 of the 110 lesions attempted were stented (1.2 stent/lesion). Mean stents length was 21 mm. Complete revascuarisation was achieved in 24 pts (31%). Primary success rate (residual stenosis < 50% and no in-hospital complication) was 97% (76/78 pts); there was one non-Q wave MI caused by side-branch occlusion (1%), and one failure of stent deployment. No patient was lost to follow-up. Of the 13 deaths during FU, 8 were caused by intractable heart failure. Kaplan Meier probability of survival was 88% at 6 months, 85% at 1 year and 75% at 2 years. There was no non fatal MI during FU but 16 pts (20%) were re-admitted for congestive heart failure; 10 pts had target vessel revascularisation (1 CABG, 9 re-PTCA) and 5 pts had PTCA of another artery. In patients alive at FU, 14% had stable angina, and 19% described incapacitating dyspnea. Therefore, intracoronary stenting appears to offer an acceptable alternative to CABG in pts with severely depressed LVEF, with very few in-hospital complications. Long-term follow-up, however, remains complicated by the frequent occurrence of fatal or non fatal congestive heart failure.

P2052 Small-vessel stenting with two different dedicated stents

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Introduction: A few preliminary studies of coronary stents implanted in vessel < 3.0 mm have provided conflicting results. The stents used in the previous studies however were designed to achieve an optimal scaffolding and wall coverage in the 3.0–4.5 mm vessel. We evaluated the results of elective stenting in small coronary arteries (<3.0 mm) employing two dedicated stents: NIR 5 cells stent, 19 mm of length (Medinol-SciMed) and the slotted tubular Mini stent, 11 or 15 mm of length (Cordis, J & J Inc).

Materials and methods: We treated 89 denovo or restenotic lesions in 83 pts with clinical or objective evidence of myocardial ischemia (age 63 ± 10 yrs, M/F 47/16). The lesion distribution was: 19 LAD (12 distal segment), 17 diagonal artery, 16 right coronary artery, 13 Cx, 8 posterolateral-RCA, 7 obtuse marginal, 3 posterolateral-of circumflex, 3 ramus and 3 posterior descending. Stent expansion was performed at 12–16 atm. All patients received aspirin and ticlopidine for four weeks.

Results: Stent deployment was successul in all lesions but two cases in the MINI group (1 diagonal and 1 LAD); in both cases stents were retrived without problems. No case of acute or subacute thrombosis, nor in-hospital complications were observed. Six-month angiographic follow-up was available in 31 pts (35%) NIR/MINI 15/16. Quantitative angiographic data are listed below (expressed in mm):

	Pre PTCA			Post STENT		Follow-up	
	Les length	Ref diam	% sten	Ref diam	% sten	% sten	Rest rate
NIR (n = 41)	11 ± 6	2.3 ± 0.4	76 ± 17	2.6 ± 16	9 ± 10	56 ± 24 (n = 15)	60%
MINI (n = 48)	12 ± 6	2.3 ± 0.5	75 ± 16	2.5 ± 0.4	11 ± 11	52 ± 20 (n = 16)	50%

p = n.s. for all comparisons between the two groups (unpaired T-test)

All remaining patients have been scheduled for an angiographic six-month follow-up that will be completed at the end of July.

Conclusions: Stenting in small vessels with dedicated stents is associated with a high procedural success and no increase in stent thrombosis. No difference was observed in immediate results between NIR 5-cell and Mini stents. Our preliminary follow-up results indicate unacceptably high restenosis rates. Probably a larger patients population needs to be evaluated to have a definitive answer to this problem.

P2053 The BESMART study: in-hospital clinical and angiographic results

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Background: The BESMART (BEstent in SMall ARTeries) study is an ongoing french prospective randomized multicenter trial comparing stent (Bestent, Medtronic inc.) implantation versus balloon angioplasty in small coronary arteries (<3 mm) in order to evaluate the immediate results and 6-month angiographic restenosis rate (380 Pts to be enrolled).

Methods: Pts with documented myocardial ischemia and with a de novo lesion in a native coronary artery < 3 mm diameter were included. The use of a balloon ≥ 3 mm diameter was an exclusion criteria. The Bestent was manually crimped on a 2.5 mm diameter balloon. After stenting, Pts received ticlopidine (500 mg/d) and aspirin (160 mg/d). The CMS 3.0 version (edge detection) was used by an independant corelab for quantitative angiographic analysis (QCA) of reference diameter, minimal lumen diameter (RD, MLD) and % diameter stenosis (% DS).

Results: To date, 249 consecutive Pts (61 ± 10 yrs) with 258 lesions were randomized to PTCA (n = 124 pts) or stent (n = 125). On basis of intention to treat, procedural success rate was 99% with both techniques. Major adverse events were: death (PTCA 0, stent 0), myocardial infarction (PTCA 3, stent 4), rePTCA (PTCA 2, stent 2) and hematoma (PTCA 1, stent 1). In 31 Pts of PTCA group (25%) there was a crossover to the stent group because of unsatisfactory results of PTCA. QCA results:

	PTCA		Stent	
	Pre	Post	Pre	Post
RD (mm)	2.17 ± 0.37	2.36 ± 0.41	2.18 ± 0.38	2.46 ± 0.38
MLD (mm)	0.80 ± 0.28	1.73 ± 0.48	0.71 ± 0.27	2.13 ± 0.38
% DS	64 ± 11	27 ± 14	67 ± 12	13 ± 11

Conclusions: The preliminary in-hospital results of this multicentric study show that stenting is feasible and safe in small coronary arteries and is associated with results at least comparable to those of PTCA.

P2054 Differential behaviour of stents in curved vessels dependent on their design

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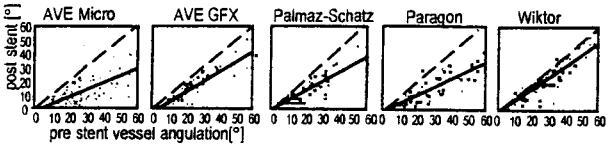
Stent implantation changes the arterial geometry, therefore we examined the straightening effect of different stents on arterial curve and the possible asociation between changes in vessel angulation and occurrence of major adverse cardiac events (MACE).

Method: Pre-, post-stent and follow-up (FUP) vessel angulation (angles defined by the tangents of the proximal and distal parts of stenosis or stent) after implantation of 148 sinusoidal ring (76 AVE Micro and 72 AVE GFX), 89 tubular slotted tube (Palmaz-Schatz), 78 cell-type (Paragon) and 181 coil (Wiktor) stent were compared and correlated to the occurrence of MACE. Receiver operating characteristic curves were used to determine the maximal vessel angulation (as cut-off point by different stents), which can be safely stented with a less incidence of MACE.

Results: Different stent types straighten the tortuosed vessel to a different degree; coil stents influenced the vessel curve to a lesser extent in comparison with the other stents (figure).



Stenting of a tortuosed vessel with an angulation of more than 28° with AVE Micro, 30° with AVE GFX or Paragon, 32° with Palmaz-Schatz and 34° with Wiktor stent was associated with higher incidence of MACE. After six months FUP, tubular, cell-type and ring stents, but not coil stents exhibited a further decrease in vessel angulation (table).

Vessel angulation [°]	Pre-stent	Post-stent	Follow-up
AVE Micro	32.2 ± 19.5	19.6 ± 14.8*	17.0 ± 12.2
AVE GFx	36.3 ± 24.8	26.3 ± 20.2*	21.2 ± 15.4
Palmaz-Schatz	32.0 ± 18.3	17.7 ± 14.5*	12.4 ± 10.8+
Paragon	38.8 ± 24.8	26.8 ± 18.4*	20.2 ± 14.4
Wiktor	34.6 ± 22.6	30.0 ± 21.2	31.1 ± 22.3

*p < 0.05 between pre-post stent, +p < 0.05 between post-stent and FUP in the same stent group.

In **conclusion**, flexible coil stent does not have an implication on vessel angulation, therefore stenting of tortuous vessel with coil stent could be recommended.

P2055 Coronary stent placement in two or more vessels: 1-year clinical and angiographic outcome and comparison with single-vessel stenting

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The issue of the optimal treatment option for patients (pts) who need multivessel revascularization is not fully resolved. They are often referred to aortocoronary bypass surgery. However, recent advances in interventional cardiology may be beneficial also for this category of pts.

Methods: A consecutive series of 3212 pts without acute myocardial infarction (MI) is included. Pts were divided in 2 groups: group MV composed of 334 pts with same session stenting in ≥2 vessels (309 in 2 vessels, 25 in 3 vessels), and group SV composed of 2878 pts with single-vessel stenting. All pts had 1-year clinical follow-up. 6-month angiography was performed in 2700 pts. All angiograms were assessed with QCA.

Results: In comparison with pts in the SV group, pts in the MV group were older, more often men, with higher frequency of diabetes and unstable angina, more often reduced left ventricular function, prior bypass surgery and MI. One-year follow-up results are presented:

	MV	SV	P
Procedural success, %	98.8	98.3	0.52
Death, %	4.8	3.6	0.28
Death or MI, %	6.9	5.4	0.27
Bypass surgery, %	5.1	2.5	0.007
Target lesion repeat angioplasty, %	16.9	16.9	0.99
Any of the above events, %	28.4	22.7	0.02
Angiographic late lumen loss, mm	1.23 ± 0.87	1.17 ± 0.84	0.16
Angiographic restenosis rate, %	36.0	32.5	0.15

Conclusions: Despite the more frequent presence of high risk characteristics, stenting multiple vessels in these pts is not associated with any significant increase in mortality and MI rate as compared with single-vessel stenting. If corroborated by randomized studies, this may become a strategy of choice for pts needing multivessel revascularization.

P2056 Preliminary clinical experience of bifurcarted coronary stent

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Many options have been proposed to cover complete bifurcation lesion with coronary stents, using step by step techniques. Bifurcated stent (BS) is a theoritical one-step alternative. In the setting of a preliminary feasibility study, 12 pts were treated, from 06/98 to 10/98, with a XT Carina Bard* on 8 LAD/diagonal and 4 Circumflex/obtuse marginal branch bifurcations. Baseline lesion were D type in 11 and C type in 1. Procedure was conducted through a 9 F access using a 23 mm long Carina. One failure was related to proximal calcification and another one to the lack of legs rotation in a calcified bifurcation. These 2 cases were treated with stenting in main branch and balloon in side branch. There was one nonQ MI (3 times CK upper limit). Off-line QCA results (mm):

	RD	preMLD	postMLD
Proximal main branch	3 ± 0.32	0.72 ± 0.42	3.05 ± 0.46
Distal main branch	2.9 ± 0.4	0.74 ± 0.42	2.91 ± 0.37
Side branch	2.6 ± 0.57	0.7 ± 0.27	2.52 ± 0.57

RD: reference diameter, MLD: minimal lumen diameter

At this time, clinical follow-up ranged from 3 to 8 m. One pt underwent re-PTCA for symptomatic restenosis at 4 m., 3 pts need revascularisations in non-target vessels. A systematic angiographic was planned at 7 months in all pts, among whom 1 pt had isolated restenosis in the side branch without re-PTCA.

Thus, these preliminary feasibility results are encouraging and allow to consider larger study to validate this strategy.

P2057 Triple vessel stenting for triple vessel disease: a two-centre prospective study

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Randomized clinical trials have shown that multivessel coronary stenting is feasible and provides similar short-term suvival as CABG in selected pts. However, the unknown and probably low frequency of triple-vessel (3V) 'treatable' with triple stenting has not yet been assessed and may reduce the clinical impact of these studies in everyday practice.

We conducted this prospective two-center study to assess the frequency and short- and mid-term results of 3V PTCA combined with elective stent implantation.

Population: From Jan 1996 to Jan 1999 in a total of 6,810 PTCA procedures, 115 pts (1.69%) were treated by PTCA and elective stenting for 3V disease whatever the indication. Mean age was 62.9 years (range 35–85), 83% were male and 13 pts (11.4%) were diabetic. The procedure was performed in 1 session in 77.6% and 362 vessels were dilated. (3.07/pt): left main coronary artery (3.5%), LAD (85.2%), diag (27.2%), circ. (48.6%), marginal (53.5%), RCA (84.3%), PLA (4.3%), PDA (7.8%) and graft (1.7%). Pts received 362 stents (4.06 stent/pt, range 3–10). Mean total stent length was 66.9 ± 24.9 mm. In-hospital complications included 2 emergency CABG (1.7%) and 2 myocardial infarctions (1.7%), 2 pts (1.7%) died. Mean hospital stay was 2.7 ± 2.2 days. Follow-up: no systematic angiogram was performed, however, all pts but one (99.1%) were followed clinically for 1 to 36 months (mean 16.7). During this period, 2 pts died, 2 were operated on, and 22 (19.1%) were dilated. Event-free survival at 16 months was 72.2%. No clinical or angiographic procedural characteristics were found to be predictors of events.

In conclusion, very few pts are eligible for 3V stenting; when eligible, feasibility is high and immediate results are satisfactory. However, long-term event-free survival will remain lower than what can be expected after CABG as long as the restenosis problem will not be solved.

P2058 Percutaneous coronary revascularization for multivessel disease in the stent era: acute and long-term outcome

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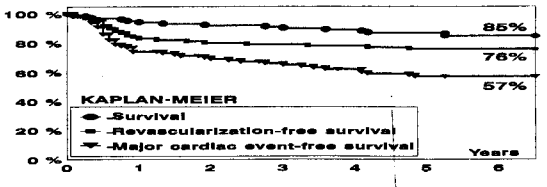
To assess the efficacy of coronary stenting (CS) in the setting of multivessel disease we followed 583 consecutive pts (62 ± 10 yr., 86% male) with multivessel coronary disease who underwent CS. Indication for PTCA was unstable angina in 63% of pts and 16% were diabetics. Seven percent of pts had previous heart failure and 52% previous myocardial infarction. Mean ejection fraction was 0.59 ± 13 and the mean number of diseased vessels was 2.4 ± 0.5. Clinical follow-up was completed for 94% of pts (follow-up duration: 3 ± 18 months, range: 18–78). In 70% of pts revascularization was accomplished by means of Stent exclusively, while in the remaining 30% the procedure combined Stent and balloon.

Initial clinical success (angiographic success without major complication at one month) was 87%. The incidence of angiographic restenosis for any of treated vessels was 34% (Stented vessels: 31%, ballooned vessel: 45%). The long-term evolution is shown in the figure:



The multivariate analysis (logistic regression) showed that diabetes (OR: 1.46, 95%CI: 1.13–1.88), the minimal lumen diameter after PTCA and the occurrence of AMI during the procedure (OR: 2.2 95%CI: 1.15–3.88) were independent predictors of major adverse cardiac events in the long-term follow-up.

Thus, initial outcome and long-term survival and revascularization free survival are acceptable in pts with multivessel disease treated with percutaneous revascularization using Stent.

P2059 Coronary stenting for isolated left anterior descending stenosis: acute and 6-month clinical and angiographic results

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We evaluated acute and mid-term safety and efficacy of coronary stent implantation for isolated LAD stenosis.

Methods: 401 pts (mean age 58 ± 10 yrs) were enrolled from May '92 through June '98. Indication for revascularization was stable and unstable angina and acute myocardial infarction in 61.5%, 29% and 9% of pts, respectively. Coronary stenosis (mean lenght 15 ± 8 mm, range 7–40 mm) was located at the ostium (8.5%), proximal (50%), middle (41%) and distal (0.5%) segment of LAD artery. Lesion type was A in 4.1%, B in 44% and B2-C in 52% of pts. Different types of stent were implanted (Palmaz-Schatz: 48.5%, NIR: 20%, Multilink: 15%, beStent: 8%, AVE: 4%, others: 4.5%) according to lesion morphologic characteristics, with an elective indication in 86% of pts. Multiple or long stents (>16 mm) were deployed in 11% and 31.5% of pts, respectively. High pressure post-dilation was routinely used (maximal inflation pressure of 15 ± 2.5 atm). The antithrombotic treatment was anticoagulation in 25%, aspirin alone in 17.5% and aspirin + ticlopidine in 58.5%.

Results:

Acute (401 pts):		6-mos F/U (288 pts, 71.8%):	
Procedural success	98.5%	Death	0%
Stent thrombosis	0.5%	Q-MI	0.7%
Major bleeding	1.1%	Angina	8.6%
Urgent CABG	0.8%	Total TLR	14.1%
Death	0.8%	– *RePTCA*	11.1%
Q-MI	2.3%	– *CABG*	3.1%
Any event	8.5%	Event Free Surv.	85.9%
		Restenosis Rate	26%

Independent predictors of 6-month were diabetes, previous CABG, reference vessel diameter between 2.8 and 3.2 mm, and % post-procedure stenosis.

Conclusions: coronary stenting is a safe and effective treatment in pts with isolated LAD stenosis. The high acute procedural success and the long-term event-free survival compares favorably with previous randomized studies despite more complex coronary anatomy and unstable clinical presentation.

P2060 Unprotected left main stenting with elective or stand-by cardiopulmonary support

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The increasing experience with percutaneous stent treatment for unprotected left main coronary lesions leads to the search of the best technique and safest methods for adequate revascularization, even in complex patients (pts). Percutaneous cardiopulmonary support (CPS) during the procedure provides a safe environment to achieve a tailored designed strategy. Since September 92 to January 99 we have studied 69 pts with unprotected left main coronary stenosis who were treated with stent implantation. The mean age was 62 ± 11 years; the clinical condition was unstable angina in 55 (80%), acute myocardial infarction in 5 (7%) (4 of them in cardiogenic shock) and stable angina in 9 (13%). Elective CPS was used in 29 patients as a prophylactic measure because of: 1) poor left ventricular function (n = 2), 2) unstable hemodynamic condition (n = 8), 3) repair needing complex bifurcation procedures (n = 12) and 4) the need for combined right coronary artery revascularization (n = 7). In 13 pts more than 1 indication for CPS was present. In the remaining 40 pts, stand-by CPS was available (groin access for possible fast canulae insertion, if needed); in 7 of them the CPS was established once observed the inability to proceed without hemodynamic deterioration. In 29 pts ultrasound guidance was used for bifurcation assessment. Primary success (adequate revascularization with 30 days event-free survival) was obtained in 65 (94%). Major 1-month complication included: peri-interventional death 3 (4%) and myocardial infarction 1 (2%). No subacute stent thrombosis was observed. A close clinical follow-up was obtained in all survival and 41 (59%) were angiographically re-evaluated at a mean of 6 ± 5 months. Late major adverse clinical events (death, surgery, myocardial infarction or additional percutaneous revascularization) were observed in 12 pts (18%). The remaining 54 pts remain symptoms free after 16 ± 16 months.

Conclusion: Elective or stand-by CPS allows for safe and adequate stent revascularization of unprotected left main, even in complex clinical and/or anatomic conditions.

P2061 Is the angiographic guidance sufficient for optimal stent deployment in ostial stenoses? Insight from IVUS

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Precise positioning of stents in ostial lesions under fluoroscopic guidance is difficult because of poor stent visibility and angiographic foreshortening or overlapping. In this study the adequacy of stent deployment in ostial stenosis was evaluated with intravascular ultrasound (IVUS) in 86 consecutive patients (90 native de-novo lesions).

Methods: Based on stent position relative to the vessel ostium we distinguished 3 groups: "optimal" – stent deployed within ± 1 mm to ostium (39 lesions); "too proximal" defined as >1 mm protrusion from the ostium (mean 2.7 mm, range from 1.5 to 7.0 mm; 32 lesions) and "too distal" defined as >1 mm distal to the ostium (mean 1.7 mm, range from 4.5 to 1.5 mm; 19 lesions). Aorto-ostial lesions were: in RCA 18%, LAD 46%, LCX 10% and branch-ostial 19%. All deployed stents were balloon expandable with PS-154 used in 46 lesions (50%). Rotational and directional atherectomy were used in 23% and 14% of lesions, respectively. Angiographic follow-up was obtained in 86% of eligible patients 6.8 ± 2.0 months after stenting.

Results: There were no statistically significant differences in clinical characteristics among the 3 groups.

	Optimal	Too Proximal	Too Distal
Type B2 & C les, %*	67	68	74
Calcium, %*	28	19	21
RVD (pre/final), mm*	3.3 ± 0.5/3.4 ± 0.4	3.1 ± 0.6/3.4 ± 0.4	3.1 ± 0.3/3.3 ± 0.5
MLD (pre/final), mm*	1.1 ± 0.7/3.3 ± 0.6	1.0 ± 0.6/3.3 ± 0.5	0.9 ± 03/3.2 ± 0.7
B/V ratio*	1.11 ± 0.30	1.19 ± 0.21	1.16 ± 0.16
Acute gain, mm*	2.27 ± 0.73	2.29 ± 0.78	2.19 ± 0.85
Late loss, mm*	0.94 ± 0.83	1.10 ± 0.95	0.93 ± 0.99
Loss index*	0.45 ± 0.42	0.67 ± 0.82	0.42 ± 0.33
Fin stent CSA, mm^{2*}	9.83 ± 2.66	9.70 ± 2.39	9.5 ± 3.37
Fin vessel CSA, mm^2	17.43 ± 4.76	17.33 ± 4.40	17.25 ± 5.36
Restenosis/TLR, %*	25/25	22/20.7	19/18.7

*p = NS; RVD = reference vessel diameter; MLD = minimal lumen diameter; TLR = target lesion revascularization.

Conclusions: With modern stents and angiographic guidance precise stent positioning can be achieved in most cases with a trend to moderate stent protrusion. Suboptimal (too proximal or too distal) stent position within the small range observed does not predict an increased risk of restenosis.

P2062 Immediate results of the RAP study: a randomized trial that compares stent and balloon angioplasty in small vessels

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The RAP study (Restenosis en Arterias Pequeñas) is a multicenter prospective randomized trial which compares the results of Bestent implantation versus balloon angioplasty in 440 patients with lesions located in small vessels. The primary endpoint of the study is to compare angiographic restenosis of each group at six months. Secondary endpoints include the incidence of Major Adverse Cardiac Events at six months. Cost- effectiviness at one year will also be analysed for patients in each group. Patient and procedural characteristics include: 1 or 2 de novo focal lesions located in a native coronary artery with a reference diameter between 2.2 and 2.7 mm. Balloon angioplasty is performed with a balloon ≤ 52.75 mm. In the stent arm, a small Bestent mounted on a 2.5 mm balloon is deployed and post dilation if necessary, is performed with a ≤2.75 mm semicompliant balloon.

Results: We report the inmediate results of the first 295 (149 balloon and 146 stent) patients having completed a 30 day follow up. Mean reference diameter of the target vessel was 2.29 ± 0.36 mm. There were 20 (13%) cases cross-over to stent and 2 (1.5%) to balloon. Target lesion location was: LAD-Diagonal (54%), Circunflex-Obtuse marginal (34%) and Right coronary (12%) Procedural succees was obtained in 98% in the stent and 96% in the balloon group. Twenty six (8.8%) major adverse cardiac events have been accounted at 30 day follow up: 17 (11.4%) in the balloon and 9 (6.1%) in the stent arm. Post-procedure average minimal luminal diameter (MLD) in the stent group was 0.42 mm larger than the MLD obtained in the balloon group.

In conclusión: The inmediate analysis of the first 295 patients enrolled in the RAP study shows good inmediate result in both groups with a tendency toward better angiographic and clinical results in the stent arm. Enrollement is expected to be finished in July 1999.

P2063 Treatment of small vessels with complex lesions

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The impact of stenting on small vessels (<3.0 mm) with complex lesions (B2-C) is controversed. In this study we retrospectively evaluated clinical and angiographic follow-up in patients with complex lesions in small vessels, treated with in lab successful percutaneous transluminal angioplasty (SPOBA) or with elective stent implantation (Stent).

Methods: SPOBA group (n = 207) and Stent group (n = 202) were comparable for all clinical and angiographic characteristics, except vessel treated (p = 0.001) and target lesion location (p = 0.003). Major adverse cardiac events (MACE) were evaluate at 30 days and at >6 months. Angiographic follow-up was performed in 227/349 (65%) of elegible patients.

Results: Angiographic success was 95% in SPOBA group and 98% in Stent group (p = NS). There was no difference in procedural, and in-hospital cardiac events. Follow-up is shown below:

	SPOBA	Stent*	p
MACE Early	6/207 (2.9%)	1/202 (0.5%)	0.25
MACE Late	10/137 (6%)	17/131 (13%)	0.10
TLR	24/104 (22.4%)	63/158 (39.9%)	0.003
Restenosis Rate	29/92 (31%)	60/135 (44%)	0.05

By logistic regression analysis, vessel diameter (p = 0.0017), final balloon pressure (p = 0.0023), and stent length (p = 0.007) were the predictors of restenosis.

Conclusion: Stent implantation in small vessels with complex lesions does not improve both early and late outcome, and seems to negatively influence the occurrence of restenosis compared to successful POBA.

P2064 Stenting of small coronary arteries: interim report from a randomized multicenter trial in patients with a vessel reference diameter of 2.3-2.9 mm. The SISA study

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Background: The Stenting In Small Arteries trial (SISA) is a randomized, multicenter, worldwide stent study in 350 pts with a reference diameter (RD) of the target vessel of 2.3–2.9 mm. Angiographic F-U after 6 mos and clinical F-U at 12 mos will be obtained.

Methods: Pts with one de-novo lesion in native coronary arteries and stable angina are included. Either a standard PTCA procedure was performed or a Medtronic BeStent (8 mm or 15 mm length) was implanted. Before inclusion the RD of the target vessel was calculated using on-line quantitative coronary analysis (QCA) measurements. During the procedure pts received 10,000–15,000 U of heparin. After the procedure pts were treated with aspirin and ticlopidin (stent patients only) for 28 days.

Results: Thusfar 262 pts (128 stent pts, 134 PTCA pts, age: 60 Y, 81 F) have been included. The RD before inclusion was: 2.52 ± 0.23 mm (stent pts) and 2.50 ± 0.20 mm (PTCA pts). The procedural success rate (<50% residual diameter stenosis (DS) with a decrease in DS of > 20% after the procedure) was 97.9% for the whole group. Crossovers: Stent to PTCA: 3(1.1%); PTCA to Stent: 21(8%). The clinical success rate (procedural succes without MACE at discharge) was 93.9%. Complications at one month (n = 170): death: 0, Q-wave MI: 3 (1.7%), Non Q-wave MI: 4(2.3%), CABG: 2(1.2%), Re-PTCA: 5(2.9%).

Conclusion: Stenting of small vessels with a RD of 2.3–2.9 mm is feasible and relatively safe. Interim results for 350 patients will be available at presentation.

P2065 Clinical and angiographic long-term follow-up of stenting for long coronary lesions

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In order to assess the role of the stent length on long-term PTCA results, we retrospectively compared 732 consecutive patients (study period: 25 months) receiving 843 coronary stents using 20 mm as a threshold to separate short and long stenting. The stents used were: NIR stents (9, 16, 25 or 32 mm), Wiktor I stents (10, 20 or 30 mm), Bard XT stents (6, 11, 15, 19, 34 mm).

Results are presented in the table.

Conclusions: In comparison with short lesions, coronary stenting on long lesions can be safely used with a high rate of primary success, a low rate of subacute thrombosis and a similar TLR at long term follow-up.

	≥20 mm	<20 mm	p
n (pts)	202	530	
Lesion length (mm)	14.72 ± 5.9	10.29 ± 3.65	<0.0001
Stent length (mm)	23.23 ± 4.85	14.15 ± 2.9	<0.0001
Stent/lesion ratio	1.81 ± 0.81	1.52 ± 0.6	<0.0001
– "de novo"	147 (72.8%)	361 (68.1%)	
– bail out	15 (7.4%)	47 (8.9%)	
– restenosis	40 (19.8%)	122 (23%)	
Procedural success	195 (96.5%)	515 (97.2%)	ns
Clinical success	186 (95.4%)	489 (94.9%)	ns
Non Q MI	3/195 (1.49%)	7/515 (1.32%)	ns
Q MI	1/195 (0.5%)	5/515 (0.94%)	ns
CABG	0	2/515 (0.38%)	-
In hospital mortality	1 (0.50%)	6 (1.51%)	ns
2-years mortality	5 (3.2%)	10 (3.4%)	ns
12 months TLR*	23 (14.3%)	57 (12.2%)	ns
24 months TLR	25 (20.6%)	64 (14.8%)	ns

*TLR (Target lesion revascularization) – Kaplan Meier – 614 stenosis

P2066 One-year follow-up after long (>40 mm) coronary stenting

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Coronary artery reconstruction (CAR) defined as the treatment of a >40 mm long native coronary segment is a limitation of balloon angioplasty. In order to assess safety/efficacy of stent-assisted CAR, we studied 163 pts (60 ± 11 y.) consecutively treated with CAR on 164 lesions using stents (S). Indication was predominantly: unstable angina 40%, recent MI 34%. Artery (RCA 54% LAD 36% Circumflex 10%) diameter was 3.03 ± 0.58 mm. S were deployed with a 3.29 ± 0.4 mm balloon at 11 ± 2 atm. Mean treated length was 53 ± 19 mm. MLD went from 0.52 ± 0.5 mm up to 2.9 ± 0.5 mm. Technical succes rate was 95.2% (1.8% S loss). Pts received a ticlopidine/aspirin drug regimen. Stent thrombosis rate was 3%. We noted no emergent CABG or death but 2 cases of Q MI (1.2%) and 3 cases of nonQ MI (1.8%). Clinical success rate was 97%. At 6 m. follow-up, we noted 2 cardiac deaths (1.4%), 34 recurrent angina (25%) and target late revascularisation (TLR) in 20 pts (14.7%). TLR increased in single stenting group from 8% (6 m.) to 10.7% at 12 m. and in multiple stenting group from 21.3%* to 24.7%* at 12 m. (* = p < 0.05 versus single stenting group). Reintervention was associated with a higher number of S/lesion (2.4 ± 1.1 vs 1.8 ± 0.8, p < 0.05).

Thus, CAR is highly feasible and associated with a good outcome at 12 months in case of single stenting.

P2067 A matched comparison between spot stenting and traditional stenting for the treatment of long lesions

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Various approaches in the treatment of long lesions have to date yielded disappointing results. In this retrospective analysis we compared the technique of utilizing long stent lengths (LS) with full lesion coverage vs the approach of spot stenting (SS) where IVUS guided PTCA is performed and short stents are placed only in the segments of a lesion where IVUS criteria are not met (CSA > 5.5 mm2 or >50% of reference vessel CSA at the lesion site). The SS group (70 patients with 87 lesions) and the LS group (688 patients with 769 lesions) had similar baseline clinical and lesion characteristics including lesion complexity and reference vessel diameter (2.97 ± 0.5 vs 3.04 ± 0.5, p = ns). The SS group contained significantly longer lesions (28 ± 11 vs 23 ± 8, p < 0.01).

Characteristic	SS	LS	p
Mean age	60 ± 11	60 ± 10	ns
LVEF%	60 ± 11	60 ± 12	ns
3 vessel disease, n (%)	24 (37)	190 (28)	ns
Calcified lesion, n (%)	27 (31)	125 (17)	<0.05
Stents/Lesion	1.3 ± 0.6	1.6 ± 1.0	<0.05
Stent length (mm)	21 ± 13	29 ± 17	<0.05
Max inflation press. (atm)	14.6 ± 3.5	15.3 ± 3.4	<0.05
Balloon/artery ratio	1.25 ± 0.2	1.18 ± 0.2	<0.05
Min lumen diameter pre (mm)	0.7 ± 0.4	0.8 ± 0.5	<0.05
Final min lumen diameter (mm)	2.8 ± 0.7	3.0 ± 0.5	<0.05
Stent thrombosis, n (%)	1 (1.1)	15 (1.9)	ns
Procedural MACE, n (%)	3 (4.3)	32 (4.7)	ns
Restenosis, n (%)	14 (25)	183 (39)	<0.05
Target lesion revasc., n (%)	12 (17)	165 (31)	<0.05

Angiographic follow-up was achieved in 77% of eligible lesions.

Conclusions: Despite the use of shorter stent lengths to treat longer lesions, the SS group had similar short-term event rates but significantly better long-term outcome with lower restenosis rates and TLR.

P2068 Coronary artery reconstruction by stenting. initial and long-term clinical and angiographic evolution

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Background: Coronary reconstruction (CR) by stenting (non-interrupted covering of a coronary segment longer than 40 mm) is frequently used for treating long lesions or coronary dissection but its impact on restenosis and clinical outcome is not well-known.

Methods: To assess the clinical and angiographic evolution after CR, as well as the differences between elective and unplanned CR, we followed 89 consecutive pts who underwent CR in 90 arteries. Reconstruction required ≥40 mm of non-interrupted stent covering. The procedure was elective in 54 pts (ELR group) and unplanned (long dissection) (LDR group) in 24 pts. The stented segment length was 56 ± 17 mm. Patients from ELR group were older (ELR: 65 ± 10 yr., LDR: 59 ± 10 yr., $p < 0.01$) and no other baseline differences between groups were found. Long-term clinical follow-up was completed for 97% of pts at 19 ± 11 months.

Results: Initial success (angiographic success without major complications at 30 days) was achieved in 91% of cases whereas 5 pts (5.5%) suffered subacute occlusion, 3 pts (3%) needed urgent CABG and 1 pts died. Initial outcome was similar in both groups apart from a higher rate of optimal result (96 vs 80%, p = 0.03) and a lower incidence of vascular complications (22 vs 4%, p = 0.04) in ELR group. Both groups had similar long-term clinical and angiographic outcome. Six-month restenosis (50%-QCA criterion) rate was 55% (95% CI: 42–68%) but only 35 patients (35%) developed symptoms. During follow-up, 7 pts (8%) had cardiac death and 20 pts (23%) needed target vessel revascularization (TVR). The incidence of major adverse cardiac events (readmission, TVR or death) was 35%.

Conclusion: Coronary reconstruction by stenting is associated with a high, incidence of angiographic restenosis and an acceptable clinical outcome, without differences between elective and unplanned (dissection) reconstruction.

P2069 Immediate and medium-term outcome following the treatment of very long (50 mm) chronic coronary artery occlusion

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The long term angiographic patency and the angiographic variables associated with long term angiographic success of coronary artery stenting for chronic (>6 months) coronary artery occlusion of very long lesions (>50 mm) is not known. Aim of the present study was to evaluate the early results and outcome following the treatment of very long chronic coronary artery occlusion. Between January and December 1998 we treated 220 chronic occlusions of these and 45 of these (45 patients) were ^{3} 50 mm long. An early angiographic success of coronary stenting for lesions >50 mm was obtained in 39 patients (86%). A total of 102 coronary stents (2.3 ± 1.1 stent/patient) were implanted. No major complications were observed during the procedures and in-hospital stay. During a 7.6 ± 2 months follow-up, 18 (46%) patients remained angina free, no reinfartion occurred. Twenty seven (70%) patients with early angiographic success underwent angiographic follow-up. Significant restenosis (^{3}50%) was observed in 13 patients (48%), and complete reocclusion was observed in 4 patients (14.8%). The mean stenosis angiographic follow-up was 51 ± 33%. A significant correlation was observed between restenosis and number of stents used (R 0.52) and percent of residual stenosis (R 0.73). All total reocclusion during the follow-up were observed in vessels with a post-procedure mld < 2.75 mm.

In conclusion, although coronary artery stenting for long (>50 mm) chronic occlusion is feasible, safe and is associated with a low incidence of adverse clinical events, these complex and expensive procedures are still associated with a high 6-month restenosis rate.

P2070 Elective stenting of the unprotected left main artery: acute and long-term result

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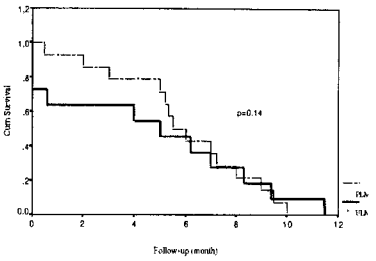
Elective stenting in patients with unprotected left main coronary artery (ULM) has generally been judged to be contraindicated, primarily due to the potential for consequences of abrupt closure and of restenosis. Recent improvements in stent implantation technique and post-stent antithrombotic regimen prompted us to evaluate the role of elective stenting of ULM.

Methods: we analyzed 85 consecutive patients (90 lesions) which underwent elective stenting of ULM (45 patients, 46 lesions) and compared them with 40 patients (44 lesions) with protected left main (PLM). All patients received aspirin and ticlopidine. Intraoartic balloon pump (IABP) was used in 53% in ULM group and in 31% of patients from PLM group (p = 0.04). Angiographic follow-up was obtained in 78% and 71% of the patients, respectively.

Results: The only different clinical factor was left ventricular ejection fraction (60.1% in ULM-group vs 52.4% in PLM group; p = 0.009). There were no significant differences in lesion characteristics (p = ns).

	ULM	PLM	p
Debulking, %	39	50	ns
Ac/Subac St Thromb, %	0	0	ns
Acute MACE, n (%)	5 (11.1)*	0	0.03
1 mo MACE, n (%)	7 (15.5)	1 (2.5)	0.03
6 mo MACE, n (%)	17	8.3	0.3
Restenosis/TLR, %	24/19	26/21	ns

*3 CABG; 2 Q-wave MI. MACE = major cardiac adverse event; TLR = target lesion revascularization.



Subanalysis in patients who have had a IABP showed a strong tendency toward procedural MACE in ULM group (p = 0.08).

Conclusions: In selected patients with good left ventricular function, elective stenting of ULM can be performed with a moderate risk of periprocedural complications. Long-term follow-up and repeat angiography shows similar clinical outcome and restenosis rate in patients with protected and unprotected left main coronary artery.

P2071 Comparison of debulking plus stenting versus stenting alone for aorto-ostial saphenous vein graft lesions: immediate and late clinical outcome

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Background: Stent implantation in saphenous vein graft (SVG) aorto-ostial lesions may improve procedural and late clinical outcome. However the impact of debulking prior to stent implantation in this complex lesion subset is not known.

Methods: We studied 320 consecutive patients with 340 lesions treated with Palmaz-Schatz stent implantation under intrvascular ultrsound guidance in aorto-ostial SVG disease. Debulking with excimer laser or transluminal extraction catheter was performed in 133 patients prior to stenting and 107 patients received stents without prior atheroablation.

Results: Baseline clinical and lesion characteristics, and procedural success were similar between the groups.

	Debulking + Stent	Stent alone
Diabetes	38.7%	27.9%
In-hospital complications	0.7	3.1
Procedural success	99%	100%
MACE at 1 year follow-up	44%	39%
TLR	29.6%	23.4%

TLR = target lesion revascularisation; MACE (death, MI and any repeat revascularisation).

Conclusion: We therefore conclude that there is no difference in the immediate procedural outcome, late clinical events and TLR between patient undergoing debulking prior to stenting or stenting alone. These results question the value of debulking prior to stenting in SVG/aorto-ostial lesions. This important issue needs further investigation.

P2072 Procedural outcome and follow-up after saphenous vein graft treatment

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The aim of the present study was to evaluate the impact of improved strategies over the last 3 years on procedural early and late outcome in diseased SVG.

Methods: 194 consecutive patients (pts) underwent interventional procedure on 278 SVG lesions (65% B2 and C) during the last 3 years. Mean graft age was 8.8 ± 5.5 years. 89% of lesions were stented (directional coronary atherectomy in 2.1% prior to stenting) and 11% received only PTCA. 39 covered stents were deployed. In 11 pts the Guard Wire (PercueSurge) temporary occlusion and aspiration system was used to prevent distal embolization. Lesion location was aorto-ostial in 21% of pts, midgraft in 53.5% and distal anastomosis site in 25.5%. Total occluison and thrombus containing lesions were treated in 13.6% and 11%of cases respectively. Reo-Pro was given in 15% of pts.

Results: Angiographic success was obtained in 266 lesions (95.7%) 11/12 failures were in total occlusions. Quantitative angiographic results are summarized below. In-hospital MACE occurred in 6 (3.09%) patients (1 death and 5 myocardial infarctions). Clinical success rate was 92.6%. 6-month angiographic follow-up was obtained in 121 patients (62%). Restenosis occurred in 35 (18%). 12-month clinical follow-up was obtained in 186 patients (96%). Nine patients (4.6%) died, 3% had a myocardial infarction, 22.1% had a re-PTCA procedure at the target vessel and 3.6% had a new CABG surgery.

	RD (mm)	MLD (mm)	DS (%)
Pre-treatment	3.46 ± 0.96	0.64 ± 0.65	80.9 ± 16.75
Final	3.63 ± 0.79	3.34 ± 0.83	7.53 ± 12.14

RD: reference diameter, MLD: min. lumen diameter, DS: Diameter stenosis.

Conclusion: SVG revascularization procedures can now be performed, even in complex lesions, with low periprocedural adverse events. Although, the need for repeat revascularization is still higher than in native arteries, approximately 70% of pts are free from major cardiac events after one year.

P2073 Stenting of territories with prior coronary bypass grafts: should the target be the vein graft or the native vessel?

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Background: Interventions in saphenous vein grafts (SVG) are associated with increased morbidity and mortality when compared to interventions in the native vessels. The relative risks and advantages of native coronary vs. saphenous vein graft stenting in patients who present with SVG stenosis are poorly understood.

Methods: We evaluated the in-hospital and one year major adverse cardiac events (MACE) including death, MI, or target lesion revascularization (TLR) after elective stenting in 1451 SVG lesions of 935 consecutive patients and in 1092 native coronary lesions of 718 consecutive patients with prior CABG and SVG disease.

Results: Adjunct Abciximab was used 15.2%. In hospital MACE was similar (1.9% vs. 1.8%, p = NS), but SVG stenting was associated with a higher incidence of non-q wave MI (18% vs. 13%, p = 0.04). Long-term results:

Follow-up (1 year)	Native Coronaries n = 718	SVG n = 935	p
Death (%)	4.3	9.1	0.001
MI (%)	2.3	4.5	0.001
TLR (%)	19.1	16.9	NS
MACE (%)	29.6	32.7	NS

Independent predictors of late death or MI included SVG location (OR 2.1), post procedural non-Q wave MI (OR 2.5), and low LV ejection fraction (OR 0.80).

Conclusion: In patients with prior CABG, SVG stenting is associated with higher post-procedural MI and higher late major events including death and MI, compared with native coronary stenting. Our data suggest that revascularization of the native vessel rather than the SVG should be the preferred interventional choice in this clinical setting.

P2074 Transcatheter microcoil embolisation of side branch of the left internal mammary artery in patients with recurrent angina and anterior wall ischaemia after coronary artery bypass grafting

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Background: Angina following coronary artery bypass grafting (CABG) may be caused by coronary steal due to a large side branch of the left internal mammary artery (LIMA). Objective evidence of reversal of anterior wall ischaemia due to trancatheter microcoil embolisation (TME) of unligated side branch of LIMA is lacking. We aimed to assess the effect of TPME in patients re-presenting with angina and documented anterior wall myocardial ischaemia post CABG.

Methods: We studied 6 males (44–75 yrs) who underwent complete revascularization; (2 patients had a solitary LIMA graft to the left anterior descending (LAD) artery, the other 4 had a LIMA graft to LAD plus vein grafts to both the circumflex and right coronary arteries) and re-presented (6–72 months, mean 23.6 months post-CABG) with angina (Canadian Class III–IV) and coronary angiography (11–96 months post-CABG, mean 34.2) showing patent grafts and a large unligated LIMA side branch with reversible anterior wall perfusion defects on dobutamine-tetrofosmin SPECT. TPME was performed via the femoral artery using a 7 French LIMA guide catheter (Cordis), 0.014 inch floppy guidewire, Tracker 18 catheter and coil pusher-16 (Target Therapeutics). After coil deployment, LIMA angiograms were performed to confirm the occlusion of the side branch and SPECT studies were repeated at, 22–40 days. Patients were followed up at 3 and 6 and 12 months clinically.

Results: TPME was successful in all six cases and resulted in reversal of the perfusion abnormalities detected on myocardial SPECT. One patient had a minor stroke with full recovery. All patients were free of angina at 3 and 6 and 12 months.

Conclusion: TPME of LIMA side branch is effective in relieving angina and reversing anterior wall ischaemia.

P2075 Angioplasty of mammary artery grafts after coronary surgery: a multicentre experience including stented patients

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Background: Early recurrent ischemia after coronary artery bypass surgery may be related to mammary artery graft stenosis, mainly at the site of anastomosis. The goal of this multicenter registry was to collect a large experience with the percutaneous transluminal coronary angioplasty (PTCA) of mammary arteries (MA) including stented patients and a systematic clinical follow-up.

Method: Since July 1991 to February 1998, 87 patients (pts) (62 ± 9 years, 77% males) underwent PTCA within an internal MA in a mean time of 29 ± 34 months after surgery. Of the 87 pts, 80 had dilatation of the distal anastomosis. Thirty five percent of pts were in unstable angina. The approach was femoral in 68 pts (78%).

Results: Initial angiographic success of the MA angioplasty was achieved in 68 pts (78%). In 24 pts (27%), balloon PTCA was followed by an attempted stent implantation, successfully in 23 pts. Of the 19 pts with failed MA angioplasty, one required a urgent redo CABG and two a delayed CABG surgery. One unsuccessful case lead to an anterior myocardial infarction. No pt died. Clinical follow-up was obtained in 98% of pts (25 ± 20 months). Six pts died (7%). The actuarial rate of pts alive and free of major events (myocardial infarction, CABG) at 4 years was 88 ± 10%. Most of the pts were either asymptomatic or had stable angina class I or II at follow-up. Thirteen pts required revascularization during the follow-up period, but only 8 pts returned with a focal IMA restenosis. Six pts underwent a new PTCA and two a repeat CABG.

In conclusion, PTCA of MA and stenting can be safely performed with however a lower success rate than in native vessels and is associated with good mid-term results in successfully dilated patients.

PROGNOSIS AFTER ACUTE CORONARY SYNDROME

P2076 The long-term prognosis in 30-day survivors after acute myocardial infarction in the pre and thrombolytic eras: a national study

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Early mortality after AMI declined significantly in the reperfusion era. Late mortality improvement remains questionable. We compared the 4-year mortality rate among 30-day survivors after AMI hospitalized in Jan–Feb, 1982–83 (n = 839) with 814 counterparts hospitalized in Jan–Feb, 1992.

	1982–83 (n = 839)	1992 (n = 814)	p Value
Men	77%	77%	NS
Mean age	62 ± 11	62 ± 12	NS
Prior MI	25%	27%	NS
Diabetes	19%	23%	0.05
Hypertension	39%	36%	NS
Current smoking	36%	38%	NS
P. edema/CHF	19%	12%	0.001
Aspirin	2%	79%	0.001
β-Blockers	15%	35%	0.001
ACE-Inhibitors	-	20%	0.001
Thrombolysis	-	46%	0.001
Coronary angio.	0.7%	24%	0.001
PTCA/CABG	-	11%	0.001
Mortality			OR* (95% CI)
4-year	28%	20%	0.76 (0.67–0.86)

** Mortality risk of 1992 vs. 1981–83 adjusted for age, gender, past MI, diabetes, CHF, hypertension and smoking*

Conclusion: The characteristics of MI survivors in both periods were comparable, but the management was totally different. This study suggests that changes in management of AMI in the '90s as compared with the '80s was associated with a better long-term prognosis in hospital survivors after AMI.

P2077 In patients with a patent infarct artery, rapid 50% ST-segment recovery is associated with improved regional wall motion at 48 hours

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Both early ST recovery and a patent infarct artery after thrombolytic therapy are associated with improved outcome after infarction. In patients with a patent infarct artery (TIMI 2 or 3 flow) at 90 minutes, it is not known whether the beneficial effect of rapid ST recovery is maintained.

Methods: We examined the effect of rapid 50% ST recovery on chord motion in the infarct zone by contrast ventriculography at 48 hours in patients with TIMI 2 or 3 flow at 90 minutes. Patients with acute myocardial infarction had continuous ST monitoring, received aspirin and streptokinase, and were randomised to intravenous heparin or one of two doses of Hirulog. Time to Steady State Recovery was to the first ECG showing 50% ST recovery sustained for 4 hours.

Results: Of 137 patients, 40 had TIMI 2 and 57 had TIMI 3 flow. The table below compares Time to Steady State Recovery (either ≤ or >45 min or 60 min) with chord motion in patients with TIMI 2 or 3 flow:

	TIMI 2						TIMI 3					
	≤45 min	>45 min	P	≤60 min	>60 min	P	≤45 min	>45 min	P	≤60 min	>60 min	P
Mean Chord Score	−1.2	−2.5	*0.048*	−1.2	−2.5	*0.03*	−1.4	−2.5	*0.01*	−1.6	−2.5	*0.04*
% Chords Abn	17.8	52.3	*0.02*	15.3	55.5	*0.01*	19.9	49.4	*0.002*	28.3	48.8	*0.07*

Conclusion: Rapid 50% ST recovery is associated with improved infarct zone wall motion at 48 hours even amongst patients with a patent infarct artery. Resolution of ST elevation may therefore be a more accurate marker of myocardial reperfusion than epicardial artery patency.

P2078 Prognostic value of coronary blood flow velocity investigated by intracoronary Doppler in patients with acute myocardial infarction after successful coronary angioplasty

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The objective of this study was to determine the prognostic value of coronary blood flow velocity investigated by intracoronary Doppler in patients with acute myocardial infarction within one year of angiographically successful coronary angioplasty.

Methods: In 40 patients (mean age 60.2 ± 15.4 y) who were consecutively referred for direct or rescue PTCA because of a primary myocardial infarction either inferior (n = 22) or anterior (n = 18), average peak velocity (APV) was measured after coronary angioplasty using a 0.014 doppler guidewire. Cardiac events were defined as cardiac death (CD), myocardial infarction (MI), congestive heart failure (CHF) and myocardial revascularization (REV).

Results. Subsequent PTCA was successful (percent diameter stenosis < 40%, TIMI 3) in 38/40 patients. Distal APV, which was 18.7 ± 10.4 cm/s, appeared highly varied quantitatively speaking. An adverse outcome was present in 6/40 patients (2 CD, 1 MI, 2 CHF, 3 REV) during in hospital follow-up and in 15/40 patients (2 CD, 2 MI, 5 CHF, 7 REV) during one-year follow-up. Distal APV was significantly lower in patients with in-hospital and one-year cardiac events than in those with cardiac event free (10.6 ± 6.0 cm/s vs 20.1 ± 10.4 cm/s, $p < 0.03$; 14.7 ± 8.3 cm/s vs 21.1 ± 10.9 cm/s, $p < 0.05$; respectively). An abnormal distal APV < 10 cm/s is independent predictor of one-year adverse cardiac events (66.6% vs 29%, $p < 0.04$) and hospitalization for congestive heart failure (44.4% vs 9.7%, $p < 0.01$).

Conclusion. Thus, APV disparity seems to be a useful and safety tool for enhancing patient characterization, to isolate a subset of risk patients for subsequent cardiac events.

P2079 Angiographic no-reflow is an independent early predictor of long-term cardiac complications and mortality in patients with acute myocardial infarction recanalized by angioplasty

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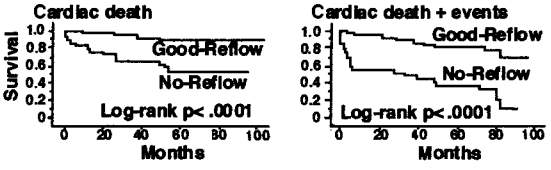
Angiographic no-reflow (NR) refers to substantial coronary antegrade flow reduction (less than TIMI 3 flow) without mechanical obstruction occasionally seen after recanalization. Our aim was to elucidate the importance of angiographic NR as a predictor of long-term outcome in the patients with AMI.

Method: We studied 119 consecutive patients with their first AMI successfully recanalized by PTCA without residual stenosis ≥ 50%, or major dissection or thrombus that may restrict coronary flow. The patients were divided into either NR (n = 29) or good-relow (TIMI 3) (GR, n = 90) based on the angiogram obtained at the end of PTCA, and were followed up (69 ± 14 months) with regards to cardiac death and cardiac events including cardiac rupture, recurrent AMI, congestive heart failure, and malignant arrhythmia.

Results: Kaplan-Meier event-free survival curves are as follows:



Multivariate Cox regression analyses disclosed the following variables as early independent predictors of event-free survival:

	Variable	b ± SE	Relative Risk	P value
Cardiac death	No-reflow	1.67 ± 0.50	5.31	<.001
	Age ≥ 70	1.02 ± 0.50	2.76	0.040
Cardiac death + events	No-reflow	1.48 ± 0.35	4.39	<.001
	Killip class ≥ 2	0.80 ± 0.36	2.22	0.027

Conclusion: Angiographic NR may be an independent early predictor of adverse long-term outcome in the patients with AMI.

P2080 Is carotid artery intima-media thickening a reliable marker of early atherosclerosis?

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It is widely believed that carotid artery intima-media thickening represents an early marker for the development of atheroma. It has been shown to be related to the all of the commonly accepted risk factors for cardiovascular disease, including left ventricular hypertrophy. However, carotid intima-media thickening might also be expected to occur in response to an increased shear wall stress; if this were to be the case it would caution the increasing enthusiasm for the use of this measurement as a marker for cardiovascular risk.

In order to test the hypothesis that an increased carotid artery wall shear stress may cause an increase in carotid intima-media thickness (IMT) 24 athletes (professional footballers) were compared to 14 age, sex and race matched control subjects. Each subject underwent bilateral common carotid and femoral ultrasonography and echocardiography. The athletes had a significantly greater left ventricular mass index compared with the controls – 135 (127–143) versus 104 (91–116) g/m^2, $p < 0.001$. In addition, they had a greater carotid IMT – 0.55 (0.52–0.57) versus 0.51 (0.48–0.54) mm, $p < 0.05$. However, carotid artery diameters, femoral IMT and femoral artery diameters were similar – 6.0 (5.9–6.2) versus 5.8 (5.6–6.1) mm, 0.43 (0.42–0.45) versus 0.43 (0.41–0.45) mm and 8.3 (8.0–8.6) versus 8.4 (8.0–8.7) mm, respectively.

The increased carotid IMT in the athletes is likely the result of the high cardiac output that is periodically delivered during exercise, causing an increased carotid wall shear stress. This is an important observation, since it suggests that an increased carotid IMT cannot be relied on as a marker of early atherosclerosis.

P2081 Impaired flow-dependent dilation of coronary arteries is predictive of subsequent adverse coronary events during long-term follow-up

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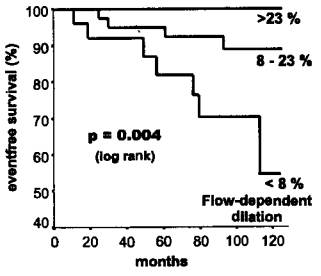
Experimental studies indicate, that endothelial dysfunction plays a key role in the pathogenesis of coronary artery disease. However, so far, no clinical data are available linking endothelial dysfunction to prognosis of patients. Thus, in 103 patients, endothelium-dependent, flow-dependent dilation of epicardial arteries (FDD) after infusion of 7 mg papaverine or 2.4 mg/min adenosine as well as endothelium-independent dilation (i.c. nitroglycerin, 250 μg) was assessed by quantitative coronary angiography. Then, long term follow up (FU; 13–125; median 94 months) was performed. Cardiac events were defined as sudden death, myocardial infarction, unstable angina, PTCA or coronary bypass surgery.



Results: Patients with cardiac events during FU had initially a significantly impaired FDD compared to patients without events (8.5 ± 8.6%, n = 11 vs. 17 ± 10%, n = 92; p = 0.01). By cox regression analysis, FDD was significantly associated with development of future events (p = 0.02). Patients with FDD > 23% (upper quartile, n = 25) experienced no event, whereas patients with FDD < 8% (lowest quartile, n = 25) had 7 events (figure). In addition, NTG-response was reduced in patients with events (23 ± 11% vs. 36 ± 20%; p = 0.04). However, this association was not significant by cox regression analysis (p = 0.06).

Conclusion: Impaired flow-dependent dilation is associated with cardiac events during long term follow up. This finding underscores the crucial role of endothelial dysfunction for progression of coronary artery disease.

P2082 Vasospastic angina: long-term follow-up

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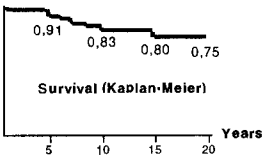
The objective of this study was to assess the long-term outcome of patients (P) with symptomatic vasospastic angina without significant coronary lesions.

Methods: All 86 consecutive P with vasospastic angina without significative coronary lesions were prospectively followed-up for a mean of 8.8 years (range 0.5–22 years). The diagnosis of coronary spasm (CS) was established in presence in one of the following criteria: 1) ↑ST during angina; 2) positive ergobasine test; 3) CS at angiography not induced by catheter. Coronariography was performed in all patients and provocative ergobasine test in 74. All of them were discharged on calcium channel blockers. An angiographic reevaluation was performed in presence of effort angina or myocardial infarction at a long-term. Follow-up was obtained in all P (100%).

Results: Mean age was 51.2 years, and 76 (88.4%) were male. The outcome was: 10 P (12%) died; 5 (6%) suffered a myocardial infarction; 25 (29%) had a recurrent rest angina; 13 (15.1%) developed effort angina; 49 (59%) were alive and free of events at the end of the follow-up. The cause of death was cardiac in 5 P (50%), all of them sudden death. Development of significative coronary lesions at angiography was demonstrated in 13 P (15%).



In conclusion: Vasoespastic angina without significative coronary lesions is associated with a low long-term mortality. However, sudden death is the main cause of mortality, and recurrent ischemia is frequent despite treatment with calcium channel blockers. Development of significative coronary lesions was demonstrated in 15%.

P2083 Clinical characteristics and long-term prognosis of 91 patients with myocardial infarction and normal coronary angiogram

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Background. Few data exist concerning the prognosis of patients (pts) with myocardial infarction (MI) and angiographically normal coronary arteries.

Methods. A group (Gr) of 91 pts admitted in our institution between january 1990 and december 1998 for a MI with normal coronary angiogram (smooth contours and no focal diameter reduction) (34 females/57 males; mean age 50 ± 13 yrs, range 24–78 yrs) (Gr I) were matched for age, sex, and year of MI onset with a Gr of 91 MI pts with coronary artery stenosis (>50% diameter stenosis) (Gr II).

Results. The percent of smokers was similar between the 2 groups; higher prevalence of coronary heart disease family history, obesity, hypertension, hypercholesterolemia and diabetes mellitus were found in GR II (p = 0.043 to 0.0001). In Gr I, coronary spasm was found in 13%, congenital coagulation disorders in 11%, collagen tissue disorders in 2.2%, embolization in 2.2%, and oral contraceptive use in 1.1%. LV ejection fraction (LVEF) at hospital discharge was higher in Gr I (60 ± 13%) than in Gr II (55 ± 13%, p = 0.04). The mean follow-up was 35 months (range 1–100 months). Kaplan-Meier event-free survival, with end-points defined as death, reinfarction, heart failure and stroke was 75% in Gr I vs 62% in Gr II (p = 0.01). Univariate predictors of any event in Gr I were LVEF (p = 0.03), age (p = 0.02), diabetes (p = 0.01), and smoking (p = 0.03). Using Cox multivariate analysis, independent predictors of long-term outcome in Gr I were LVEF (p = 0.003) and diabetes (p = 0.004).

Conclusion. Patients with MI and normal coronary angiogram have a better long-term prognosis than MI patients with coronary artery stenosis. In MI patients with normal coronary angiogram, the only two independent risk factors for cardiovascular events are left ventricular function and diabetes.

P2084 Prognostic value of step-by-step ischaemic diagnostics following uncomplicated acute myocardial infarction

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After acute myocardial infarction (AMI), invasive diagnostics and therapeutic procedures are performed routinely in a high percentage of patients, especially in Germany. A more reluctant approach based on non-invasive diagnostic methods in patients with uncomplicated AMI would be socioeconomically preferable, but only if the prognosis is not compromised.

Method: Between 10/96 to 12/97, 318 consecutive patients (median 65 years, range 22–88 years, 65% men, 35% women) with first uncomplicated myocardial infarction were included for non-invasive ischemic diagnostics. Depending on the evidence of ischemic signs in an exercise ECG (n = 110) or during stress echocardiography (n = 90) or the occurrence of recurrent angina pectoris (n = 36), the patients were assigned to group I (n = 195, invasive) or group II (n = 123, conservative) and were then followed for 12 months with regard to the composite primary endpoint 'death or myocardial infarction (MI)' and secondary endpoints (death alone, death, MI or hospitalization for cardiac reasons, PTCA or CABG).

Results: There were no differences between the groups in terms of age, sex, infarct location, thrombolytic therapy or left-ventricular function. 56 (29%) of the group I patients were treated by coronary surgery, 77 (39%) by PTCA and 62 (32%) conservatively. After a median follow up of 14 months, the primary endpoint was experienced by 15 group I patients (7.7%) and 8 group II patients (6.5%, logrank test n.s.). Similarily, there were no significant group differences in terms of the secondary endpoints (death: group I: n = 10, 5.1% versus group II: n = 6, 4.9%, death, MI or hospitalization: group I: n = 30, 15.4% versus group II: n = 21, 17.1%).

Conclusion: Following first uncomplicated myocardial infarction, conservatively treated patients with no signs of ischemia revealed a one-year prognosis that was comparable to the prognosis of patients who were diagnosed by invasive techniques and conditionally treated by PTCA or CABG.

P2085 Stress hyperglycemia and prognosis of myocardial infarction in nondiabetic and diabetic patients: a systematic overview

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A systematic review and meta-analysis of the literature was done to determine the risk of in-hospital mortality or cardiogenic shock after myocardial infarction (MI) in nondiabetic and diabetic patients with "stress" hyperglycemia at the time of admission.

Two independent MEDLINE searches of English-language articles from 1966 to October 1998, a computerized search of Science Citation Index from 1980 to September 1998, and hand searching of bibliographies were done. The retrieved citations were reviewed independently by two researchers to identify all retrospective and prospective cohort studies in which in-hospital mortality or cardiogenic shock were described in relation to admission blood glucose level. 13 articles describing 14 studies were identified.

Study quality was assessed based on specific methodologic criteria. Whenever possible, the relative risk of in-hospital mortality and/or cardiogenic shock in hyperglycemic compared to normoglycemic patients was calculated. Other relevant descriptive information was abstracted from each study.

Relative risks were calculable in 10 of 14 studies. Data from nondiabetic patients (in 6 studies) and diabetic patients (in 4 studies) were analyzed separately. Nondiabetic patients whose admission blood glucose at the time of MI was ≥ 6.1–8 mM (110–144 mg/dL) had a 4.0-fold increased risk of in-hospital mortality (95% confidence interval 2.89–5.55), and nondiabetic patients with an admission blood glucose > 10 mM (180 mg/dL) had an increased risk of cardiogenic shock. In diabetic patients, admission hyperglycemia did not significantly increase the risk of mortality or cardiogenic shock.

In conclusion, stress hyperglycemia on admission with MI is strongly associated with an increased risk of in-hospital mortality and cardiogenic shock in nondiabetic patients. Such an association was not observed consistently in diabetic patients.

P2086 A risk-score for prediction of cardiac mortality after an episode of unstable coronary artery disease

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The contributions of different pathophysiological mechanisms operating in unstable coronary artery disease (UCAD) and hence, the prognosis, differs considerable. Therefore, an early assessment of these mechanisms is important in order to be able to adequately risk stratify the patient. We therefore developed a risk score for prediction of cardiac mortality based on, easily available, clinical-, laboratory-and ECG-variables mirroring different mechanisms.

Methods: The patients were participating in FRISC – a double blind, randomised, placebo controlled trial of l.m.w. heparin (dalteparin) in UCAD and followed for at least 3 years. A risk score with a maximal of 8 points was developed based on 7 variables, who were independently associated with an increased risk of cardiac death in a Cox regression analysis: age ≥ 70 (**1p**), diabetes (**1p**), history of CHF (**1p**), ≥1 anti-anginal drugs on admission (**1p**), ST-segment depression on admission (**1p**), C-reactive protein ≥ 10 mg/L on admission (**1p**) and elevated (≤24 h) troponin T (0.06–0.6 μg/L **1p;** ≥0.6 μg/L **2p**).

Results: The median age at inclusion of the 917 patients were 70 years (25^{th}–75^{th} perc. 63–75) and 65% were males. After 3 years there were 114 (12.4%) deaths of which 91 (9.9%) were cardiac in origin.

Risk points	0–2 n = 254	3–4 n = 420	5–6 n = 226	7–8 n = 17
1-month c. mort., %	0	1.0	4.0	17.6
1-year c. mort., %	0.4	4.0	14.6	29.4
3-years c. mort., %	0.8	7.4	22.6	41.2

Conclusion: With this risk score based on variables easy to obtain within the first 24 hours after admission, large subsets of UCAD patients with low (≤2 p) and high (≥5 p) short- and long-term cardiac mortality, respectively, might be identified. However, the risk score has to be validated in prospective studies.

P2087 Superoxide dismutase activity in platelet: an independent predictor of long-term prognosis after acute myocardial infarction

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Animal, clinical and pathologic studies have established platelet thrombus formation as the key event in the etiology of acute coronary syndromes.

The purpose of this study was to investigate the prognostic significance of main phospholipid platelet (ptl) contents, lipid peroxides products and antioxidant enzymes in ptl, measured before hospital discharge, in patients (pts) with acute myocardial infarction (MI). We studied 147 consecutive pts (all men, age 50 ± 9, first AMI in 80%, Q-wave MI in 76%). At the time of hospital discharge, 24-hour electrocardiogram Holter monitoring and quantitative two-dimensional echocardiographic were performed in all pts. Follow-up was for 19 ± 9 months. During follow up, there were 17 cardiac deaths (10 sudden death and 7 fatal MI). According to univariate Cox analysis, the variables identified as significant predictors of cardiac death were: left ventricular aneurysm (LVA) (relative risk [RR] 5.61; 95% confidence interval [CI] 2.12–14.81, p = 0.0005), left ventricular ejection fraction < 40% (RR 4.53; 95% CI 1.68–12.18, p = 0.003), previous MI (RR 4.24; 95% CI 1.64–11.02, p = 0.003), superoxide dismutase (SOD) activity in ptl (RR 0.61; 95% CI 0.39–0.95, p = 0.03), left ventricular end-systolic volume (RR 1.05; 95% CI 1.002–1.09, p = 0.04), anterior location of Q-MI (RR 4.94; 95% CI 1.08–22.6, p = 0.04). Multiple stepwise Cox regression analysis identified the SOD activity in ptl (RR 0.36; 95% CI 0.19–0.69; χ^2Wald = 9.51, p = 0.002), previous MI (RR 6.77; 95% CI 1.69–27.12; χ^2Wald = 7.3, p = 0.007), anterior location of Q-MI (RR 6.67; 95% CI 1.29–23.54; χ^2Wald = 5.1, p = 0.024), LVA (RR 4.52; 95% CI 1.21–16.88; χ^2Wald = 5.0, p = 0.025) as independent predictors of cardiac death.

In conclusion, our data suggest that reduced activity of SOD in ptl, measured at hospital discharge, is an independent predictor of cardiac death in the 19 ± 9 months following acute MI.

P2088 Chronotropic incompetence after acute myocardial infarction: prognostic impact and relationships with heart rate variability

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The association of chronotropic incompetence and its relation with autonomic dysfunction has not been characterized after acute myocardial infarction (AMI), as well as its prognostic value.

Methods: patients at discharge after AMI (290, 263 men, <65 years, 55 ± 8 m ± sd) underwent graded exercise testing, and 24 hr Holter monitoring. Chronotropic incompetence was assessed as a low chronotropic index (CRI), a measure of exercise heart rate that accounts for age, resting heart rate, and peak VO_2, whereas relevant time and frequency heart rate variability HRV indices were averaged on the 24 h period from Holter ECG recording: in particular, RR interval total power, low frequency (LF), and high frequency (HF) power (both in absolute and normalised units – nu), as well as LF/HF ratio, were computed by means of autoregressive spectral analysis. Stepwise multiple regression analysis was applied to the HRV indexes, adjusting for age, sex and an echocardiographic index of left ventricular function (WMSI = wall motion score index).

Results: A significant positive relationship was found between CRI and a spectral index of parasympathetic drive (HFnu, $r = 0.22$, $p < 0.01$), whereas a negative correlation was found with sympathetic markers (LF nu, $r = -0.28$, $p < 0.001$, LF abs, $r = -0.21$, $p < 0.01$) and LF/HF ratio, an index of sympatho-vagal balance ($r = -0.23$, $p < 0.01$). During follow-up there were 70 endpoint events (9 deaths, 17 new AMI, 44 revascularisation procedures). After adjusting for age, gender, effort ischemia, WMSI, and other confounders, low CRI remained predictive (Kaplan-Meier – KM – rates 31.5% vs. 11%, adjusted RR 1.53, 95% CI 0.95–2.49, P = 0.08).

Conclusions: parasympathetic withdrawal and reciprocal sympathetic overactivity is associated with chronotropic incompetence during physical stress in subacute phase of an AMI. Moreover, chronotropic incompetence is independently predictive of major events among patients undergoing stress testing as part of post-AMI evaluation.

P2089 Recurrent ischaemia in patients with clinical heart failure but preserved left ventricular systolic function after acute myocardial infarction

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The occurrence of clinical heart failure (HF) after acute myocardial infarction (AMI) is an adverse prognostic factor even when left ventricular (LV) systolic function is preserved. We examined whether clinical HF but preserved LV systolic function after AMI is associated with an excess of residual and recurrent ischaemic events.

Methods A cohort of 508 patients with overt clinical HF and a LV ejection fraction (EF) measured 6.9 ± 4.9 days after AMI were identified from patients recruited to the AIRE study. 25 patients also underwent early myocardial perfusion studies. Clinical outcomes during an average of 15-month follow-up in those with an EF ≥ 0.45 (n = 163) were compared with those with EF < 0.45 (n = 345) using time to event statistical analysis.

Results The risks of death or developing severe HF were lower with EF ≥ 0.45 versus EF < 0.45 (14.1% vs. 22.1%, logrank p = 0.049; 9.2% vs. 20.9%, p = 0.002). In contrast, those with EF ≥ 0.45 were at a higher risk of recurrent ischaemic events indicated by the combined end-point of need for surgical or catheter-based revascularization or reinfarction or hospitalization for angina (HR 1.50, 95% CI 1.06 to 2.13, p = 0.021). In the subgroup who had myocardial perfusion studies those with EF ≥ 0.45 had 1.00 ± 1.26 LV segments which manifested partial or complete reperfusion whereas those with EF < 0.45 had 0.07 ± 0.47 such segments (p = 0.04).

Conclusions Patients with clinical HF after AMI and preserved LV systolic function have a lower mortality than those with reduced LV systolic function, but are at increased risk of recurrent ischaemic events.

P2090 Atherosclerosis of the descending aorta predicts cardiovascular events independently of left ventricular function: a transesophageal echocardiography study

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The aim of our study was to evaluate whether the presence of atherosclerosis on the descending aorta as assessed by transesophageal echocardiography (TEE) has any prognostic impact in predicting cardiovascular events in non-revascularized patients.

Methods: The initial study group consisted of 238 consecutive in-hospital patients referred for TEE testing. Of these, 34 patients were excluded for early revascularization. The remaining 204 patients (99 females, mean age 58 ± 11 years) were followed up for at least 2 years (mean 29 ± 8 months). The atherosclerotic process on the descending aorta was scored as follows: 0 – no sign, 1 – intimal thickening, 2 – plaque < 5 mm, 3 – plaque > 5 mm, 4 – plaque with ulcerated or mobile parts.

Results: In the follow-up period there were 23 cardiovascular events: 14 cardiac deaths, 4 fatal strokes, 5 non-fatal myocardial infarctions. During TEE significant atherosclerosis (score ≥2) was observed in 82 patients. Nine events occurred in 122 Patients with TEE score ≤1 and 14 in 82 patients with TEE score ≥2 (7% vs 17%, p < 0.05). By multivariate analysis, only left ventricular function with EF < 40% (OR 3.0, CI 1.3–7.1) and TEE atherosclerotic plaque ≥2 (OR 2.4, CI 1.0–5.5) predicted cardiovascular events.

Conclusion: Atherosclerosis of the descending aorta observed during transesophageal echocardiography is useful predictor of cardiovascular events in non-revascularized patients.

SOCIAL AND ECONOMIC ISSUES IN ACUTE CORONARY SYNDROMES

P2091 Is permanent heart damage, too high a price for cocaine?

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Cocaine is a powerful manifold cardiovascular toxic with a myriad of pharmacological and electrophysiological potentially deleterious actions.

We analyzed 39 successive occasional users presenting to the emergency room with cardiovascular symptoms following cocaine inhalation. A total of 17 patients (P) suffered acute strokes, atrial fibrillation, pulmonary edema, bronchospasm, upper digestive tract bleeding, retinal thrombosis, syncope or hypertensive crisis. Up to 23 patients complained of chest pain., 5 (22%) had angina and myocardial infarction (MI) was confirmed in 14 cases (61%). Infarctions occurred in young males (33.5 years mean age); only 5 P had other cardiovascular risk factors besides smoking (79%). All P underwent thrombolysis; angiographic studies performed on the 13 survivors revealed complete single vessel occlusion in 8 cases (62%) and absence of significant disease in the remaining 38%. Successful percutaneous rescue revascularization (PTCA & stent) was performed in 62.5%. Up to 93% of MI were asymptomatic after a 2-year follow-up and were still non-smokers.

In conclusion: Occasional inhalation of cocaine can induce life-threatening complications in young and otherwise low risk individuals. Chest pain is a major symptom, often related to acute ischemia (78%). Lytic therapy achieves low reperfusion rates in cocaine-induced thrombosis but occluded vessels remain patent following percutaneous rescue procedures.

P2092 Role of a dedicated unit for evaluation of patients with chest pain and non-diagnostic ECG presenting to the emergency department

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Background: The correct evaluation of chest pain (CP) remains a major problem in the E.R. (5% of patients in Europe), involves very high costs and requires a well planned investigational program. In this study, we investigated the clinical utility of assessing pts with chest pain and non-diagnostic ECG with a validated clinical chest pain score in order to identify those at high risk for coronary events and to standardize the admission to the chest pain unit (CPU).

Methods and Results: During 1996–1998, we evaluated a total of 5467 consecutive pts (age 65+17 years) with CP and non-diagnostic ECG, using a clinical score based on location, radiation, character of CP and associated risk factors and symptoms (Stowers et al, J. Nucl. Cardiol 1995). Patients with a score <4 were considered "low risk" and discharged from the E.R. (n = 3684; 67%); these pts had a 3% readmission rate, but only a <1% final diagnosis of CAD. Patients with a score >4 ("high risk") were admitted to the CPU for further investigation (n = 1783; 33%) including ECG monitoring, serial 12-lead ECG, cardiac enzymes and echocardiograms. Resting MIBI myocardial scintigraphy was performed in pts >40 years, >3 risk factors. Maximal exercise tolerance tests and stress-echocardiograms were performed when the final diagnosis was still uncertain at 24 hours from admission. All pts with >1 positive test underwent urgent angiography. Evidence of CAD was found in 19% of pts (n = 1018) within 6 hours from admission: of these 1018 pts, 22% had acute myocardial ischemia and were transferred to CCU for aggressive management, whereas the remaining 78% without clinical instability were tranferred to the wards. Conversely, the nature of CP remained unclear at 6 hours in 765 pts (14%). Of these, 299 pts (5.5% of total study group) were later found positive for CAD (angiographically confirmed in 89%) based on >1 test including raised cardiac enzymes (40%), late ECG changes (44%), positive exercise test (10%) and positive nuclear scan (9%).

Conclusions: Triage based on clinical presentation allows effective risk stratification of patients with chest pain and non-diagnostic ECG. Among "high risk" patients, non-invasive management in a dedicated unit allows a 19% early and 5.5% delayed detection of acute myocardial ischemia, allowing selective usage of costly intensive care beds and angiographic facilities.

P2093 Acute myocardial infarction occurring in the hospital: patients characteristics and hospital outcome compared to infarctions occurring outside

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Patients suffering an acute myocardial infarction (AMI) while being hospitalised (in-hospital AMI = I-AMI) are poorly characterised compared to patients with AMI occurring outside the hospital (pre-hospital AMI = P-AMI).

Methods: Between 6/1994 and 1/1997 5888 consecutive patients (pts) with P-AMI and a pre-hospital delay of less than 12 hours or I-AMI were registered at 54 hospitals by the prospective MITRA trial.

Results: 403 (6.8%) of these pts suffered an I-AMI and 5485 pts (93.2%) a P-AMI.

	I-AMI (n = 403)	P-AMI (n = 5485)	OR or p-value
Age (years, median)	70 (61/74)	66 (56/74)	0.001
Male gender	55.7%	67.4%	0.61 (0.5–0.8)
Anterior AMI	54.9%	48.2%	1.31 (1.1–1.6)
Re-infarction	36.7%	15.5%	3.15 (2.5–3.9)
Diagnostic first ECG	64.2%	72.6%	0.68 (0.6–0.8)
Reperfusion therapy	56.6%	58.3%	ns
Postinfarction angina	16.6%	14.7%	ns
In-hospital reinfarction	7.7%	4.7%	1.69 (1.2–2.5)
In-hospital mortality	27.3%	13.9%	2.33 (1.9–2.9)

Median time from onset of symptoms until start of reperfusion therapy was 55 minutes for I-AMI and 180 minutes for P-AMI. Hospitals with the facilities to perform balloon angioplasty showed a higher proportion of I-AMI compared to hospitals without such facilities (7.9% versus 6.4%; OR = 1.26 (1.02–1.56).

Conclusion: In non-selected pts with AMI, I-AMI account for 6.8% of all cases. Compared to pts with P-AMI, pts with I-AMI represent a high risk subgroup. The proportion of pts treated with reperfusion therapy was not different between the groups. However, hospital mortality was about twice as high in I-AMI (27.3% vs 13.9%, OR: 2.33 (1.9–2.9)).

P2094 Mortality and quality of life four months after myocardial infarction: effects of depression and anxiety

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Depression and anxiety following myocardial infarction (MI) have been implicated in cardiac-related mortality. Less is known about the influence of depression and anxiety on quality of life among survivors.

Methods: Between 2–15 days post-MI, 288 patients completed questionnaires including the Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), and the Dartmouth COOP, which measures quality of life. There were 215 men and 73 women. Average age at entry was 62.7 years, mean number of years of education was 10.1, and 93% were Caucasian. At four-month follow-up, 25 had died, all from cardiovascular causes. Questionnaires were readministered to survivors.

Results: Neither depressive symptomatology nor state or trait anxiety, measured at entry predicted mortality. The Peel Index, a prognostic device for grading the severity of infarction, was significantly associated with 4-month mortality.

	Four-month survival status	
	Alive	Dead
Depression (BDI)	7.71 ± 6.33	7.84 ± 5.54
State Anxiety (STAI)	33.55 ± 11.88	32.17 ± 21.11
Trait Anxiety (STAI)	31.97 ± 10.45	29.58 ± 9.43
Peel Index	10.59 ± 5.10	14.79 ± 5.51*

*$p < 0.05$

In contrast, initial BDI scores and STAI measures of state and trait anxiety predicted four-month quality of life among survivors. The Peel Index did not predict quality of life. In a regression model in which both depression and anxiety were entered, initial BDI scores afforded the best independent prediction of quality of life.

Conclusions: At odds with some, but not all, previous research, depression and anxiety following myocardial infarction did not predict short-term mortality. However, depression was predictive of quality of life of those patients who had survived at follow-up.

P2095 Influence of the climate on incidence and inhospital mortality of acute myocardial infarction: results of the MITRA study

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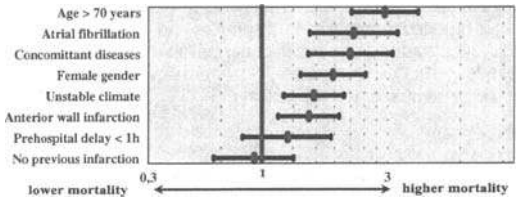
The influence of the climate on the incidence of acute myocardial infarction (AMI) has been discussed controversially based on results of very different regional observations.

Methods: MITRA is a registry of 54 clinics in the Southwest of Germany, in which consecutive patients (pts) with AMI have been enrolled to document actual clinical practice and clinical outcome in AMI. Because of the very homogenous climate in this area we brought together the daily meteorological data and the data of AMI-pts of the time between July 1994 and January 1996. Based on 13 biosynoptical climate classes we defined stable (classes 1–3 and 8–13) and unstable (classes 4–7) climate. We examined the influence of the unstable climate on the incidence of AMI and on inhospital mortality.

Results: During the observational period 3327 pts (median age 66 y, 66.7% male, prehospital delay 165 min) with AMI had been enrolled. Unstable climate was present on 220/580 days (38%). We did not find any difference in daily AMI incidence between unstable and stable climate (5.9 ± 2.6 vs 5.9 ± 2.6, p = 0.29). There were no differences in pts characteristics (age, gender, prehospital delay, anterior wall AMI, reinfarction) on the days with unstable as compared with stable climate. The multivariate analysis identified the unstable climate as an independent determinant of inhospital mortality (OR 1.47, 95% CI 1.10–1.97):



Conclusion: Unstable climate did not influence the incidence of AMI. Pts at risk for AMI dependent on climate could not be identified. Unstable climate on the day of AMI was associated with a marked increase of inhospital mortality after AMI.

P2096 Compared prognostic factors in the elderly and in younger patients after myocardial infarction: one-year results from the nation-wide French USIK study

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Elderly patients have a poorer prognosis after myocardial infarction. However, whether predictors of adverse outcome are the same in the elderly and in younger pts is unclear. The aim of the USIK study was to collect information on the management and outcome of pts admitted to a CCU for acute MI, on a nation-wide scale. All pts admitted <48 hours of symptom onset during the month of November 1995 were prospectively included and followed-up for 1 year. Compared with younger pts (n = 1165), pts >70 years (n = 929) were less likely to be men (55% vs 84%), had more often hypertension, diabetes mellitus, history of stroke or peripheral vascular disease, prior MI or prior CHF. Reperfusion therapy by thrombolysis or primary PTCA was used more scarcely in the elderly (24% vs 55%). Five-day mortality was 14% vs 4% ($p < 0.0001$) and 1-year mortality (Kaplan Meier) was 67% vs 91% ($p < 0.0001$). By Cox multivariate analysis, age, history of heart failure, history of MI and anterior location of MI were independent predictors of 1-year outcome both in young and elderly pts; female gender was an adverse prognostic factor in young pts, while history of stroke or PVD were adverse factors in the elderly. In pts alive at 5 days, age, diabetes, history of heart failure, anterior MI were independent predictors of one year outcome regardless of age; use of reperfusion therapy was an independent predictor of improved survival in the elderly only (RR 0.40, 95% CI: 0.24–0.67).

Conclusion: age, history of heart failure, anterior MI are adverse prognostic factors, regardless of the age of the pts. In the elderly, extent of atherosclerosis (history of stroke or peripheral vascular disease) also has an independent prognostic significance. Reperfusion therapy is associated with improved 1-year prognosis in the elderly, but is not a significant prognostic factor in younger pts, stressing that it has a particularly beneficial effect in pts >70 years of age.

P2097 The long-term association of HDL cholesterol and triglyceride with mortality of women with coronary heart disease

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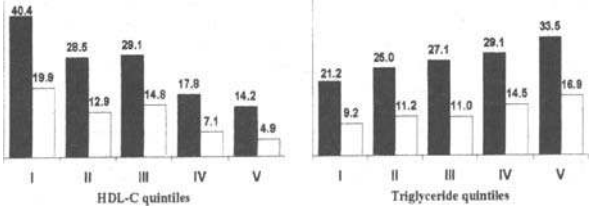
The efficacy of reducing blood levels of triglycerides (TG) and raising HDL cholesterol (HDLC) in men with coronary heart disease (CHD) using gemfibrozil has recently been demonstrated. Insufficient data exist concerning the prognosis of women with varying blood levels of these variables and no pertinent intervention has been aimed at a sufficiently large sample of women. We followed up 2,513 women, aged 40–74, screened for participation, but not included in the BIP study, over a mean period of 5.1 years. Age adjusted mortality rates/1000 person years (all-cause in black; CHD in white), by TG and HDLC baseline quintiles were:



Mortality increased stepwise with increasing TG and declined with increasing HDLC. Multivariate analysis using Cox regression indicated a covariate-adjusted hazard ratio (HR) of 0.85 for mortality associated with a HDLC increment of 10 mg/dl (95% CI, 0.75–0.96). The adjusted HR associated with an increment of 1 log TG was 1.37 (95% CI, 1.04–1.88) prior to adjustment for baseline HDLC. Upon adjustment for the latter, HR declined to 1.10 (95% CI, 0.80–1.50). Correction for regression dilution bias made negligible difference. Contrary to findings reported from CHD-free samples, no synergism of low HDLC (<35 mg/dl) and elevated TG in terms of association with mortality was noted. The issue of low HDLC and elevated TG in women with CHD requires a trial with a substantial number of female patients.

P2098 Treatment of AMI by cardiologists is associated with a lower intrahospital mortality: results of the Myocardial Infarction Registry in Germany

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Purpose: To determine the effect of specialty care on in-hospital mortality in patients with acute myocardial infarction in Germany.

Methods: The Myocardial Infarction Registry (MIR) is a multicenter, prospective registry with 217 participating hospitals in Germany. The primary aim of the study is to optimise therapy strategies in the treatment of AMI. All patients with q-wave AMI, admitted within 96 hours after the onset of pain were included from 12/96–5/98. The use of the combined therapies improving prognosis (reperfusion therapy, aspirin, betablocker and ACE-inhibitor) was documented. The treatment by a cardiologist was compared to the treatment by physicians with a high volume of AMI patients.

Results: In total 14598 patients with AMI were registered.

	Cardiologist n = 4683	Non-cardiologist n = 9915	p value
Age (years)	66	67	ns
Male (%)	66	64	ns
Prehospit. delay (min)	192	195	ns
Diagnostic ECG (%)	69	65	<0.001
Thrombolysis (%)	34	37	ns
Primary PTCA (%)	20	5*	<0.001
Aspirin (%)	92	90	ns
Betablocker (%)	55	53	ns
ACE-Inhibitor (%)	51	54	ns
Inhospital mortality (%)	14	16	<0.001

*referred to a center with PTCA facilities

Conclusions: Treatment of patients with AMI by a cardiologist is associated with a lower intrahospital mortality which may be the result of a higher rate of diagnostic first ECG's and the presence of a catheterization laboratory with PTCA facilities.

P2099 Panic disorder based chest pain and/or palpitations in patients presenting at the first heart aid

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Background: In the literature an important number of patients presenting with chest pain at the emergency department have no cardiac abnormalities after screening but are found to suffer from a panic disorder (PD): numbers range from 25% to 47%. No information is available on the magnitude of this problem in the Netherlands.

Methods: During 3 months all patients coming to our emergency department for cardiac complaints called First Heart Aid (FHA) with chest pain or palpitations and who were sent home after diagnostic procedures excluded a cardiac cause requiring admission, received an informed consent form and the Hospital Anxiety and Depression Scale (HADS) questionnaire. Patients scoring above the cut off score of 8 on the HADS were considered as having a possible PD and were invited for a Mini International Neuropsychiatric Interview (MINI). The psychiatric diagnosis according to the Diagnostic and Statistical Manual (DSM) IV criteria, was made after the MINI.

Results: In 3 months 205 of 621 patients presenting with chest pain or palpitations at the FHA were sent home after screening: there were 52% males and 48% females. The study group consisted of 205 patients. 133 of 205 patients (65%) gave informed consent. Of this group 71 patients (53%) scored above the cut off score on the HADS. Following a structured interview 79% had a panic disorder. A depressive disorder was found in 50%. In 14% no psychiatric diagnosis could be made after the interview.

Conclusions: Panic disorder and/or depression are common problems in patients presenting with chest pain or palpitations to a FHA. 50% of the patients sent home scored above a preset cut off on the HADS. After a structured interview, in 79% of the patients panic disorder was confirmed while depression was diagnosed in 50% of the patients. Only 4 patients (6%) were suspected as panic disorder by the cardiologist. Further studies should be conducted to improve recognition and treatment of panic disorder based chest pain or palpitations.

P2100 Cost benefit analysis on the use of glycoprotein blockers versus conventional antiplatelet therapy alone in acute coronary syndromes

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Background: Results from recent clinical trials demonstrate the benefits of tirofiban plus heparin versus heparin alone in management of acute coronary syndromes (ACS). These clinical benefits included significantly reduced incidence of refractory ischemia, and the composite endpoint of reduced mortality, infarction, re-hospitalization for unstable angina, and refractory ischemia in PRISM-PLUS. However, the combination of tirofiban-heparin was associated with greater incidence of bleeding versus heparin alone, which may make this combination approach less cost-effective in clinical practice.

Methods: This cost analysis was conducted to determine the cost-effectiveness of tirofiban-heparin versus heparin alone. Wholesale drug costs and mean 1996 New York State Medicare/Medicaid charges were applied to drug, ACS-related procedure rates, and complication-related procedure rates reported in PRISM-PLUS for up to 6 months.

Results: Heparin alone was associated with cost-savings of $477.19 per patient in drug costs and $85.59 per patient in procedure-related costs for patients with bleeding complications requiring transfusion. Heparin alone also was associated with overall cost savings over the combination ($562.78 per patient) and was the more cost-effective therapeutic approach. Combined tirofiban-heparin therapy required an additional expenditure of only $12.80 per refractory ischemia episode avoided, and only $8.15 per patient to achieve the combined endpoint of lives saved, and infarctions, re-hospitalizations for unstable angina, and refractory ischemia episodes avoided.

Conclusion: While tirofiban-heparin therapy is less cost-effective than heparin alone, added costs become incremental when clinical benefits for patients with ACS are considered.

P2101 Cost benefit analysis of tissue plasminogen activator versus primary coronary angioplasty in treatment of acute myocardial infarction

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Background: Recently, GUSTO IIb demonstrated modest clinical advantages for angioplasty over tissue plasminogen activator (t-PA) in treatment of acute myocardial infarction (AMI). This cost analysis was conducted to compare the cost-effectiveness of these two treatment approaches.

Methods: Wholesale drug costs and mean 1996 New York State Medicare/Medicaid charges were applied to drug, procedure, and complication rates reported in GUSTO IIb for up to 30 days. Cost effectiveness was assessed for lives saved; complications avoided; and the composite endpoint of lives saved, and nonfatal reinfarctions and disabling strokes avoided at 30 days.

Results: Angioplasty resulted in lower per patient drug ($49 versus $3,447) and complication-related charges ($49 versus $2,804) versus t-PA. t-PA resulted in lower per patient procedure-related charges ($3,447 versus $18,242) versus angioplasty. Overall mean per patient charges were lower for t-PA ($17,315) than angioplasty ($20,605). t-PA was more cost effective than angioplasty for lives saved (−$2,605); complications avoided (−$3,370); and composite endpoint of lives saved, and reinfarction and disabling strokes avoided (−$2,090).

Conclusion: t-PA resulted in greater overall cost savings and cost effectiveness than angioplasty at 30 days post AMI. This was due to lower procedure-related charges for t-PA that were not offset by lower drug- and complication-related charges with angioplasty.

INFLAMMATORY MARKERS AND TROPONINS IN UNSTABLE CORONARY DISEASE

P2102 Anti-endothelial cell antibodies: a marker of the immune system activation in unstable angina and a new risk factor for restenosis after percutaneous transluminal coronary angioplasty

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Background: In recent years the evidence of the role of immuno-mediated inflammation in the development and progression of atherosclerosis has accumulated and several species of autoantibodies have been demonstrated to be involved in ischaemic heart disease (IHD). The objectives of this study were: 1) to evaluate the prevalence of anti-endothelial cell antibodies (AECA) in patients with IHD and the eventual association with restenosis after percutaneous transluminal coronary angioplasty (PTCA); 2) to check if beta 2-glycoprotein I (beta2-GPI) is the major target antigen of AECA;

Methods: 93 patients (72 M and 21 F; age 62.4 ± 9.3) with IHD referred to undergo PTCA and 105 healthy subjects, matched for age and sex were included in the study. IgG and IgM AECA were detected using an ELISA technique on human umbilical vein endothelial cells (HUVEC). AECA positive sera were evaluated for IgG and IgM anti-beta2-GPI by ELISA and tested in the presence or in the absence of purified human beta2-GPI on HUVEC cultured in serum-free medium.

Results and Conclusions: Twelve of 93 (12.9%) IHD patients and only one of 105 control subjects (0.95%) were IgG AECA positive. The prevalence of AECA was higher (21.6%; 11/51) in patients with unstable angina (UA) than in patients with effort angina (EA) (2.4%; 1/42; $p = 0.01$). Three of 12 AECA positive sera were also positive for anti-beta2-GPI IgG antibodies. Sera positive for both antibody specificities showed a marked decrease in endothelial cell binding when tested on HUVEC cultured in serum-free medium. In all cases the binding was restored by the addition of purified human beta2-GPI. The rate of angiographically documented restenosis was 66.7% in the AECA positive and 14.8% in the AECA negative group ($p = 0.0004$).

Our results suggest a possible role for AECA in the immune-mediated inflammation in UA. In IHD patients beta2-GPI is not the only AECA target antigen. The high rate of clinical recurrences after PTCA, confirmed by angiography in AECA positive patients is in line with such a role and suggests further large scale "ad hoc" studies.

P2103 Interleukin-6 release in the coronary circulation of patients with acute coronary syndromes

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Elevated circulating levels of interleukin (IL)-6 are present in patients with acute coronary syndromes (ACS). It is unknown if this represents active IL-6 production from unstable coronary plaques or is simply a systemic inflammatory response. We sought to identify the site of IL-6 production in patients with ACS.

Methods: In 48 patients undergoing cardiac catheterization we obtained samples from the femoral artery (FA), femoral vein (FV), left main coronary artery (LMCA) and coronary sinus (CS) before contrast administration. The patients were grouped as no CAD if there was no stenosis >50% present ($n = 20$), stable CAD if they had at least one stenosis >50% and no clinical instability ($n = 20$), and ACS if they presented with a Q-wave MI, a non-Q MI, or unstable angina ($n = 8$). IL-6 was measured by ELISA (R&D Systems, Minneapolis, MN) and values are expressed in pg/ml.

Results: Patients with no CAD and stable CAD had similar IL-6 levels at all sampling sites (p = NS). In patients with ACS IL-6 levels were higher in the FA ($p = 0.02$), FV ($p = 0.01$) and CS ($p = 0.004$) when compared to patients without ACS. There was no difference between the LMCA and CS in patients without ACS (4.6 ± 8.7 vs 4.6 ± 8.3 pg/ml, respectively, p = NS), however in ACS patients there was a significant difference between the LMCA and CS (10.1 ± 11.1 vs 28.8 ± 34.8 pg/ml, respectively, $p = 0.03$) suggesting ongoing release from the coronary circulation. Since IL-6 levels are also elevated in CHF, we compared left ventricular ejection fraction in patients with and without ACS and found no significant difference between the two groups (56 ± 10% vs 54 ± 18%, respectively, p = NS).

In conclusion, we found that in ACS elevated IL-6 levels are not just a systemic inflammatory reaction, but are due to active cardiac release. Our findings further support the central role of inflammation and cytokine production in the process of plaque destabilization and the genesis of acute coronary syndromes.

P2104 Troponine T levels after very brief coronary oclusions

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In a new model of stunned myocardium due to very brief, repeated coronary occlusions, we have seen a progressive deterioration of the systolic function including structural alterations, mainly at the mitochondrial level. Cardiac troponine T is a regulatory contractile protein usually not found in the blood. Its appearance in blood is a clear signal of myocardial damage. In the present work we have studied biochemically the plasma levels of glutathion (GSH), ATP, troponine T, and creatine kinase (CK) activity and the CK-MB percent in our animal model. twenty successive complete occlusions, each one lasting 2 min, were provoked in the left anterior descending coronary artery, with 3 min recovery intervals between occlusions.

Methods: Venous blood samples from 10 dogs were collected at baseline, during the last reperfusion period, and 24 h and 10 days after ischemia. Samples were centrifuged and plasma separated and stored at −80°C until analysis. GSH, GSSG, ATP and total CK were examined using standard enzymatic protocols. CK-MB isoenzyme was separated by electrophoresis on agarose. Troponine T were measured by Elecsys Troponine T assay supplied by Boehringer-Mannheim.

Results: Our model of stunned myocardium did not show significant variations either in the plasma levels of GSH/GSSG (baseline: 115 vs 155 ug/dl) or ATP (13.9 vs 15.4 umol/dl) after ischemic protocols. The values were completely recovered 10 days after the last coronary occlusion, and the percentage of CK-MB did not show any modification during the 4–24 h after the last ischemia. However, troponine T was detected in plasma after ischemia (baseline: <0.01; ischemic: 0.316 ng/ml, $p < 0.001$); 24 h after the ischemia protocol the levels of troponine T were also increased (0.634 ng/ml, $p < 0.001$). However, these levels return to baseline values at 10 days.

Conclusions: Small variations in the GSH/GSSG, ATP, and CK-MB plasma levels during ischemia suggest weak, reversible myocardial damage with our stunned myocardium model. However, our data point to a progressive deterioration of the systolic function with some structural alterations without necrosis, as shown in the alterations of troponine T plasma levels. We can conclude that troponine T is the most sensitive, specific marker for myocardial cell damage after very brief ischemia.

P2105 Comparison of qualitative versus quantitative determination of troponin T in unstable coronary artery disease

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In unstable coronary artery disease (UCAD) an elevated troponin T (tnT) has been associated with an increased risk for subsequent cardiac events. Already minor elevation of tnT in the range of 0.06–0.2 μg/L implies an adverse prognosis. A rapid test for qualitative analysis of tnT on whole blood has been developed (TropT2/CardiacT, Roche diagnostics) with a detection limit of 0.1 μg/L. In the present study we compared the qualitative tnT test with a standard quantitative tnT test in a large group of UCAD patients.

Methods: Blood samples were obtained from 3022 patients at randomisation, into a multicenter trial of UCAD (FRISCII). The diagnosis was established by history (81% chest pain at rest last 48 hours) and signs of ischemia in ECG or biochemical markers of cardiac damage. The blood samples were taken for immediate qualitative analysis of tnT at each centre by the nurse on duty. Aliquots of plasma was stored frozen at −70C for subsequent central quantitative analysis of tnT (Elecsys, Roche diagnostics).

Results:

	Quantitative tnT, μg/L			
Qual.-tnT	<0.05	0.05–0.19	0.2–0.39	≥0.4
Negative	1026 (95.4)	272 (52.3)	123 (29.4)	105 (11.5)
Positive	50 (4.6)	248 (47.7)	296 (70.6)	902 (88.5)

The sensitivity, specificity, positive and negative predictive value for detection of a tnT ≥ 0.1 μg/L for the qualitative test was 79, 91, 92 and 76%, respectively.

Conclusion: In patients with a clinical suspicion of UCAD a positive qualitative tnT test indicates myocardial damage (tnT > 0.05 μg/L) with a high degree of certainty. However, a negative qualitative tnT test might still be associated with myocardial damage in a considerable proportion of UCAD patients. Therefore, quantitative determinations of tnT is recommended for evaluation of diagnosis and prognosis in UCAD.

P2106 Discordant results for cardiac troponins in patients with renal failure asymptomatic for ischaemic heart disease

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Overall mortality in patients with endstage renal failure is determined by cardiovascular diseases. Thus, it is important to diagnose myocardial lesions with certainty. We studied whether patients on chronic haemodialysis (64 M, 41 F, 3× haemodialysis per week) without overt symptoms of coronary heart disease would have increased serum levels of cardiac Troponin T and cardiac Troponin I (exclusion criteria: acute coronary syndromes < 3 months, systemic autoimmune diseases, hereditary muscle diseases, malignancies, trauma < 3 months, known myocarditis, idiopathic dilatative or hypertrophic or restrictive cardiomyopathies)

For analysis we used TropT®sensitive-rapid assay (bedside-test, cut off 0.1 ng/mL), Troponin-T-ELISA (cut off 0.1 ng/mL), Stratus®cardiales Troponin I (ELISA, cut off 0.1 ng/mL), Troponin I-bedside test (cut off 0.4 ng/mL) and CK-MB concentration (cut off 4.7 ng/mL).

	TnT-bedside	TnI-bedside	TnT-ELISA	TnI-ELISA	CK-MB
Assay with elevated result	41%	27%	22%	7%	2%
Several assays elevated per pt.	32%	21%	20%	7%	2%

In chronic haemodialysis patients who were asymptomatic for ischaemic heart disease elevated serum markers were displayed by Troponin T-bedside-assay in 41%, by Troponin I-bedside assay in 27%, by quantitative Troponin-T-assay in 22% and by quantitative Troponin I-assay in 7%. Frequently more than one assay per individual patient indicated elevated serum markers.

The increased serum levels of cardiac troponins were not a result of neither uraemic perimyocarditis (pericardial effusion), changes in the hemodialysis regimen, pulmonary congestion nor consistent with a certain aetiology of renal failure. For explanation cross reacting antibodies or the extracardial expression of cardiac troponins have to be considered. In the diagnosis of acute coronary syndromes in patients with endstage renal failure the assays for Troponin T and Troponin I have to be assessed with great care because of reduced specificity. Especially rapid bedside assays have lower specificity than quantitative assays. Whether or not in these patients elevated serum levels of cardiac troponins are of prognostic value needs to be investigated.

P2107 Quantification of the prognostic role of cardiac troponins through a cumulative meta-analysis of the available clinical trials

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Multiple studies have shown that elevation of either of the cardiac troponins T (cTnT) or I (cTnI), are predictive of adverse outcomes in patients (pts) with acute coronary syndromes (ACS). However, the relative risk of adverse outcome in pts with cardiac troponins elevations varies in the available studies from 2 to 31 fold. To conclusively quantify on a larger database the relative risk of cardiac troponins elevations, we conducted a meta-analysis of the 20 available studies to separately assess the risk of nonfatal MI and cardiac death in pts without ST-segment elevation (noSTup) and in pts with ST-segment elevation (STup).

Methods: We used two statistical models, which gave comparable results, to better control for heterogeneity in calculating the odds ratio (OR): the fixed-effects model by Mantel-Haenszel-Peto and the random effects model of DerSimonian and Laird. OR were calculated for short (30 days) and long-term (6 mos-3 yrs) follow-up, and separately for cTnT and cTnI.

Results: Among 4,722 patients with noSTup, those with elevated troponins showed a 4.84 fold higher risk (95% CI: 3.61 to 6.48, $p < 0.0001$) of death or nonfatal MI during short-term follow-up and a 2.6 fold increase (95% CI: 1.94 to 3.44, $p < 0.0001$) long-term. Among 13,227 patients with STup, elevated troponin levels carried a 2.8 fold higher risk (95% CI: 2.31 to 3.41, $p < 0.0001$) at 30 days and a 3.9 fold increase (95% CI: 2.47–6.63, $p < 0.0001$) long term. cTnT and cTnI provided similar information, eg. for all patients, a risk of 4.43 fold (95% CI: 3.4 to 6.30) and 4.43 (95% CI: 2.95 to 6.67) respectively; p = NS.

Conclusions: Patients with ACS who have elevations of either of the cardiac troponins have a substantial increase in risk during both short and long-term follow-up. The risk is high enough that identitifcation of these patients should result in attempts to craft specific treatment regimens for this group. cTnT and cTnI share the same capability of predicting adverse outcome in such pts.

P2108 Vascular inflammation and future ischaemic events in acute coronary syndromes

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Elevated levels of the acute phase reactant C-reactive protein are predictive of an adverse outcome in patients presenting with the acute coronary syndromes of unstable angina (UA) and subendocardial infarction (SEMI). We set out to determine if soluble cellular adhesion molecules (sCAMs), which reflect the endothelial inflammatory process underlying acute coronary syndromes, could be used as prognostic markers in patients presenting with UA and SEMI.

Methods: Patients with UA and SEMI had serum samples taken at presentation and were followed for 6 months. Ischaemic end points were defined as (i) recurrent UA, (ii) non fatal MI and (iii) cardiovascular death. Soluble ICAM-1, VCAM-1, E-selectin and P-selectin levels were measured using an ELISA technique. Data are expressed in ng/ml as mean ± SEM.

Results: 87 patients enrolled in the study (male/female = 70/17, mean age 62 ± 10 yrs). 27 patients (31%) had ischaemic events during follow up (15 recurrent UA, 6 non fatal MI and 6 deaths). Levels of soluble VCAM-1 were significantly higher in those patients who had ischaemic events during follow up (888 ± 54 ng/ml event group v's 713 ± 26 ng/ml non event group, $p < 0.02$). There was no significant difference in the levels of soluble ICAM-1, E-selectin or P-selectin between the ischaemic event and non event groups (359 ± 15 ng/ml v's 314 ± 15 ng/ml for ICAM-1, 55 ± 4 ng/ml v's 57 ± 4 ng/ml for E-selectin and 109 ± 10 ng/ml v's 115 ± 6 ng/ml for P-selectin respectively).

Conclusion: Elevated levels of soluble VCAM-1, reflecting coronary vascular inflammation, are predictive of future ischaemic events in the 6 months following presentation in patients with UA and SEMI.

P2109 An assessment of the relative value of cardiac markers in the early triage of "high-risk" patients with chest pain

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Few previous studies have compared the relative value of simple, widely available, rapid biochemical tests in the early in-hospital triage of patients who would otherwise be considered to be at high risk for adverse events. The aim of the current study was, therefore, to evaluate the utility of cardiac troponin I (cTnI), creatine kinase-MB mass ($CK\text{-}MB_{mass}$), myosin light chain-1 (MLC-1) and myoglobin (Mgb) in identifying 'high risk' patients with chest pain who will experience serious cardiac events (SCEs) in hospital.

Methods: Cardiac TnI, $CK\text{-}MB_{mass}$, MLC-1 and Mgb levels were obtained on 208 patients with chest pain who were at >7% risk of acute myocardial infarction (AMI), but without new ST segment elevation on their presenting electrocardiogram (ECG). Samples were taken on admission (0 h) and at 4, 8, 16 and 24 h. The sensitivity, specificity, positive and negative predictive value (PPV & NPV) of patients suffering a SCE in hospital were determined for each marker and time-point. SCEs included cardiac death, AMI, cardiac arrest, life threatening cardiac arrhythmia, cardiogenic shock and urgent coronary revascularisation.

Results: Admission levels of all markers were poor predictors of SCEs in hospital but improved substantially thereafter. Mgb was the least sensitive marker, with lowest NPV. cTnI and $CK\text{-}MB_{mass}$ were the most useful prognostic indicators. If both of these markers were negative at 0, 4 and 8 h, then 99% (95% confidence interval 96–100%) of patients remained free from SCEs during their hospital stay. The only SCEs not predicted in this manner were revascularisation procedures and their associated complications. Additional tests after 8 h, or the inclusion of additional markers, did not further improve predictive accuracy.

Conclusions: Patients with high risk clinical features who have negative cTnI & $CK\text{-}MB_{mass}$ 0, 4 and 8 h after admission have a favourable in-hospital prognosis and could be considered for early triage out of CCUs.

TROPONIN ELEVATION IN ACUTE CORONARY SYNDROMES

P2110 Possible reasons for the prognostic value of troponin T on admission in patients with ST-segment elevation myocardial infarction

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Troponin-T (**tn-T**) on admission seems to be associated with an increased mortality in patients with ST-elevation myocardial infarction (**AMI**). Also other factors e.g. a recent previous infarction, the rate of TIMI grade 3 flow after thrombolysis, the time from onset of chest pain to treatment (**delay**) and the size of the infarction are related to mortality.

Methods: In the present trial 101 patients with AMI were included, all with ST-elevation and Streptokinase treatment. We investigated the delay, the incidence of repeated episodes of chest pain the last 24 hours (**h**) before admission, the level of Tn-T at entry (cut-off level of 0.1 ug/L), and the size of infarction (tn-T level at 72 h). A coronary angiography was performed after 24 h and the rate of TIMI grade 3 flow and grade of stenosis in the infarct-related artery (**IRA**) were measured. The patients were followed for 2.5–4.5 years.

Results: Fifty-six (55%) patients had tn-T > 0.1 ug/L on admission.

Tn-T (ug/L)	<0.1	≥0.1	p-value
Repeated chest pain < 24 h	11%	50%	<0.001
Median delay from onset h	2.0	4.2	<0.001
Rate of TIMI grade 3 flow	72%	50%	0.03
Median tn-T at 72 h	5.7	7.0	NS
Mortality (2.5–4.5 years)	9%	25%	0.0035

In a multivariate analysis (Cox regression) these factors were evaluated regarding relations to mortality during follow-up. Repeated chest pain was a prognostic independent variable with odds ratio (**OR**) of 4.2 (95% CI, 1.4 to 12.8). None of the other factors were significant independent risk factors although the rate of TIMI grade 3 flow in IRA showed a trend with OR of 2.8 (95% CI, 0.9 to 8.6).

Conclusion: The present trial verified the relation between tn-T on admission and long-term mortality in patients with ST-elevation MI. One explanation to this relation might be that repeated chest pain the day before the infarction identifies patients with poor outcome based on previous myocardial damage and therefore elevated tn-T at admission. An additional possible explanation might be the less successful reperfusion in those with elevated tn-T.

P2111 Prognostic value of new biochemical markers in unstable angina

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Background and Purpose: Elevated cardiac-specific troponins (cTn) are valid predictors of adverse events in patients (Pts) with acute coronary syndromes. Our aim was to assess the prognostic value of new biochemical markers-CK-MB mass and Myoglobin (Myo) – in Pts with unstable angina.

Methods: We prospectively studied 144 consecutive Pts (mean age 63 ± 12 years; 19% female) hospitalized for rest angina in the previous 48 hours associated to ischemic electrocardiographic changes and without elevation of conventional total CK and CK-MB activities within 24 hours after admission. Measurements of total CK and CK-MB activities, cTnI (negative < 0.1 μg/L) CK-MBmass (negative < 5 ng/mL) and Myo (negative < 45 μg/L) were performed on admission and every 6 hours during the first day of hospitalization. We used a composite 30 day event rate of death, non-fatal myocardial infarction (MI) or recurrent myocardial ischemia.

Results: Elevation of cTnI was detected in 46 Pts (32%), of CK-MBmass in 40 Pts (28%) and of Myo in 55 Pts (38%). At 30 days follow-up, 4 Pts (2.8%) had died, 3 (2.1%) experienced non-fatal MI and 36 (25.0%) recurrent myocardial ischemia. In 40 Pts (27.8%), at least one event occurred during follow-up. The table shows the combined frequency of events at 30 days follow-up with respect to each biochemical marker analysed.

Marker	Any Event (%)	P
cTnI pos	43.5	0.008
cTnI neg	20.4	0.008
CK-MBmass pos	43.9	0.006
CK-MBmass neg	19.4	0.006
Myo pos	27.8	NS
Myo neg	28.7	NS

Conclusion: In this population of Pts with unstable angina, elevation of CK-MBmass had a similar prognostic value to cTnI with respect to prediction of death, non-fatal MI or recurrent ischemia in the 30 days follow-up. Elevation of Myo did not identify Pts at risk for these events.

P2112 Relationship of troponin T and C-reactive protein with transient myocardial ischaemia in patients with unstable angina

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Both transient myocardial ischemia (TMI) on 24-hour ECG Holter monitoring (HM) and plasma levels of troponin T (TnT) and C-reactive protein (CRP) have been shown to predict clinical events in unstable angina (UA). However, the correlation of TnT and CRP levels with TMI has never been appropriately investigated.

TnT and CRP levels were measured and HM was performed within 24 hours from admission in 129 UA pts. (93 men, 63 ± 10 yrs). TMI on HM was diagnosed in case of ST segment depression (rectilinear or downsloping) or elevation > 1 mm, lasting for >1 min.

Episodes of TMI were detected in 11 of 16 pts (68.8%) with high (>0.2 μg/L) and in 38 of 113 pts (33.6%) with low TnT levels ($p < 0.01$). On the other hand, TMI episodes were found in 30 of 66 pts (45.4%) with high (>3 mg/L) and in 19 of 63 pts (30.2%) with low CRP levels ($p = 0.07$). Furthermore, TMI was detected in 9 of 13 pts (69.2%) with high levels of both TnT and CRP, in 23 of 56 pts (34.8%) with high levels of either TnT or CRP, and in 17 of 60 pts (28.3%) with low levels of both TnT and CRP ($p = 0.02$). The number of ischemic episodes and the total daily time of TMI were not significantly different between pts with and those without high levels of TnT, CRP, or both.

In conclusion, in UA pts: (1) TMI on HM is more closely associated with increased levels of TnT than of CRP; (2) TMI is less frequent in pts with low levels of both TnT and CRP; (3) however, TMI is somewhat independent of TnT and CRP levels, suggesting that these biochemical markers of prognosis have some limitations for assessing the severity of the ischemic activity of the disease.

P2113 Admission levels of fatty acid-binding protein and troponin I and inhospital ischaemic events in patients with unstable coronary artery disease

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Background: Heart fatty acid binding protein (FABP) has been recently proposed as an early marker of myocardial damage. Cardiac troponin I (TnI) is an accepted marker of cardiac muscle injury and its value for prognosis of recurrent coronary events is believed to be proven. The aim of this study was to compare admission levels of FABP with those of TnI in patients with unstable angina (UA) and non-Q-wave infarction (nQ-AMI) with and without complications during hospitalization.

Methods: Serum FABP and TnI (HyTest, Finland) levels were measured in 59 pts (mean age ± SD – 62 ± 8.9 years, 35/59% male) at admission within 24 h from index angina attack (mean ± SD – 5.2 ± 5 h). Fifty pts had UA and 9 pts – nQ-AMI (confirmed by serial total CK). Ischemic events (IE) (Q wave AMI and attacks of angina at rest > 10 min) were registered during period of hospitalization which lasted 17.4 ± 7.05 days.

Results: FABP exceeded >0.6 ng/ml in most of the pts – 42 (71%) while TnI level was elevated (>0.4 ng/ml) in 16 (27%) pts. IE occurred in 20 pts (Q-wave AMI in 2 and attacks of rest angina in 18).

Patients	FABP (ng/ml)	TnI (ng/ml)
With IE (n = 20)	26.4; 11.2–52*	0.18; 0.07–0.44
Without IE (n = 39)	7.2; 1.5–23.1	0.14; 0.05–0.40

(median; 1–3 interquartile range, *$p < 0.001$ vs without IE)

FABP level exceeded 0.6 ng/ml in 19/20 pts (95%) with IE and in 23/39 pts (59%) without IE, ($p = 0.009$). The incidence of elevated TnI level at admission was similar in pts with (6/20, 30%) and without (19/39, 25.6%) IE ($p = 0.9$). The prognostic utility of markers was as follows:

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
FABP	45.2%	94.1%	95%	41%
TnI	37.5%	67.4%	30%	74.3%

Conclusion: In this group of patients with unstable coronary artery disease characterized by relatively short interval from index attack of angina to blood sampling admission level of fatty acid binding protein was often elevated and turned out to be more powerful predictor of inhospital ischemic events than admission level of troponin I.

P2114 Prognostic impact of elective myocardial revascularization in unstable angina: influence of cardiac troponin I levels after admission

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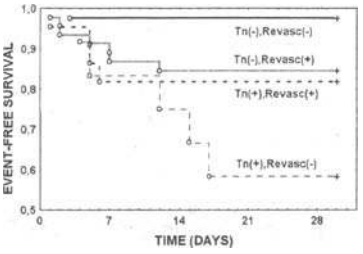
Background: Prognostic benefit of myocardial revascularization (MyoRevasc) in patients (Pts) with unstable angina (UA) stabilized with medical therapy is uncertain. Troponin (Tn) I may help selection of Pts for MyoRevasc.

Objective: We sought to examine the influence of elective MyoRevasc according to cardiac TnI levels after admission for UA.

Methods: We measured serial TnI and CK-MB levels (on admission and every 6 hours during the first 24 hours) in 164 consecutive Pts admitted to our CCU with UA defined as angina at rest in the previous 48 hours with ischemic ECG changes and normal CK-MB levels. We excluded 41 Pts that presented recurrent myocardial ischemia and underwent urgent coronariography. The remaining 123 Pts stabilized with medical therapy and were enrolled in analysis. TnI was considered positive if any value was >0.1 ng/ml. We used a 30 day composite event rate of death or myocardial infarction or re-hospitalization for UA.



Results: TnI was positive in 36 Pts. Elective MyoRevasc was performed in 68 Pts (22 TnI positive). Event-free survival in TnI negative Pts was 84.8% after elective MyoRevasc and 97.6% in Pts not revascularized ($p = 0.036$). In TnI positive Pts, event-free survival was 81.2% after elective MyoRevasc and 64.3% in Pts not revascularized ($p = 0.092$).

Conclusion: Elective MyoRevasc had a negative impact on prognosis in Pts with negative troponin I levels after admission for UA. Further studies are needed to confirm the tendency for benefit in Pts with positive troponin I levels.

P2115 Short-term prognostic significance of coagulation and inflammation markers in unstable angina

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Activation of the coagulation system and inflammation are frequently associated with unstable angina (UA) presentation. The purpose of this study was to identify coagulative and inflammatory markers that would predict an unfavourable outcome in UA patients.

Methods:. Fifty-eight pts admitted to the CCU for Braunwald Class III UA had blood samples taken on admission and on day 3 to measure the following variables: interleukin-6 (IL-6), von Willebrand factor antigen (vWF), thrombomodulin (TM), prothrombin fragments (F1 + 2), thrombin-antithrombin III (TAT). At 30 days, 39 pts had an uneventful clinical course (group I) while 19 pts (group II) either died (n = 4) or had recurrent angina or myocardial infarction (n = 15).

Results:

	Group I (n = 39)		Group II (n = 19)	
	admission	day 3	admission	day 3
IL-6 (pg/ml)	7.2 ± 6.7	5.9 ± 9.1	5.2 ± 5.4	10.2 ± 11.5*
vWF (%)	112 ± 28	119 ± 17	117 ± 13	119 ± 12
TM (ng/ml)	42.5 ± 37	47.5 ± 30	41.5 ± 31	55 ± 40
F1 + 2 (nmol/l)	1.39 ± 0.78	1.46 ± 0.5	1.28 ± 0.5	1.45 ± 0.57
TAT (mg/l)	5.45 ± 8.4	4.59 ± 4.98	4.68± 2.3	5.02 ± 1.68

*$p < 0.05$ day 3 vs admission

In conclusion, no difference was found in the baseline values of coagulative and inflammatory markers between pts with or without an unfavourable 30-day outcome. Rising IL-6 values were the only prognostic indicator, suggesting that a mounting inflammatory process is associated with a worse short-term outcome.

P2116 Prognostic value of D-dimer assay in unstable angina

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Background and Purpose: In unstable angina (UA), risk stratification is crucial for guiding management decisions during the acute phase. High levels of cross-linked fibrin degradation products (measured as D-dimer) may reflect increased fibrin turnover suggestive of ongoing thrombosis. Therefore, we aimed to determine the prognostic value of elevated D-dimer in Pts with UA.

Methods: We prospectively studied 32 Pts (mean age 63 ± 12 years; 19% female) hospitalized for Braunwald class IIIIB UA and not presenting co-morbid conditions known to increase D-dimer. D-dimer was measured on admission using a quantitative fibrin-specific ELISA (normal < 500 ng/mL). Cardiac-specific troponin I (cTnI) was measured on admission and every 6 hours during the first day of hospitalization (negative < 0.1 μg/L). We used a composite 30 day event rate of death, non-fatal myocardial infarction (MI) or recurrent myocardial ischemia.

Results: High levels of D-dimer were present in 7 Pts (22%) and elevation of cTnI was detected in 9 Pts (28%). At 30 days follow-up, 1 Pt (3%) had died, 8 (25%) experienced non-fatal MI and 11 (34%) recurrent myocardial ischemia. In 14 Pts (44%), at least one event occurred during follow-up. The table shows the 30 day combined event rate with respect to each test used.

Test	Any Event (%)	p
D-dimer pos	85.7	<0.04
D-dimer neg	32.0	
cTnI pos	55.6	NS
cTnI neg	39.1	

Conclusion: In this population of Pts with UA, D-dimer identified Pts at higher risk for thrombotic complications and who may benefit from more aggressive therapies.

P2117 Significance of increased plasma levels of inflammatory mediators in unstable angina

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Recent data have shown that an inflammatory process takes place in unstable angina (UA), resulting in the secretion of cytokines. Scanty information however is available on the relation between plasma values of inflammatory mediators, like interleukin (IL)-6, interferon-gamma (IFN-g) and the monocyte chemoattractant protein-1 (MCP-1) and the level of Troponin T, a biochemical marker of myocardial injury.

Methods: Three groups of pts were studied: 29 with UA, 28 with stable exertional angina (SA) and 19 healthy controls (C). All pts in UA and SA groups had significant CAD (>50% reduction of luminal diameter in at least 1 major vessel at coronary arteriography). Il-6 and IFN-g plasma levels were measured using the ELISA method. Data are expressed as mean + SE and ANOVA for repeat measurements was used to compare data in groups and subgroups.

Results: IL-6 was increased in the UA and SA groups as compared to the C group (UA4.68 ± 1.17; SA3.6 ± 1.6; C 1.9 ± 0.27 pg/ml, $p < 0.005$), without significant difference between SA and UA pts. IFN-g was higher in the UA group than in the the other 2 groups (UA 0.27 ± 0.09; SA 0.05 ± 0.03; C 0.02 ± 0.02 pg/ml, $p < 0.001$). Higher values of MCP-1 were also observed in UA pts (UA 1114 ± 431; SA 169 ± 34; C 101 ± 23 pg/ml, $p < 0.0001$). Among UA pts, 11 with increased Troponin T levels (>0.1 microg/L) had significantly higher IFN-g and MCP-1 values than 18 pts with undetectable Troponin T levels (IFN-g: 0.60 ± 0.04 vs 0.10 ± 0.04 pg/ml, $p < 0.001$; MCP-1: 2099 ± 906 vs 393 ± 241 pg/ml, $p < 0.01$). On the contrary, no difference was found in IL-6 values between UA pts with or without increased Troponin T (5.4 ± 1.7 vs 4.1 ± 0.9 pg/ml).

Conclusion,. IFN-g and MCP-1 plasma levels are elevated in UA pts, such increase being mostly related to myocardial cell injury and Troponin T release. IL-6 increased plasma levels are less specific for UA, as they can also be observed in SA pts. However, in UA pts they are not related to myocardial cell injury.

P2118 Troponin T release is related to a disturbed fibrinolysis in unstable angina pectoris

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Detection of Troponin T is a strong prognostic marker in patients with unstable angina pectoris (UAP). We investigated molecular markers of fibrinolysis and hemostasis in 85 patients with UAP in relation to the troponin T status (TNTpos./TNTneg.). Thrombin-antithrombin complex (TAT), tissue-type plasminogen activator mass (TPA), and D-dimers (DD) were measured initially (0 d) and 2 d later vs. controls.

	TNTpos.	TNTneg.
TAT 0 d	7.25 ± 1.49	4.42 ± 0.84
(μg/l) 2 d	4.24 ± 0.49	5.96 ± 2.5
TPA 0 d	10.24 ± 0.68#	7.58 ± 0.54
(ng/ml) 2 d	12.90 ± 1.73	9.74 ± 1.05
DD 0 d	457 ± 39*	316 ± 22
(ng/ml) 2 d	451 ± 42*	275 ± 37

means ± SEM; * = $p < 0.05$, # = $p < 0.01$ for TNTpos. vs. neg..

The thrombin activation (TAT) in UAP is not related to the TNT-status, while a strong correlation between alterations of fibrinolysis and the troponin status exists.

Conclusion: The troponin status of patients with UAP is strongly associated with the alteration of fibrinolysis, while an increased thrombin activation is present independently of TNT-release in UAP. Differentiation of these pathways enables future development of targeted therapeutical approaches.

P2119 Timing of troponin T measurement to risk stratify patients admitted with chest pain in routine clinical practice

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It has recently been suggested in patients presenting with chest pain that a negative Troponin measurement after six hours from chest pain onset or four hours from admission is sufficient to stratify these patients into a low risk group who can be discharged.

We studied 324 patients admitted to a single hospital with chest pain who were followed for outcome for a median of 3 years. 76/324 (23.4%) were positive for cTnT on admission cut at 0.2 mcg/l; of these 37 (48.7%) had presented more than six hours from the onset of their worst chest pain (median 12.4 hours Lower Quartile 7.4 hours, Upper Quartile 24.7 hours). In this group 28/37 had a final diagnosis of MI and 9/37 a final diagnosis of Unstable Angina.

Of the remaining 248 patients initially cTnT negative, a further 91 (37%) were positive when tested 12–24 hours following admission. Of these 28/91 (30.1%) had presented more than six hours from the onset of their worst chest pain (median 10 hours Lower Quartile 7.2 hours, Upper Quartile 13.4 hours). In this group 12/28 had a final diagnosis of MI and 16/28 a final diagnosis of Unstable Angina. Of the 91 patients who subsequently became positive for cTnT, four hour from admission samples were available for 53 patients. 38% (20/53) were still negative for cTnT at this time point.

In routine clinical practice therefore, neither sampling at either six hours from symptom onset or four hours from admission or both are sufficient to 'rule out' high risk patients.

P2120 Absence of a prognostic value of troponin I in unstable angina

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Cardiac Troponin I (cTn-I) isoform has been proposed as a prognostic marker in acute coronary syndromes. Aim of the study was to investigate long-term prognostic value of cTn-I in unstable angina (UA). To this purpose 104 patients (pts) (mean age 62.3 ± 5.3 years) in Braunwald Class IIIB UA were enrolled for the study. Blood samples for cTn-I (measured by immunofluorescency, time to perform the test: 20 minutes) were obtained every 6 hours in the first two days after admission. Coronary angiography was performed in all patients within the 5th day; 93 pts (89%) underwent revascularization procedures (RP) (CABG 58 pts, PTCA 35 pts) during admission. Primary end-points were cardiac death, non-fatal AMI and repeated RP at 6 months and 1 year after hospital discharge.

Results: In the first 48 hours after admission, 65 pts (group 1, 63%) had an increase of cTn-I in at least one sample, with values of 0.6–4.2 mgL(mean 2.5 ± 1.1). In the remaining 39 (group 2) Tn-I did not exceed 0.5 mgL(cut-off value). 6-months and 1-year mortality was 2.1 and 2.2% in pts with raised Tn-I and 2.2 and 2.3% in pts with normal Tn-I, respectively (p = NS). At 6 months 4 non fatal-AMI occurred in pts of group 1 and 5 in pts of group 2 (p = NS); at 1 year 5 AMI in each group were recorded; there were no differences, between the two groups, regarding number of new RP performed during the study. On the contrary, greater incidence of death, AMI and RP was recorded in medically-treated pts (11%) and in pts in whom dissection, acute occlusion, distal embolism or peri-operative AMI occurred during revascularization.

Conclusions: In pts with unstable angina RP abolishes any prognostic value of Tn-I increase; possibility to perform full revascularization, the techniques utilized and complications following PTCA or CABG affect prognosis of these pts.

DIRECT ANGIOPLASTY

P2121 Characteristics and in-hospital outcome of patients included in the registry of the Stent PAMI trial

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The stent PAMI trial randomized 900 pts to stent or balloon at the acute phase of MI in 62 centers worldwide. 1458 pts were eligible (inclusion-exclusion criteria met, informed consent signed) and 558 pts were secondarily excluded from the main study and followed on a registry. Population. 170 pts were excluded before PTCA (lesion requiring surgery: 12.9%, culprit lesion < 70%: 3.2%) and 388 after PTCA (high likelihood of requiring stent: 20.8%, major side branch: 10%, high likelihood of requiring CABG within 6 months: 10.3%)

Demographics. The registry pts were older than the randomized pts (62.6 ± 12.7 vs 60.9 ± 12.3 years, p = NS), presented more often with diabetes (20.4% vs 15%, p = 0.01), and had more frequently multivessel disease (61.5% vs 45.0%, p < 0.001).

Treatment received. 14.3% of pts had medical treatment, 13.8% had emergency or elective CABG, 36.6% had PTCA alone and 29.6% PTCA with stent. In the 388 pts who had PTCA, procedural success was obtained in 84.3% of cases (vs 99.4% for randomized pts, p < 0.001). In-hospital recurrent ischemia occurred in 9.0% of the registry pts (vs 8.4 for randomized pts) and in-hospital mortality in 5.0% (vs 2.4% in the randomized pts, p = 0.01).

In conclusion, patients excluded from the main study of the Stent Pami trial had a more severe presentation, procedural success was lower and subsequently, mortality rate was higher.

P2122 Rescue coronary stenting improves clinical outcome in patients with acute myocardial infarction

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Background: The effectiveness of intracoronary stenting as a rescue intervention in patients with acute myocardial infarction and unsuccessful thrombolysis has not been assessed. Since an extensive intimal disruption is frequently the reason for failure of thrombolytic therapy, coronary stent placement seems to be well suited in this setting. The objective of the present study is to assess the clinical outcome of patients with acute myocardial infarction, failed thrombolysis and rescue coranary stent implantation.

Methods: The analysis is referred to 167 consecutive patients, 60 ± 11 year old and 23% women. Nineteen patients were in cardiogenic shock. Patients were followed-up for 1 year after the intervention.

Results: On average 1.2 ± 0.7 stents were implanted in each patient using a mean balloon pressure of 13.3 ± 2.9 atm and a balloon-to-vessel ratio of 1.03 ± 0.10. Stent placement procedure was successful in 98.2% of the patients. Within the first 30 days after the procedure, stent vessel occlusion occurred in 1.2%; the combined endpoint of cardiac death or recurrent myocardial infarction was recorded in 1.4% of patients without shock and 47.4% of those with cardiogenic shock. At one year the probability of death or myocardial infarction was 4.7% in patients without shock and 52.6% in those with cardiogenic shock.

Conclusion: These findings suggest that in this particularly high risk cohort of patients with acute myocardial infarction and failed thrombolysis, rescue coronary stenting is associated with favorable short- and long-term clinical outcome in comparison with historical data for this subset.

P2123 Outcome of stenting in acute myocardial infarction without routine administration of abciximab

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In the era of ticlopidine and aspirin for prevention of stent thrombosis stenting in acute myocardial infarction has become a promising approach. Despite the results of the EPISTENT trial the question remains whether the administration of Abciximab is necessary in all cases of stent implantation in acute myocardial infarction.

Methods: In order to determine the safety of stenting in myocardial infarction without routine administration of Abciximab the acute results and 30 days outcome of 100 patients treated for acute myocardial infarction from 8/97 until 11/98 were analysed retrospectively.

Results: In all cases single stent implantation (NIR, GFX, Crossflex) of different lengths (12–24 mm) were done with 10–12 atm after mechanical recanalisation and pre-dilatation of the vessel. Three patients developped acute stent thrombosis (2 × LAD, 1 × RCA) within 8 hours after the inital procedure. In one case (RCA) a lethal myocardial perforation appeared after successful recanalisation. In a fourth patient stent thrombosis appeared after rescue stent implantation for failed thrombolytic therapy. In all other cases the course was uneventfully over a period of 30 days.

In conclusion, acute stent thrombosis after stent implantation for myocardial infarction without routine administration of Abciximab is a rare event (3%) with a low mortality rate (1%). The use of bolus and infusion therapy of Abciximab over 12 hours only in high risk cases (rescue stent implantation after previous thrombolytic therapy or TIMI II flow after stent implantation) seems to be a cost saving strategy with excellent results.

P2124 Primary angioplasty and stenting in non-selected elderly patients with acute myocardial infarction: in-hospital and mid-term outcome

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Background: Acute myocardial infarction (AMI) in elderly patients is associated with a high mortality and reinfarction rate. The risk and benefit of intracoronary stenting in this setting have not yet been assessed.

Methods: Between January 1995 and December 1997, 106 consecutive elderly patients >75 years old were admitted for AMI within 24 hours of symptom onset (mean time to admission 6.3 ± 4.8 hrs), 30.2% of whom were in cardiogenic shock. We analyzed the acute and long-term clinical outcome after primary stenting in this cohort of patients

Results: A total of 100 patients (94.3%) had percutaneous transluminal coronary angioplasty (PTCA), 80 (80%) of whom (mean age 81 ± 5, 51% female) underwent subsequent stenting. Mean time from admission to reperfusion was 38.2 ± 15 minutes. PTCA was successful in 96 patients (96.0%). No emergent coronary artery by-pass grafting or repeat MI were reported. In-hospital death occurred in 27 patients (27.0%), 62% with cardiogenic shock and 12.6% without. Vascular complications occurred in 4 patients (4%) and minor stroke in 2%. Repeat PTCA for recurrent ischemia was performed in 2 patients (2.0%). At a mean follow-up of 16 ± 10 months, 6 patients needed repeat revascularization (8.2%). Total survival was 57% (85% of in-hospital survivors).

Conclusion: Mortality in non-selected elderly patients with acute MI is high. Primary angioplasty using elective stenting in this setting seems to be associated with a very favorable short- and mid-term outcome.

P2125 Primary angioplasty in acute myocardial infarction: is there an influence of time from onset of symptoms to start of treatment on in-hospital delay and clinical course?

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Early initiation of treatment in patients (pts) with acute myocardial infarction (AMI) receiving thrombolysis is associated with lower mortality. For pts treated with primary angioplasty there are no data concerning this issue.

Methods: Out of 3 German AMI registries (MIP, MITRA, MIR; time of recruitment: 1992–1997) all AMI pts treated with primary angioplasty were analysed. 1272 pts showed a pre-hospital delay of ≤24 hours and documented in-hospital delays of ≤12 hours.

Results: Time from onset of symptoms until start of primary angioplasty (time to treatment) was ≤3 hours in 177 pts (13.9%), 3–6 hours in 649 (51%) pts and 6–24 hours in 446 (35.1%) pts..

Time to treatment (hrs)	In-hospital time (hrs)	In-hospital mortality
≤1 (n = 30)	0.33	0%
1–2 (n = 147)	0.67	5.4%
2–3 (n = 253)	1	8.3%
3–4 (n = 189)	1.67	6.4%
4–5 (n = 113)	1.67	7.1%
5–6 (n = 94)	1.33	4.3%
6–8 (n = 105)	1.42	5.7%
8–12 (n = 121)	1.75	5%
12–24 (n = 220)	2.67	5.5%
p-value	*0.001*	*0.71*

Conclusion: An increasing pre-hospital delay was associated with an increase of in-hospital time to start of primary angioplasty. In contrast to treatment with thrombolysis, time to treatment with primary angioplasty showed no association with hospital mortality, with the exception of the first hour ("golden hour").

P2126 Influence of segment location on outcome after primary angioplasty for anterior acute myocardial infarction

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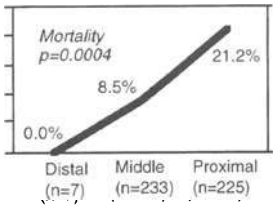
Patients with anterior acute myocardial infarction (AAMI) are a higher subset of patients even when treated with primary angioplasty (PTCA). The objective of this study was to evaluate the importance of the level of the occlusion of the left anterior descending coronary artery (LAD) on the outcome of patients with AAMI that are treated with PTCA.

Methods: From 1.991 to 1.998, 465 patients with AAMI were treated with PTCA within the first 12 hours after the onset of symptoms in our institution. The in-hospital outcome was compared between patients with a proximal vs. non-proximal LAD occlusion.

Results: Mean age was 64 ± 12 years and 80% were male. The in-hospital mortality was 16.6% in the entire population and 9.3% after excluding patients in cardiogenic shock. The mortality was 0%, 8.5% and 21.2% (p = 0.0004) in patients with distal (n = 7), middle (n = 233) and proximal (n = 225) occlusion, respectively. The comparison between patients with a proximal (n = 225) and non-proximal (n = 232) LAD occlusion in summarized below:



	Prox.	No prox.	p
Mortality	21.2%	8.3%	0.0001
No shock	12.3%	3.9%	0.0012
Angio. success	90.4%	91.9%	NS
LVEF < 0.40	46.7%	26.0%	0.0087
Age (years)	64 ± 9	64 ± 0	NS
Female gender	23.8%	27.9%	NS
Prior thrombolysis	5.9%	6.9%	NS
No. vessels	1.7 ± 0.8	1.6 ± 0.8	NS
Killip > 1	42.4%	20.7%	<0.0001
Diabetes	28.8%	21.6%	NS
Hypertension	44.3%	40.4%	NS
Free wall rupture	4.4%	2.3%	NS
Re-AMI	3.4%	3.7%	NS
Stent	46.2%	44.7%	NS

Conclusion: In the group of patients with AAMI that are treated with PTCA, those with a proximal LAD occlusion constitute a very high risk subset, especially due to a higher incidence of cardiogenic shock. In these patients, there should be no delay in action directed to obtain reperfusion.

P2127 Influence of time to reperfusion on in-hospital outcome after primary angioplasty for acute myocardial infarction

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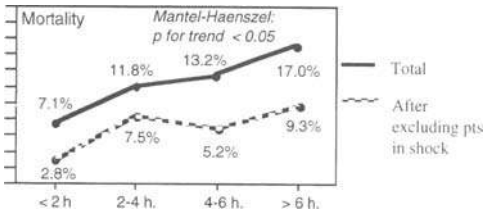
It has been recently suggested that mortality is relatively constant with increasing time to reperfusion in selected patients with acute myocardial infarction (AMI) that are treated with primary angioplasty (PTCA). The purpose of this study was to evaluate the influence of time to reperfusion on the outcome in a non-selected series of patients with AMI that were treated with primary PTCA.

The study population is constituted by 713 patients (64 ± 13 yrs, 80% male) with AMI that were treated with PTCA from 1,991 to 1,998 in our institution within the first 12 hours after the onset of symptoms. The in-hospital outcome was studied in different subgroups of patients depending on the time interval from the onset of symptoms to reperfusion.

Results: Mortality in patients with <2 hours was significatively lower than in those with >2 hours: 7.1% vs. 12.9% (p = 0.0410) for the entire population, and 2.8% vs. 7.2% (p = 0.0427) after excluding patients in cardiogenic shock. The mortality was directly associated with the time to reperfusion: 7.1%, 11.8%, 13.2% and 17.0% for patients with <2, 2–4, 4–6 and >6 hours, respectively, in the whole population (Mantel-Haenszel: p for trend < 0.05).



Conclusion: In a non-selected series of patients with AMI that are treated with primary PTCA, the in-hospital mortality is directly related with the time to reperfusion.

P2128 Troponin T release during reperfusion predicts better left ventricular function recovery in patients with acute myocardial infarction treated with primary stenting than direct balloon angioplasty

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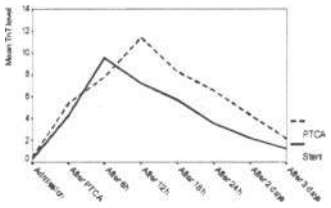
There is still lack of information regarding the recovery of left venticular (LV) function after primary stenting compared to balloon angioplasty. For this purpose we study the release kinetics of Troponin T (TnT) as a marker of reperfusion in order to determine their influence on recovery of global LV function studied by echocardiography.

Methods: Eighty patients with AMI (mean age 57.33 years, 62 men and 18 women) who underwent primary PTCA in the first 3 hours after the onset of symptoms were stratified into two groups: Group A patients (n = 40) were treated with one or more stents (for suboptimal results), while Group B patients (n = 40) were treated with balloon angioplasty. Acute angiographic success was achieved in 98% of patients in both groups. Serial venous blood samples for TnT measurement were obtained during the first 3 days, as also serial echocardiograms were obtained on 7th, 30th, 90th and 180th day after procedure and global ejection fraction (EF) was evaluated. The two groups were compared with regard to TnT kinetics and EF by Student's t-test. There were no substantial differences in sex, age, clinical or angiographic characteristics and infarct's size between the two groups.

Results: Means ± standard errors are shown in the following table and TnT kinetics is shown in the graph:

Group	Time of peak TnT level	TnT level	EF at 7th day	EF at 30th day	EF at 90th day	EF at 180th day
A	7.48 ± 0.4 h	4.22 ± 0.3	49.8 ± 0.6	52.0 ± 1.0	56.5 ± 0.9	59.7 ± 0.6
B	14.65 ± 0.8 h	5.85 ± 0.3	45.9 ± 0.6	48.6 ± 0.5	52.3 ± 0.6	55.0 ± 0.5
	p < 0.001	*p < 0.001*	*p < 0.001*	*p = 0.004*	*p < 0.001*	*p < 0.001*



In conclusion, in the stent group mean levels of TnT were lower, while TnT reached the peak level earlier (better reperfusion rate) and this predicts better LV function recovery compared to balloon angioplasty group.

P2129 Transradial approach for direct PTCA in acute myocardial infarction

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Background: Femoral access is usually the preferred approach for direct PTCA in acute myocardial infarction (AMI). However, radial approach (Radial) may be of interest in pts with high femoral risk (thrombolytics, antiplatelet drugs, obesity, peripheral arterial disease).

Purpose of the study: To evaluate the feasibility and safety of transradial coronary angiography and PTCA in AMI.

Methods: Retrospective analysis of Radial pts included in our prospective AMI Database (AMI < 24 hours, direct admission to the cathlab for coronary angiography). The use of Radial was left to the operator's judgment.

Results: Out of 735 AMI pts, 60 (8.6%) were treated through Radial. They were 61.8 ± 14.8 years old, 80% male, Killip III 3% and IV 8%. Localization of MI was anterior in 38% and inferior in 50%. Thrombolysis was used prior to admission in 28% of cases. Onset to door time was 311 ± 262 min. The right Radial was used in 75% of cases. Technical failure occurred in 1 case (1.7%) with successful femoral access. Infarct related artery was the RCA in 45%, LAD 30% and LCX 13%. Mean ejection was 52 ± 14%. Reopro was used in 5% of cases and transfemoral IABP in 7%. Procedural success was obtained in 98.3% of cases (TIMI III flow in 90.0%) using stents in 93.3%. Door to reperfusion time was 38 ± 19, door to stent 42 ± 22 and total fluoroscopy 19.1 ± 12.2 min. During hospital stay, death occurred in 3 patients (40% in pts with shock at admission and 1.8% in pts without), SAT in 1 (1.7%), stroke in 2 (1 frontal hematoma in a thrombolysed patient, 1 TIA). No access site complication or MACE occurred. Mean hospital stay was 6.7 ± 3.3 days.

Conclusion: Transradial approach for PTCA in AMI is feasible, with a high procedural success rate. Time to reperfusion is comparable to transfemoral approach. The absence of vascular complications may be of particular interest in high risk femoral access pts.

P2130 Clinical long term outcome in a randomized trial comparing primary angioplasty vs. streptokinase

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Primary Angioplasty (PTCA) has demonstrated to be an alternative to thrombolysis in the setting of an acute myocardial infarction (AMI). Long term benefit remains controversial. In order to evaluate this issue, we analyzed the long term outcome in the population of our "FAP" randomized trial comparing PTCA with SK.

From October 1993 to August 1995, 112 patients (p), with AMI within 12 hs. from symptoms onset, were randomized to SK 1.500.00 U (58 p) or PTCA (54 p). Mean age was 66 ± 13 years with 44.6% being > 70 years old and anterior localization in 43.4%. Primary end points were ST reduction in >50% at 120 min. from randomization and TIMI3 flow in the culprit vessel at discharge. A combination of major clinical events (death, PTCA, CABG, heart failure, re-AMI, stroke and major bleeding) were considered as a secondary end point at discharge. We considered these variables to analyze clinical outcome in long term follow-up.

ST resolution was achieved in 79.6% in PTCA group compared with 50% in SK (P: 0.002). Pre-discharge angiography was performed in 101 p (93.7%). TIMI3 flow was present in the infarct related artery in 95.6% of PTCA group and 64.5% in SK group (P: 0.001). Three year follow up (36 ± 2 months) was obtained in 98.9% of p. Survival analysis using Kaplan-Meier curve (log rank test) was made. We found a survival of 66.67% for PTCA and 60.34% for SK (P: 0.48). Event free survival was 53.7% for PTCA vs. 31.03% for SK (P: 0.008).

We conclude that in our population, PTCA achieved higher rates of ST resolution and TIMI3 flow at discharge. At three years follow-up, event free survival was better in patients treated with PTCA.

P2131 Coronary stenting in patients with acute myocardial infarction and cardiogenic shock

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Coronary stenting (CS) seems to improve the outcome of patients with acute myocardial infarction (AMI). However, whether CS represents a clinical advantage in patients with cardiogenic shock remains unknown. The objective of this study was to evaluate if coronary stenting improves the outcome of patients with AMI in cardiogenic shock.

Methods: The study population is constituted by 69 patients (68 ± 12 years, 77% male) with AMI and cardiogenic shock that were treated with PTCA within the first 12 hours ofter onset of symptoms. Of them, 32 (46%) were treated with balloon alone PTCA (POBA), and 37 (54%) with CS. The in-hospital outcome of both groups was analyzed.

Results: Except for a higher incidence of prior thrombolitic therapy in patients treated with POBA (16% vs. 0%, p = 0.004), both groups of patients had a comparable risk profile. The in-hospital outcome is summarized below:

	CS (n = 37)	POBA (n = 32)	p
Angio. success	89%	71%	0.056
Death	62%	75%	NS
Re-AMI	0.0%	3.1%	NS
Death/ReAMI	62%	75%	NS
Free wall rupture	2.7%	0.0%	NS

Conclusion: There was a tendency to higher angiographic success in patients treated with CS. However, although a small beneficial effect of CS can not be ruled out in patients with AMI and cardiogenic shock, the mortality in the group of patients treated with CS was not statistically lower than in patients treated with POBA. These patients constitute a very high risk subset even with the use of CS.

P2132 Improved outcomes after gradual reperfusion angioplasty for acute anterior myocardial infarction: two-year follow-up results of a randomized trial

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The myocardium may be damaged by a sudden reperfusion. Primary gradual and prolonged dilatations cause less arterial trauma as compared to standard dilatations in elective angioplasty. The purpose of this study was to evaluate the impact of prolonged inflation versus standard short dilatations in patients undergoing direct angioplasty.

Methods: We performed a prospective analysis on 80 patients with acute anterior myocardial infarction. One or two prolonged (10 minute) dilatations were performed in 40 patients using a perfusion balloon catheter (Gradual reperfusion group), and the other 40 patients received two or five standard (1 minute) dilatations using a standard balloon catheter (Sudden reperfusion group).

Results: The Gradual reperfusion group had a higher success rate after the initial inflation (<50 residual stenosis) (93.5% vs. 54%; p = 0.0003), less recoil (6% vs. 31%; p = 0.011), and a lower rate of major dissections (0% vs. 14%; p = 0.036) in the acute phase. Regional wall motion improved significantly over the baseline (−2.65 SD/chord) at the time of the acute anterior myocardial infarction when seen at 1 month (−2.35, p = 0.048) and 6 months (−2.20, p = 0.047), and 2 years (−2.12, p = 0.045) after the infarction in the Gradual reperfusion group, which was not observed in the Sudden reperfusion group. Discrepancy of thallium-201 and fatty acid metabolism imagings was 33% in the Gradual reperfusion group, as compared to 11% in the Sudden reperfusion group (p = 0.038). And, cardiovascular events (sudden death, congestive heart failure, reinfarction, bypass sugery, and repeat angioplasty) followed for two years occurred less frequently in the Gradual reperfusion group (40% vs. 67%; p = 0.048).

Conclusion: These findings suggest that gradual reperfusion in primary angioplasty may prevent the initial complications and ventricular remodeling of the infarct zones in acute anterior myocardial infarction, reducing cardiovascular events for a long time.

P2133 Five-year follow-up after coronary stenting in acute myocardial infarction

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Coronary stenting has become a treatment option for acute myocardial infarction (AMI), but so far few data are available for a long-term follow-up. There is little data on long-term results and quality of life of the patient (pat.) after coronary stenting in AMI. Therefore, we examined the patients at a mean of five years after coronary stenting in AMI.

Methods: We studied 97 pat. (mean age 58 ± 11 y), in whom coronary stents were implanted after bailout PTCA in AMI between October 1993 to December 1997. 78 (80%) of them could be examined with a structured questionnaire after 5 years either by letter or phone. Major events (death, MI, CABG and RePTCA) were analyzed. Data were evaluated for a progression in angina pectoris (AP), limitation in daily activity (LA) and patient judgement of therapy (JT).

Results: See tables.

N = 97	<30 d	30 d – 5 y	during 5 y
Death	10 (10.3%)	9 (9.3%)	19 (19.6%)
MI	1 (1.0%)	0	1 (1.0%)
CABG	2 (2.1%)	4 (4.1%)	6 (6.2%)
RePTCA	3 (3.1%)	7 (7.2%)	10 (10.3%)

N = 78	during 5 y
No AP	32 (41.0%)
No LA	70 (89.7%)
Good JT	74 (94.9%)

Conclusion: The present study has demonstrated: 1. an acceptable death and revascularisation rate after coronary stenting in AMI at a mean follow-up of five years; 2. most of the patients are satisfied with the treatment of stent implantation and only 10% patients are limited in daily activity in the long-term.

P2134 Coronary stenting within 24 hours of thrombolysis: feasibility, safety and effect on reocclusion, left ventricular function and clinical outcome

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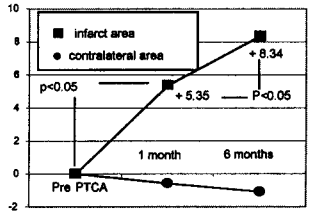
Reocclusion (RO) after thrombolysis (T) prevents recovery of the left ventricular function and worsens initial and long-term prognosis of AMI.

To determine the feasibility and safety of early post-T coronary stenting (CS), as well as its efficacy in preventing RO, we studied 137 consecutive pts with AMI (57 ± 10 yr, 86% male) who underwent T (accelerated rt-PA 176 ± 248 min. from onset of symptoms) followed by angiography 17 ± 7 h after T. Stenting was carried out if technically possible and flow ≥ TIMI-II existed. All pts underwent 1 and 6 months clinical and angiographic follow-up (FU).

Initial success was achieved in 99% of cases, and MLD improved from 0.89 ± 0.52 to 3.5 ± 05 mm. Hospital stay lasted 4.1 ± 2.5 days. At 30 days no adverse cardiac events occurred, all stented arteries remained patent and MLD significantly decreased to 3.1 ± 0.8 mm (p = 0.001). Over the last 5 months of FU only 1 pt had non-fatal AMI due to RO and MLD decreased to 2.4 ± 0.9 mm. Restenosis rate was 21% (≥50% criterion). Baseline LVEF (55 ± 1.6%) increased at 30 days (61.75 ± 1.6%, p < 0.01) and an additional improvement was found at 6 months (64.97 ± 1.42, p < 0.05 vs 30 days). The LVEF improvement was related to a significant and progressive increase of the infarct-area motion (figure).



Thus: 1) Unlike balloon PTCA, CS within 24 hours of T is a safe strategy that prevents RO and related events; 2) This strategy also facilitates the recovery of the infarct-area motion and the LVEF. Further studies are necessary to define the efficacy and cost-effectiveness of this strategy in comparison with the conservative approach to AMI.

P2135 Suboptimal flow after primary PTCA in acute myocardial infarction influences death rate at follow-up: results from the Stent PAMI randomized study

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Results from the Gusto trial have shown that one-month mortality after acute MI treated by thrombolysis is related to TIMI flow at 90 min.

The purpose of this study was (1) to assess the incidence and predictive factors (clinical, biological, procedural) of suboptimal TIMI flow (TIMI 0–2) obtained by primary PTCA (balloon vs stent) in pts included in the Stent PAMI trial, (2) to evaluate the relationship between TIMI flow and mortality at follow-up.

Of 1,458 pts in whom informed consent was obtained, 900 were randomized, 452 to stent and 448 to balloon. Procedural success (TIMI 2 or 3 flow and residual stenosis < 50%) was obtained in 98.8% of cases (Corelab analysis) with a 15.0% cross-over to stent in the balloon group. TIMI 3 flow (Corelab analysis) was obtained in 91.0% of cases. Predictive factors of suboptimal flow were by univariate analysis: no heparin pre cath-lab (77.4 vs 84.8, p = 0.09), complication (pulmonary oedema, sustained hypotension or CPR) before PTCA (18 vs 5%, p = 0.03) and age (63.9 ± 12.3 vs 59.7 ± 12.6 years, p = 0.004). By multivariate analysis, the predictive factors of suboptimal flow were age (p = 0.0022, odds ratio 0.967) and complication before PTCA (p = 0.0038, odds ratio 0.434). Mortality at 210 days was 2.7% in the 818 pts with TIMI 3 flow, 9.1% in the 77 pts with TIMI 2 and 40.0% in the 5 pts with TIMI 0–1 (p < 0.001).

In conclusion, suboptimal flow is not unfrequent after primary PTCA in selected acute MI patients. It is reported more frequently in older patients and when complication occurs before PTCA. All efforts must be made to restore a TIMI 3 flow after primary PTCA and, therefore, decrease mortality at follow-up.

P2136 The effect of quantum therapy on fibrinolytic response and lipid profile in patients with acute myocardial infarction

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The aim of this study was to study the effects of autotransfusion of ultraviolet-irradiated blood (AUVIB) on endothelian fibrinolytic system and lipoprotein profile in treatment of patients with acute myocardial infarction (AMI). In 54 patients with AMI we measured the fibrinolytic index (FI), before (PreA) and 10 m after anoxia (postA), variation expressed as geometric increase (FIGI) and lipid study triglycerides (TG); total cholesterol (T-C), HDL-cholesterol (HDL-C); apolipoprotein (Apo) A1; Apo B and lipoprotein index (LPI) (Apo A1/Apo B). Examination of patients was performed in 1, 3 and 6 months after discharge from the in-patients department.

The patients received 8–10 procedures of AUVIB at a 1–2-day interval. It was revealed that the levels if FI preA (p > 0.05), FI post A (p < 0.01), FIGI (0.01) raised and TG (p < 0.05), T-C (p > 0.05), HDL-C (p < 0.05), LPI (p < 0.001) lowered after treatment with AUVIB.

These results indicate that AUVIB together with clinical effect improves the fibrinolytic response of the endothelium To anoxia, and the lipid profile.

P2137 Association of non-invasive markers of coronary artery reperfusion to evaluate new therapeutic strategies and prognosis in patients with acute myocardial infarction

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Objectives: Non Invasive markers of coronary artery reperfusion were used to evaluate prognosis and drug efficacy in the double blind Argatroban in Myocardial Infarction Study (AMI trial) This trial compared high (3.0 meg/kg./min) and low dose of Argatroban, (Arg HD, Arg LD) a direct thrombin inhibitor, to placebo (P) in patients with acute MI < 6 hours that were treated with Streptokinase 1.5 million Units (SK).

Methods: In 612 patients we determined plasma CK levels and performed 12 lead ECGs at baseline and at 6, 12 and 24 hours after onset of treatment. We defined early reperfusion by a >50% decrease in baseline ST elevation followed by inversion of T waves within the first 12 hours in the corresponding ECG leads and peak CK rise at 6 hours. We considered late reperfusion when there was <50% reduction in pretreatment ST elevation, associated to inversion of T wave within 24 hours in the infarct related ECG leads and >60% of CK rise at 6 hours. Absence of these criteria was considered as failed reperfusion.

Results: Reperfusion rates were similar in the 3 arms of the trial. Early reperfusion was achieved in 45% of Arg HD, 46% of Arg LD and 49% of P patients. Late reperfusion occurred in 24%, 21% and 17% of patients respectively. An adverse clinical event (death, reinfarction, heart failure or shock) within the first 30 days occurred in 13.7% of reperfused patients and in 29.1% of those without reperfusion ($p < 0.001$), an odds ratio adjusted to other risk factors (Age, sex, coronary risk factors, MI location) of 0.57 (95% CI 0.39–0.84).

Conlcusions: Combination of non invasive markers of coronary artery reperfusion may be utilized systematically to evaluate new therapeutic strategies in patients acute MI and to assess post treatment prognosis.

INTRAVASCULAR ULTRASOUND AND BRACHYTHERAPY

P2138 High prevalence of angioscopically yellow plaque in angiographically mild stenosis

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Background: Angioscopically-observed yellow plaques are reported to be vulnerable and likely to cause acute coronary syndrome (ACS). In addition to severe stenosis, ACS may also occur in the angiographically mild stenosis of coronary arteries. However, the prevalence of yellow plaques in angiographically mild stenosis remains to be elucidated.

Methods: We used a high-quality angioscopy with 6000 pixels. The angioscopic observation was performed in 47 angiographically mild (<50%) stenoses in 30 coronary arteries of 22 patients; 13 patients with old myocardial infarction, 4 patients with stable effort angina, 4 patients with hypercholesterolemia, and 1 patient with vasospastic angina. The lesions received coronary intervention and the culprit lesions of ACS were excluded. The diameter stenosis was determined using quantitative coronary angiographic analysis.

Results: The mean stenosis was 25.6 ± 9.6% (13–49%). The yellow plaques were observed in 44 lesions (94%). Most of the yellow plaques were focal and had smooth surface. No thrombus was detected in these lesions.

In conclusion, the angioscopic observation revealed the high prevalence of yellow plaques in the angiographically mild stenoses. Although the occurrence of ACS in such lesions remains to be investigated, the high prevalence of yellow plaque may implicate the need for the management of the mild forms of coronary artery disease.

P2139 Comparison of Electron Beam CT with intravascular ultrasound for the detection of calcified atherosclerosis: an in vitro study

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Recent work suggested a high sensitivity for Electron Beam CT (EBCT) in the diagnosis of coronary atherosclerosis. This procedure is based on the detection of calcifications (Ca) being summed up in a score. Although this methodology is increasingly entering the clinical arena, scarce in vitro data are available demonstrating the true sensitivity of EBCT for Ca. This study was therefore performed to compare the EBCT with intracoronary ultrasound (ICUS), a method known to have 100% sensitivity for the diagnosis of Ca.

Methods: 16 human coronary arteries, harvested at autopsy, were mounted horizontally in a flow chamber filled with physiologic saline. An automated pullback of an ICUS-catheter was performed at a predefined speed (0.5 mm/sec) through all vessels. The vessels were then investigated with EBCT (Imatron CT, 100-ms high resolution mode) by scanning cross-sections (3 mm single slice thickness). The cross-sections were then compared in respect to the detection of calcified lesions. After the procedure, the vessels were fixed (8% formalin) and embedded with subsequent staining and cutting (according to ICUS and EBCT cross-sections).

Results: In 8 out of 10 coronary arteries with sonographic evidence of Ca, the EBCT also showed Ca, which gives a per vessel sensitivity of 80%. In a total of 243 cross-sections investigated, 67 had Ca on histology and ICUS, but only 39 had Ca on EBCT ($p < 0.01$). The specificity of EBCT to detect Ca is 100% and the cross-sectional sensitivity 59%.

Conclusion: EBCT shows a high sensitivity when Ca-scores are compared per vessel, however, the sensitivity becomes lower when cross-sections are compared.

P2140 Influence of lesion composition obtained by histology and intracoronary ultrasound on coronary arteries remodelling

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Recent study with intravascular ultrasound (IVUS) show that coronary arteries with atherosclerotic de-novo focal plaque often develop compensatory enlargement at the lesion site (positive remodeling-PR) but may also exhibit shrinkage (negative remodeling-NR) or to be without remodeling (WR). The purpose of this study was to investigate the association of plaque composition obtained by IVUS and histology, plaque burden, eccentricity and topography with type of remodeling.

Methods: We studied 50 lesions (L) N 50 pts with CAD before directional atherectomy (DCA) using IVUS. Vessel area (VA), lumen area (LA), % plaque area [(VA − LA)/VA × 100], eccentricity index [min/max plaque thickness] were measured. PR was defined when VA at the L site was larger than that at the proximal reference site; NR, when the VA at the L site was smaller than that at the distal reference or when the ratio lesion VA/prox ref VA ≤ 0.78; lesion WR-when lesion VA was similar or intermediate with proximal and distal references VA. The specimens retrieved with DCA were examined after Movat pentachrome staining and divided based on plaque composition (prevalent (>50% plaque area) fibrous or fibrofatty) and presence of the calcium.

Results:

		PR (20 L)	NR (10 L)	WR (20 L)	P
Histology:	Fibrous	6 (30%)	8 (80%)	10 (50%)	<0.05
	Fibrofatty	14 (70%)	2 (20%)	10 (50%)	<0.05
	Microcalcium	8 (40%)	6 (60%)	4 (20%)	NS
IVUS	Macrocalcium	8 (40%)	4 (40%)	8 (40%)	NS
	General CA	16 (80%)	10 (100%)	12 (60%)	<0.05
	Arc of deep Ca	18.33 ± 9.83°*	96.66 ± 69.76°	95 ± 69.52°	
	Arc of superfic Ca	42.5 ± 32.25°	37.5 ± 10.6°	103.75 ± 36.37°#	
	Eccentricity index	0.48 ± 0.18	0.26 ± 0.20	0.43 ± 0.31	<0.05
	% plague area	81.82 ± 7.82	73.34± 16	79.2 ± 4.9	NS
Plaque	LAD prox	10 (50%)	4 (40%)	10 (50%)	NS
topography	LAD mid	4 (20%)	6 (60%)	4 (20%)	<0.05
	RCA prox	-	-	2 (10%)	NS
	RCA mid	2 (10%)	–	–	NS
	Cx prox	2 (10%)	–	2 (10%)	NS
	Cx mid	2 (10%)	–	2 (10%)	NS

*$p < 0.05$ PR vs NR and WR; #$p < 0.05$ WR vs PR and NR.

Conclusions: 1) 40% of lesions had PR, 20%-NR, 40%-were WR. 2) The prevalence of fibrotic plaque composition is significantly higher in L with NR and fibrofatty plaque composition-in L with PR. L with NR more eccentric and distributed more frequently in the mid part of LAD. Our results suggest that plaque composition, degree of superf. and deep Ca arc, plaque eccentrisity and topography influence on developing lesions with PR, NR or WR.

P2141 In vitro validation of automated plaque echogenicity quantification of intracoronary ultrasound images

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Intracoronary ultrasound (ICUS) is the gold-standard procedure for measurement of non-obstructive, lipid-rich, atherosclerotic plaque. Analysis of plaque echogenicity remains highly subjective and is dependent on the gain/compression-setting (GCS). The aim of the study was to test the reproducibility of an GCS-independent automated plaque echogenicity quantification software.

A pressure perfused, minimally diseased, coronary artery was studied with a 30 MHz mechanical ICUS-catheter (0.5 mm/s, automated pullback) at various GCS (n = 20). The video images were digitized (260 × 260 pixel, 16 shades of gray) and lumen/vessel contour was detected semi-automatically (TomTech3D-IVUS). For analysis of echogenicity of each target plaque area (n = 152), every pixel was classified as hypoechogenic or hyperechogenic with (calcified plaque) or without acoustic shadowing taking echogenicity of the adventitia as reference for the treshold. Best and worst agreement between computed areas of different GCS for total, hypo- and hyperechogenic plaque area (PA) were calculated for various gain/compression settings using linear regression analysis.

	Best	worst
Total PA	y = 0.85 + 1.1 (r = 0.80)	y = 0.89 + 1.2 (r = 0.78)
Hypoechogenic PA	y = 0.81 + 1.5 (r = 0.87)	y = 0.81 + 1.4 (r = 0.81)
Hyperechogenic PA	y = 1.0 − 0.03 (r = 0.90)	y = 1.1 + 0.16 (r = 0.86)

Conclusions: Reproducible automatic quantification of plaque echogenicity is possible at different GCS. This is a prerequisite for serial volumetric quantification of plaque composition in plaque regression studies.

P2142 In vitro intravascular ultrasound imaging of biocompound vein grafts: comparison to histology

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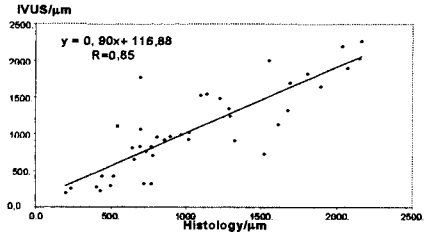
Wrapping a saphenous vein with an external, ultra-thin (30 μm) metallic meshgraft (Biocompound Graft, BG) results in reduction of vessel diameter and wall stress of veins exposed to arterial pressure. The aim of the study was to evaluate the correlation between Intravascular Ultrasound (IVUS) imaging of the BG and histology.

After intraoperative preparation of the saphenous BG vein (n = 42), one segment was taken for in vitro, pressure perfused, IVUS (30 MHz Endosonics®) and consecutive histologic examination (Elastica-von-Gieson). The metallic meshgraft is visualized by IVUS as a hyperreflective ring with an average thickness of 110 ± 12 μm. Agreement between IVUS and histologic measurements of BG max. vessel wall thickness was correlated using linear regression analysis.



Conclusion: Due to excellent visualisation of the external metallic meshgraft and good correlation to histology regarding wall thickness IVUS will be the gold standard technique for follow-up studies on intimal proliferation in BG in comparison to conventional veins.

P2143 Intravascular ultrasound assessment of culotte stent deployment for the treatment of stenoses at major coronary bifurcations

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Purpose: The use of 2 stents in a culotte configuration is a new approach for the treatment of stenoses at major coronary bifurcations. The optimal technique for the deployment of both stents is unknown and angiographic assessment of the bifurcation is inadequate.

Methods: 11 patients with stenoses at major coronary bifurcations were treated using 2 Cordis Crossflex stents in a culotte configuration. After optimising the angiographic appearance at each marginal bifurcation, IVUS was used to evaluate both limbs of the culotte stent using a 2.9 F 30 MHz imaging catheter.

Results: IVUS images were obtained from 19 of the 22 distal limbs, in 3 cases angulation of the side branch prevented passage of the IVUS catheter. The mean lumen cross-sectional area (CSA) of the proximal reference (ref) vessel was 7.6 mm^2, the distal main reference vessel was 5.0 mm^2 and the side limb reference vessel was 4.6 mm^2. Within the culotte stent, the final mean CSA in the main limb was 6.1 mm^2 (97% of ref) and in the side limb was 5.9 mm^2 (97% of ref). However, in each case within the culotte stent, the minimum CSA and the minimum lumen diameter (MLD) of both limbs was at the bifurcation point. For all patients, the final mean CSA at the bifurcation point of the main limb was 4.3 mm^2 (70% of main stent) and of the side limb was 4.4 mm^2 (75% of side stent). The IVUS MLD at the bifurcation point of the main limb was 2.1 mm (78% of main stent) and of the side limb was 2.1 mm (84% of the side stent). This significant residual stenosis was not detectable angiographically. Quantitative coronary angiography performed off-line suggested a mean final diameter stenosis at each bifurcation point of <10%.

Conclusions: IVUS evaluation of culotte stents is feasible, allowing assessment of stent deployment and objective evaluation of the bifurcation point. The minimum IVUS CSA and MLD of both limbs of the culotte stent is at the bifurcation point. Despite an optimal angiographic appearance a significant residual stenosis was noted with IVUS at each bifurcation point. Further evaluation will be needed to assess if there is a correlation between final IVUS CSA and MLD at the bifurcation point and restenosis within the culotte stent.

P2144 Longitudinal extent and distribution pattern of transplant vasculopathy evaluated by intracoronary ultrasound imaging

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Transplant vasculopathy (TVP) is the major limitation of longterm prognosis after heart transplantation (HTX). The aim of the study was to describe distribution pattern and longitudinal extent of coronary lesions after HTX by means of intracoronary ultrasound (ICUS).

In 179 post-HTX patients (12–122 months) without significant stenosis by coronary angiography ICUS of the LAD was performed using a 30 MHz phased array probe (Endosonics®). 162/179 pts. (90%) had at least one coronary lesion according to the Stanford classification (I:4%, II:7%, III:6%, IV:73%). The distribution of max. plaque thickness (MPT) within the LMCA/LAD is shown in the table.

N = 179	TVP	MPT 0.3–0.5	MPT 0.5–1.0 mm	MPT > 1 mm
LMCA	93 (52%)	21 (12%)	39 (22%)	24 (13%)
Prox. LAD	148 (83%)	26 (15%)	36 (20%)	87 (49%)
Med. LAD	103 (58%)	26 (15%)	43 (24%)	31 (17%)
Dist. LAD	67 (37%)	12 (7%)	31 (17%)	12 ((7%)

In 48 pts. (30%) only one single, discrete, coronary lesion (focal disease) was found, in 27 pts (17%) more than one discrete lesion (polyfocal disease) and in 86 pts. (53%) diffuse disease throughout more than one coronary segment was found. Non-circumferential disease was associated with focal/polyfocal disease (40/48, 83%) while circumferential disease was associated with diffuse disease (79/86, 91%).

Concl.: In more than 90% of all post-HTX patients TVP is diagnosed by ICUS. The prox./med. LAD segments are affected more often than the distal one. Circumferential, diffuse disease might have a different etiology than non-circumferential focal disease.

P2145 In vivo assessment of instantaneous wall shear stress with the IVUS flow method

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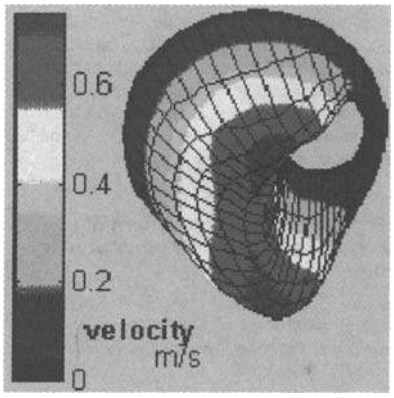
Background: Wall shear stress (WSS) has been implied as the most important local influencing factor in the development of vascular remodeling and restenosis. To date, no in vivo method offers the possibility to measure true WSS in coronary arteries.

Aim: Demonstrate the feasibility to measure WSS with the IVUS flow method and compare WSS assessment with computer simulation using finite element modeling (FEM).

Method: We have previously described the principle of velocity mapping with IVUS, based on the decorrelation rate of successive radofrequency signals in small windows over the arterial lumen. Spatio-temporal integration gives volumetric blood flow. Good agreement with Doppler derived flow estimations has been demonstrated. In this study we investigated the potential to derive WSS from the velocity measurements close to the arterial wall. On the other hand, the automatically detected area and the assessment of the mean flow permit the computation of the average WSS following the the Hagen-Poiseuille formula: WSS = 4 mu Q/pi r^3, with mu being blood viscosity (0.003 N s m^{-2}), Q blood flow (m^3 s^{-1}), r radius (m). By FEM, the increase of WSS related to the presence of the catheter has been investigated.

Results: In 12 patients, pooling baseline and hyperemia measurements, true WSS ranged from 1.7 to 16.5 N m-2, and average WSS from 1.5 to 5.2, in agreement with FEM modeling showing also that WSS was decreased close to the IVUS catheter, and increased on the opposite site.



Mapping of velocities around IVUS cath.

In conclusion, true WSS measurements are possible, although influenced by the catheter, and should be further investigated and related to clinical outcome.

P2146 Assessment of atherosclerotic lipid pools with high frequency intravascular ultrasound

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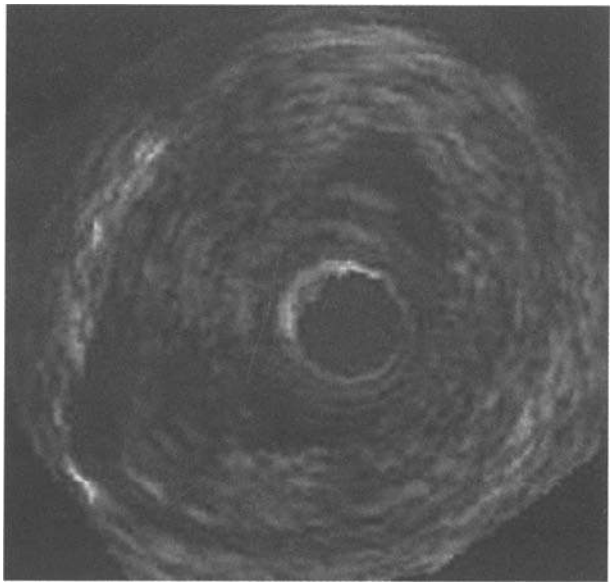
Previous intravascular ultrasound (IVUS) studies on atherosclerotic plaque characterization were limited by use of low-frequency transducers that did not define accurately soft components. The present study tested the effectiveness of high frequency IVUS transducers in identification of lipid/necrotic pools in atherosclerotic plaques. Methods. Forty MHz transducers were used for in-vitro IVUS assessment of 12 arterial segments (10 coronary arteries and 2 carotids dissected from 5 different autopsy cases). IVUS acquisition was performed at a 0.5 mm/s speed after ligature of the branching points to generate a closed system. Lipid necrotic areas were defined by IVUS as large echolucent intra-plaque areas surrounded by tissue with higher echodensity. To obtain histopathologic sections corresponding to IVUS cross-sections, vessels were divided into consecutive 3 mm-long segments using the most distal recorded IVUS image as starting reference. Then, samples were fixed with 10% buffered formalin, processed for histopathologic study, serially cut and stained with Movat penthacrome method.

Results: On histopathologic study, intra-plaque lipid pools were present in 30 of 120 cross-sections (25%). Corresponding IVUS cross-sections identified lipid lakes with a sensitivity and specificity of 70% and 94% respectively (echolucent area at 7 in the figure).



Lipid pool.

Conclusions: High frequency transducers accurately identify lipid/necrotic pools and open new perspectives on future IVUS characterization of atherosclerotic plaques.

P2147 A steerable yttrium-90 wire: development and evaluation of a novel device for intravascular radiotherapy

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Intravascular radiotherapy (IVRT) has been shown to reduce neointimal growth after balloon injury in various animal models and in first clinical trials. Beside reducing neointimal proliferation, an ideal radiation device should be 1) leak tight, 2) flexible, and 3) low in radiation exposure of the personnel. Therefore a beta-emitting source was developed and tested in a rabbit restenosis model.

Methods: Four Yttrium-90 seeds with an activity of 800 MBq each were activated at a flux of 6×10^{13} $cm^{-2}s^{-1}$. The source was then heat shrunk into a plastic tube with an outer diameter of 0.9 mm integrated in the anterior end of a standard 0.014″ guide wire. Wipe tests were performed to detect leakage of the plastic tube. In order to test its flexibility, the source was fixed in a tube so that the distal half reached the surface of a scale, where the weight necessary to bend the wire in its center by 30° was measured. To determine radiation exposure, the staff wore thermoluminescence dosimeters (TLDs) at the procedure. The efficacy of the source was tested in 18 normolipidemic rabbits after balloon injury of the iliac artery.

Results: The device proved leak tightness both in vitro and in animal experiments. Wipe tests revealed no detectable leakage of the plastic tube surrounding the source at any time. At the procedure there was no contamination detected at the used instruments. At flexibility tests, a weight of 3580 ± 60 mg was necessary to bend the wire in the middle by 30°. This was significantly lower than for an inflated angioplasty balloon (3910 ± 62 mg). Advancement of the wire was feasible in all animals, and resulted in reduction of neointimal growth by up to 70%. Total radiation exposure as measured by TLDs was 0.41 mSv for the operator.

Conclusion: The novel IVRT device is easy to handle and warrants flexibility due to its composition of single seeds, which besides allows to adjust the active length individually by the amount of pellets in the shrink tube. Because of the diameter of the source and the inherent stiffness of the device proximal parts of coronary vessels should be preferred for IVRT.

P2148 Persisting coronary artery dissection after intracoronary β-radiation

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Intracoronary β-radiation therapy (β-rad) is a means of preventing and treating restenosis in coronary arteries after balloon angioplasty (BA). However by inhibiting restenosis, β-rad may also interfere with normal healing processes. From previous reports complete healing of coronary artery dissection appears the norm after BA, but may not occur after β-rad.

Method: To evaluate this we retrospectively analysed dissection using quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) at the time of treatment and at 6 month follow-up in patients (pts) enrolled in the Beta Energy Restenosis Trial (BERT-1.5). The calculated dose of radiation received by the dissected area in those with healed versus non-healed dissection was also compared.

Results: 31 pts were enrolled in BERT-1.5. After excluding those who underwent stent implantation, the evaluable population was 22 pts (males = 17, mean age 55.7 ± 9.0 years). QCA and IVUS-proven dissection were seen in 16 patients post intervention. Dissection classification for QCA was by the NHLBI scale (QCA type A = 5, B = 7, C = 4). IVUS proven dissection was defined as partial (P) or complete (C) (IVUS: P = 12, C = 4). The following IVUS defined characteristics of dissection were described in the affected coronary segments: length, depth, arc circumference and presence of flap. Dissection was defined as healed when all features of dissection had resolved. At 6-month follow-up, 6 (38%) and 8 (50%) unhealed dissections were seen by QCA (QCA type A = 2, B = 4) and IVUS (partial = 7, complete = 1) respectively. No correlation was made between the dose prescribed to the treated area and the presence of unhealed dissection. No change in anginal status was seen despite the presence of unhealed dissection.

Conclusion: β-rad appears to alter the normal healing process resulting in unhealed dissection in certain individuals. In view of the delayed and abnormal healing witnessed, long term follow-up may be prudent.

P2149 Dose volume histograms offer new insights into the IVUS and angiographic follow-up after coronary brachytherapy

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Brachytherapy is a new therapeutic option to prevent restenosis. However, the use of different delivery devices, isotopes and dose prescriptions lead to a wide range of doses distribution over the arterial wall. Tools are required to analyze efficacy of radiation in function of the dose effectively absorbed by different arterial components.

Aim: Determine the absorbed doses in different volumes of irradiated coronary arteries and correlate them with the 6-month angiographic and IVUS outcome after PTCA of de-novo lesions.

Method: dose-volume histograms (DVH) were computed on 3-D ECG-triggered IVUS pull-backs, in 3 structures: (i) luminal surface volume (Vlum), defined with a 0.1 mm thickness from the automatically detected lumen contour; (ii) adventitial vol. (Vadv) defined with a 0.5 mm thickness from the EEL contour; (iii) a plaque+media vol. (Vp) encompassed by the lumen and EEL contours. DVH in 20 patients included in the BERT1.5 (beta-irradiation with 90Sr) without a stent implantation and with complete IVUS and angiographic f-up are reported.

Results: 8 were randomized to 12 Gy (at 2 mm from the source center), 4 to 14 Gy and 8 to 16 Gy. DVH demonstrated that, on average, 90% of Vlum received 8.5 ± 3.7 Gy or more (dV90lum), 90% of Vp 7.4 ± 3.0 Gy (dV90p) and 90% of Vadv 4.7 ± 2.0 Gy (dV90adv). As recently reported, at 6-m f-up with IVUS, the intraluminal volume was unchanged, but the plaque volume increased from 201 ± 61 to 241 ± 74 mm^3, accommodated by a similar increase of 39 ± 68 mm^3 of the vessel volume. DVH revealed that the plaque volume increase was inversely correlated with dV90lum (r = −0.62, p = 0.005). With angiographic f-up (diameter stenosis DS, late loss index LLI), DVH do not confirm that 8 Gy might be the minimal dose to give in the adventitia, as previously reported, but suggest a beneficial outcome when dV50p > 14 Gy (see table), but this requires confirmation in larger groups of patients.

Mean (sd) n =	dV50adv < 8 5	dV50adv > 8 15	p (Wilcoxon)	dV50 p < 14 9	dV50p > 14 11	p (Wilcoxon)
DS (%)	46 (19)	38 (19)	0.40	47 (22)	34 (13)	0.13
LLI	0.89 (1.47)	0.14 (0.63)	0.12	0.73 (1.14)	−0.01 (0.56)	0.07

In conclusion, direct assessment of vessel wall dose distribution with DVH appears useful for the understanding of IVUS and angiographic outcomes after brachytherapy.

P2150 Gallium-68 positron radiation combines biological efficacy, deep tissue penetration, generator availability and superior safety for liquid-filled balloon brachytherapy

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Recent data have shown that liquid-filled balloon brachytherapy using beta-emitters can prevent restenosis. However, the use of long lived beta-emitters for this application carries significant risk for severe radiointoxication if the balloon ruptures releasing the radionuclides into the bloodstream. We hypothesized that shorter-lived beta+ emitters might overcome this risk and accordingly investigated F-18 (T1/2 = 109 min), C-11 (20 min), N-13 (10 min), O-15 (2.1 min), and Ga-68 (67 min, generator produced). To assess biological efficacy, bovine aortic smooth muscle cells (BASMC) were plated at 10 k/cm^2 and irradiated with positron doses ranging from 2.5 Gy to 30 Gy. BrdU incorporation was assessed after 24 hours and cells were counted at 4 time points ranging from 1–8 days post-irradiation. In addition, GAF-chromic film phantom studies were used to quantify the depth-dependent dose response of beta+ emitters in tissue-equivalent medium. We found a dose-dependent inhibition of BrdU incorporation (1 day), with ED50 = 1.6 Gy and ED80 = 3.2 Gy; and of BSMC growth (8 days) with ED50 = 3.4 Gy and ED80 = 7.9 Gy. Cell death rate (8 days) was <5%. Phantom measurements revealed monoexponential ($r^2 > 0.99$) dose vs depth curves with half-depth layers linearly dependent on positron energy as given by D1/2 = 0.024 + 1.04*E, $r^2 > 0.99$ (D1/2, dose half-depth; E, mean positron energy). D1/2 for F-18 was 0.29 mm, C-11: 0.42 mm, N-13: 0.54 mm, O-15: 0.70 mm, and Ga-68: 0.90 mm. Accordingly, we considered Ga-68 as the most promising isotope and calculated that 50 mCi Ga-68 inside a 3.0/30 mm balloon would deploy 25 Gy to a 1 mm deep prescription point within 3.7 min. A whole-body dose of 5 rem (in the upper range of diagnostic x-ray procedures) would result from accidental systemic delivery of this activity. Since Ga-68 combines efficacy, deep tissue penetration, availability, and superior safety, its use may significantly advance liquid filled-balloon brachytherapy.

P2151 Catheter-based endovascular irradiation with the liquid β-emitter rhenium-188 to reduce restenosis after experimental wall injury

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Postinterventional irradiation seems to be a promising therapy concept in the prevention of restenosis. The liquid β-emitter Rhenium-188 allows endovascular brachytherapy with a conventional balloon catheter without the problem of centring the radiation source. In an experimental model of restenosis the practicability of the method and the dose dependent effect of irradiation with Rhenium-188 on the intimal proliferation was investigated.

In 36 male New Zealand White rabbits after endothelium denudation with a Fogarty-catheter, endovascular irradiation with a Rhenium-188 filled 2.5 mm balloon catheter in different dosages (0, 7.5, 15, 30, 45 and 60 Gray [Gy]) was performed. Four weeks after intervention the vessels were excised and histologically analysed.

Intimal Area in mm^2 (median [1. quartile; 3. quartile])

Control n = 6	7.5 Gy n = 4	15 Gy n = 6	30 Gy n = 7	45 Gy n = 6	60 Gy n = 7
0.49	0.46	0.15	0.07	0	0
[0.34; 0.66]	[0.33; 0.75]	[0.04; 0.17]	[0.04; 0.10]	[0; 0.04]	0; 0.01]

Already at a dosage of 15 Gy a significant reduction of the neointimal formation was found, from a surface dosage of 45 Gy on (equivalent to a dosage of 22.5 Gy in 0.5 mm depth) almost no proliferative response to the vessel injury could be detected any more.

In summary, the catheter-based brachytherapie with Rhenium-188 seems to be an effective therapeutical concept to prevent restenosis after balloon angioplasty. Further clinical studies are planed to investigate whether in patients a reduction of the restenosis rate can be achieved as well.

P2152 β-Particle emitting radioactive stent to prevent restenosis: final results of the Rotterdam contribution to the IRIS trial

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Introduction: The Isostents for Restenosis Intervention Study (IRIS) was a multicenter feasibility and safety trial of the radioactive Palmaz-Schatz and BX Isostent in single native coronary artery disease (lesion length max. 28 mm) with 6-month quantitative angiographic (QCA) and 12-month clinical follow-up.

Methods and study population: Phosphorus-32 (^{32}P), a pure β-emitter with a half-life of 14.3 days, was directly implanted into the metal surface of the stent. Activity was 0.75–1.5 μCi at stent implantation. After balloon predilatation an Isostent was implanted with a stent delivery system with integral sheath. A lucite shield is attached to the distal end of the stent delivery system to protect personnel against radiation. On-line QCA-measurements were done pre- and post-procedure and at 6-month follow-up. Thirty-one stents were implanted in 26 pts. The pts: 18 men, 8 women, average age 60 yrs (range: 43–74) had AP CCS 2 (n = 3), 3 (n = 10) or 4 (n = 13). RCA (n = 8), LAD (n = 12) or LCX (n = 6) were treated.

Results: Thirty of the 31 stents were successfully implanted. One stent was embolized without clinical sequelae. Twenty-two pts received 1, 4 received 2 Isostents and 5 pts received additional non-radioactive stents, because of dissection or due to the lack of a 2nd radioactive stent. All results are presented as mean ± SD. Lesion length: 13 ± 4 mm. For QCA results see Table.

Table. QCA results.

	Pre	Post	FU
RD (mm)	2.93 ± 0.47	3.31 ± 0.48	2.99 ± 0.54
MLD (mm)	0.87 ± 0.28	2.84 ± 0.35	1.85 ± 0.69
DS (%)	70 ± 9	15 ± 5	38 ± 20

DS = diameter stenosis; FU = 6-month follow-up; MLD = minimal lumen diameter; Pre = pre-procedure; Post = post-procedure; RD = reference diameter.

Twenty-three (88%) pts returned for angiographic FU. Restenosis rate was 17% and target vessel revascularization 13%. Late loss index was 0.53 ± 0.35. All pts returned for 6-month clinical follow-up: 81% were angina free with no deaths or myocardial infarctions.

Conclusions: This study reports that the implantation of a radioactive stent with an activity of 0.75 to 1.5 μCi is feasible and safe. Restenosis rate was 17%, which is comparable to conventional stent trials.

P2153 "Unwrapping the candy": does the choice of the size and length of the final balloon solve the problem of edge restenosis after radioactive β-particle emitting stents implantation?

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We have previously reported that restenosis after implantation of ^{32}P radioactive stents with an initial activity level between 3 and 6 μCi in patients with CAD is mainly due to an increased late loss at the stent margins associated with minimal intimal hypeplasia inside the stent. We coined the term "candy wrapper" for this pattern of restenosis. Aim of this study was to analyze the influence on restenosis of the size and length of the final balloon used to dilate the stents.

Methods: We analyzed 54 lesions in which a single 15 mm long radioactive ^{32}P β-particle-emitting stent was implanted and in which an angiographic follow-up at 4–6 months was performed. The lesions were divided in four groups based on the vessel size and on the size and length of the final balloon used to dilate the stent.

Results: The table below shows the procedural and angiographic results analyzed.

Vessel size, mm	Large > 3.0	Large > 3.0	Small ≤ 3.0	Small ≤ 3.0
Balloon length/ Stent length ratio	≤1 (Short Ball)	>1 (Long Ball)	≤1 (Short Ball)	>1 (Long Ball)
Number of lesions	19	10	11	14
Ref. diam, mm	3.40 ± 0.27	3.50 ± 0.37	2.75 ± 0.22	2.68 ± 0.23
Balloon-to-artery ratio	1.12 ± 10	1.06 ± 0.6	1.32 ± 14	1.26 ± 14
Radioactivity, μCi	6.7 ± 4.0	5.1 ± 5.2	4.6 ± 3.4	5.2 ± 4.4
Restenosis (DS ≥ 50%)	3 (*15.8%*)	4 (*40.0%*)	7 (*63.6%*)	7 (*50.0%*)

Conclusion: A lower restenosis rate was observed in large vessels, in which a less aggressive dilatation strategy with a lower balloon-to-artery ratio was used, compared with small vessels. In addition, the strategy to use a final balloon shorter than the stent length resulted in a lower restenosis rare in large vessels but not in small vessels. The findings in small vessels could be the result of the first vessel injury caused by the balloon used to preditate the lesion, which is usually longer (20 mm long) than the stent length and oversized, and to the persistent aggressive strategy with a balloon-to-artery ratio > 1.25 in small vessels.

P2154 Radioactive ^{32}P β-particle emitting BX stent implantation in patients with coronary artery disease: a serial IVUS analysis of the "candy wrapper" pattern of restenosis

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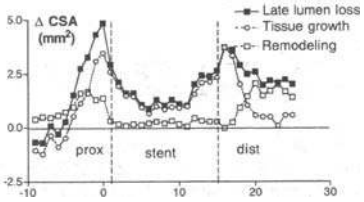
We have previously reported that restenosis after ^{32}P radioactive stent implantation in lesion of patients with CAD is higher than hystorical control lesions treated with non-radioactive stents due to an increased late loss at the stent margins associated with a dose related reduction in late loss inside the stent. We coined the term "candy wrapper" for this pattern of restenosis. Aim of this study was to analyze by serial IVUS measurements the mechanism of the "candy wrapper" pattern of restenosis

Methods: We studied 13 lesions with restenosis at 4–6 month FU after implantation of a single 15 mm long radioactive ^{32}P β-particle-emitting BX stent (Isostent) with an initial activity level between 3 and 12 μCi. IVUS imaging was performed using a motorized transducer pullback and quantitative IVUS analysis measuring stent/External Elastic Membrane (EEM) Cross Sectional Area (CSA), lumen CSA, and plaque CSA in slices analyzed 1 mm apart both inside the stent and in the proximal and distal reference segments. The following calculations were made: Remodeling = post-intervention (PI) EEM/stent CSA-FU EEM/stent CSA; Late lumen loss = PI lumen CSA-FU lumen CSA; Tissue growth (FU plaque CSA-PI plaque CSA).

Results: The graph below summarizes the results.



Conclusions: The Late lumen loss in the lesions with restenosis after ^{32}P radioactive stent implantation in the proximal and distal reference segments is mainly due to Tissue growth (intimal hyperplasia) in the first 2–3 mm and to Remodeling (shrinkage of the vessel) in the last 4–10 mm from the edges of the stent.

P2155 Reduced neointima formation and late lumen loss of stent-graft hybrid devices after irradiation of pig coronary arteries

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Background: Implantation of stent-graft hybrid devices (SG) to prevent plaque extrusion during stenting leads to neointima formation (NF) in pig coronary arteries. Endovascular irradiation (EI) prevents NF after coronary stenting. We therefore assessed the effects of EI in pig coronary arteries implanted with SG.

Methods: A SG was implanted in the LCX and RCA of pigs after overstretch balloon injury. Endovascular sites selected for SG received 30 Gy EI prior to implant. Controls were not irradiated. Quantitative coronary angiography (QCA) was done before and immediately after device implantation and at 28 days (harvest). Sections were prepared by saw-and-grinding after plastic embedding and measured by computer-assisted histomorphometry.

Results: Baseline QCA showed no difference in reference vessel diameter, balloon to artery ratio or post stent diameter between the two groups. QCA at follow-up showed that EI resulted in significantly less lumen loss in SG compared to controls.

QCA	SG	SG with EI	p-Value
Lumen Loss	2.5	0.79	<0.05

On histomorphometry, EI resulted in significantly less NF and a greater luminal area.

Histomorphometry	Luminal Area	Intimal Area	Vessel Area
Control SG	2.17 ± 0.86	6.58 ± 1.77	13.28 ± 8.84
SG with EI	5.37 ± 1.08	2.19 ± 1.00	10.87 ± 0.33
P-Value	0.003	0.008	NS

In non-irradiated SG, the neointima consisted of foreign-body response and organized thrombus close to the SG with adluminal smooth muscle cells and collagen matrix. The neointima in arteries with SG treated with EI was almost exclusively thrombus and foreign-body response.

Conclusions: The neointima in irradiated SG differs significantly both quantitatively and qualitatively compared to SG controls.

P2156 First report on safety and practicability of intracoronary radiation using a new monorail delivery system (Beta-RailTM)

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Beta or gamma radiation subsequent to coronary interventions is currently being applied as prophylaxis and/or therapy for (in-stent) restenosis. Possible safety risks during and shortly after administration may be a dissection, created by the 5F intracoronary catheter, longer periods of ischemia as well as inadvertent overdose. Further, delayed endothelialization can comprise an increased risk of acute/subacute stent thrombosis, which may possibly be avoided by extending administration of ticlopidine or clopidogrel. In a double-blind, placebo-controlled study, we are investigating the influence of a beta-emitting source train (ca. 42 mCi, Strontium/Yttrium-90, Novoste™) on restenosis following PTCA of de-novo lesions and restenoses. 40 patients have been thus far included with a single lesion and stable angina pectoris. Mean age was 60.5 ± 9 years, LV-EF was 61 ± 10%, reference diameter was 3.0 ± 0.6 mm; MLD before and directly after radiation was 0.6 ± 0.36 respectively 2.8 ± 0.4 mm. The dose for coronary vessels with a diameter of 2.7–3.35 mm is 14 Gy; for 3.36–4.0 mm is 18 Gy. Mean duration of radiation with 14 Gy was 173 ± 8 s (165–187 s) and 222 ± 12 s (212–240 s) with 18 Gy. The relatively bulky radiation catheter led neither to dissections nor to clinically relevant myocardial ischemia. Coronary overdose or a "getting stuck" of the radioactive pellets during passage of the inguinal region did not occur thanks to modifications required by the German authorities. In the 4-week period following radiation, coronary thromboses did not occur even after stent implantation. The added time needed for radiation after PTCA was ca. 18 ± 6 min.

Conclusions: Intracoronary brachytherapy with the new Beta-Rail™ catheter is safe. However, Ticlopidine may have to be routinely administered for 2 months after stent implantation and brachytherapy. Long-term results will be reported.

P2157 Intravascular radiotherapy with an yttrium-90 wire in a normolipidaemic rabbit restenosis model: influence on neointimal growth and vascular remodelling

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Intravascular radiotherapy (IVRT) has been shown to inhibit neointimal formation, a major mechanism of restenosis after balloon injury in various animal models. First data of clinical trials suggest also an efficacy in reducing restenosis in humans. However, the effect of radiation on vascular remodeling is still not completely elucidated. Studies on external high dose irradiation report media fibrosis and consecutive shrinkage, but recently also an increase in vessel size has been described. Therefore, the aim of this study was not only to assess the degree of neointimal formation, but also the vessel perimeter after beta-irradiation post injury.

Methods: Eighteen normolipidemic rabbits underwent balloon injury with a 3.0-mm balloon in both iliac arteries. One artery in each animal was randomly assigned for subsequent IVRT. The prescribed doses were 15 Gy (10 arteries) and 30 Gy (8 arteries) at 1 mm from the surface of the source, respectively. Four weeks later the animals were sacrificed, and the arteries were analyzed. Degree of neointimal formation was expressed as intima to media-ratio, and we measured the length of the external elastic lamina (EEL) to dermine vascular remodeling.

Results: IVRT reduced intima to media-ratio by 57.4% (p = 0.001) in the 15 Gy group and by 71.4% (p = 0.002) in the 30 Gy group. Whereas neointimal proliferation could thus be significantly reduced, EEL length (mm) did not differ between groups (15 Gy: 6.24 ± 0.94, 30 Gy: 6.34 ± 0.61, Control: 6.44 ± 0.61, p = n.s.). Similarly, arithmetically reconstructed circular vessel area (mm^2) did not alter significantly (15 Gy: 3.10 ± 0.07, 30 Gy: 3.20 ± 0.03, Control: 3.30 ± 0.03, p = n.s.). Thus, the total vessel dimensions were not affected by irradiation. There was no evidence of media or adventitia fibrosis in the irradiated arteries.

Conclusion: Our data suggest that the predominant effect of intravascular irradiation is rather inhibition of neointimal growth than a favourable influence on vascular remodeling.

CORONARY CIRCULATION: EXPERIMENTS

P2158 Loss of perfusion-contraction matching with coronary microvascular obstruction

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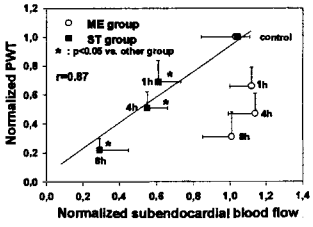
A close relationship between regional myocardial blood flow and function during acute epicardial coronary inflow restriction is well established (perfusion-contraction matching). It is unclear, whether such relationship exists also with coronary microvascular obstruction. Therefore, we compared the effects of coronary microembolization (ME) to those of an epicardial coronary stenosis (ST) on the relationship between regional myocardial blood flow and function in anesthetized dogs. The left circumflex coronary artery (LCx) was cannulated and perfused from an extracorporeal circuit. Systemic hemodynamics (micromanometer), regional myocardial blood flow (colored microspheres) and posterior systolic wall thickening (PWT, sonomicrometry) were measured under control conditions and after 1, 4 and 8 h. After control measurements, 3.000/ml microspheres with a diameter of 42 μm were injected into the LCx in the ME group (n = 6). With constant systemic hemodynamics, PWT declined over time whereas subendocardial blood flow did not. In the ST group (n = 6), inflow was progressively reduced to match PWT to that of the ME group at 1, 4 and 8 h. Subendocardial blood flow in the ST group was reduced in proportion to PWT. Infarct size (TTC, histology) was not different between groups (6.4 ± 5.5% (SD) of the area at risk in ME vs. 4.6 ± 4.7% in ST) and could not account for the observed dysfunction.



Apparently, microvascular obstruction, such as occurs after spontaneous or therapeutic plaque rupture, results in greater functional impairment than an epicardial coronary stenosis.

P2159 Arterial ATP-sensitive K-channels: evidence for preferential regulation by glycolysis

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In earlier experiments it has been shown, that key glycolytic enzymes are associated with gating properties cardiac ATP-sensitive K-channel (J Gen Physiol 94, 911–935, 1989). In the present experiments, we use bovine and pig coronary artery strips and normal Tyrode at pH 7.4 and 27°C (for meth. details see our earlier work Arch Pharmacol 310, 129–138, 1979)

Here we show that *inhibition of oxidative phosphorylation* by *dinitrophenol* (DNP; 1 mM) led to a relaxation of pre-contracted (26.8 mM KCl) bovine coronary arteries by 58% ± 2% (± SEM; n = 16), which could be reduced to 38 ± 2% and 32% ± 2% respectively by 2 μM and 20 μM glibenclamide (± SEM; n = 8; p < 0.01). Quantitatively similar results we obtained *under hypoxic conditions* (O_2 *exchanged to* N_2 in the perfusate).

Under competitive *inhibition of glycolysis* by *iodoacetic acid* (IAA; 0.5 mM) pre-contracted bovine arteries (26.8 mM KCl) relaxed by 98% ± 1%. Relaxation could **not** be inhibited by 2 μM, 20 μM or 200 μM glibenclamide (98% ± 2%; ± SEM; n = 8). Quantitatively similar results we obtained from pig coronary arteries.

In conclusion, our results show, that glibenclamide can inhibit coronary artery dilation induced by hypoxia and blockade of oxidative phosphorylation, whereas coronary dilation secondary to inhibition of glycolysis can not be prevented by glibenclamide. This observation indicates that *key glycolytic enzymes are associated with cardiac* K_{ATP}*-channels* and under conditions in which intracellular competition for ATP is high (hypoxia/ischemia), that act as a preferential source of ATP for these channels *in arterial smooth muscle* cells.

P2160 Maintenance of coronary reactivity to adventitial cholinergic stimulation in epicardial arteries submitted to ischaemia-reperfusion

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Epicardial coronary arteries submitted to ischaemia-reperfusion may develop an abnormal response to autonomic nervous discharge. However, this hypothesis has not been proven.

Methods. Left ventricular (LV) pressure, LV dP/dt, regional myocardial shortening, aortic blood flow, and coronary blood flow (CBF) at the left anterior descending (LAD) coronary artery were analyzed during pericoronary muscarinic stimulation of the LAD with topical methacholine in 11 α-chloralose anaesthetized pigs (30–40 kg). Methacholine was applied before and after a 2 h of LAD occlusion followed by 45 min of reperfusion. Changes induced by the two applications were compared by the ANOVA test.

Results. Methacholine induced a significant (p < 0.01) drop in CBF (9.6 ± 4.9 vs 2.5 ± 3.3 mL/min) followed by an hyperemic reaction (13.1 ± 8.9 mL/min). These changes were accompanied by a significant (p < 0.01) fall in LV pressure (90 ± 12 vs 79 ± 11 mmHg) and LV (+)dP/dt (1909 ± 466 vs 1388 ± 388 mmHg/s), and by a reduction (p < 0.001) in systolic segment shortening in the LAD perfused area (0.23 ± 0.05 vs 0.05 ± 0.09). Aortic blood flow was not modified during methacholine application. Application of methacholine after ischaemia-reperfusion induced a significant fall in CBF (66%) with no significant hyperemic reaction. The drop in LV pressure and LV dP/dt was comparable to baseline methacholine application.

Conclusions. Epicardial coronary arteries submitted to ischaemia and reperfusion mantain their ability to constrict under parasympathetic stimulation. Attenuation of the hyperemic reaction suggests an associated endothelial damage.

P2161 Coronary arteries from castrated rats are more sensitive to the vasodilatory action of testosterone than those from sham operated controls

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Introduction: Testosterone improves angina threshold in men and acts as a potent vasodilator in animal models in-vivo and in-vitro. Purpose: This study was performed to examine the effects of androgen depletion on the vasodilatory properties of testosterone on isolated rat coronary arteries.

Methods: Male, litter mate, Wistar rats were castrated or sham operated at 4 weeks of age (pre-pubertal). These animals were killed by chloroform anaesthesia 6–8 weeks after castration (post-pubertal). Hearts were rapidly removed and left anterior descending coronary arteries dissected free from surrounding connective tissue and myocardium. Vessels were cut into 2.3 mm lengths and mounted in a wire myograph (Cambustion UK Ltd). Vessels were pre-tensioned to 100 mmHg, bathed in physiologic saline solution, bubbled with 95%O_2/5%CO_2, and active tension recordings made. Vessels were maximally pre-constricted with 100 micromolar PGF2alpha. Dose response curves were constructed to 1 micromolar-3 millimolar of testosterone (dissolved in water).

Results: Coronary arteries from castrated animals were more sensitive to the vasodilatory effects of testosterone than those from sham operated controls. This effect was more marked at lower concentrations. Castrate vs sham (n = 15 in each group), mean (SE) EC10 (dose required to produce 10% of maximal dilatation); 24.7 (7.2) micromoles vs 41.1 (6.9) micromoles, P = 0.019: EC20; 48.9 (10.3) vs 71.6 (9.4) micromoles P = 0.016: EC 50; 204.6 (30.1) vs 275.2 (36.5) micromoles, P = 0.093. (all P values by Mann Whitney U test.)

Conclusion: Androgen depletion leads to an increase in sensitivity to the vasodilatory effect of testosterone on rat coronary arteries.

P2162 Elderly rats are less sensitive to the coronary vasodilatory effects of testosterone than young animals

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Introduction: Ageing may have adverse effects on coronary vascular reactivity due to atheroma development, endothelial dysfunction and changes in receptor density. Ageing is also associated with reduced levels of testosterone which acts as a potent vasodilator of rat coronary arteries in-vitro.

Purpose: This study was performed to examine the influence of ageing on the vasodilatory effects of testosterone.

Methods: A group of two year old, male, Wistar rats were compared with animals from the same breeding colony at 14 weeks of age. Animals were killed by cervical dislocation and the hearts rapidly removed. Left anterior descending coronary arteries were dissected free from surrounding connective tissue and myocardium, cut into 2.3 mm lengths, and mounted in a wire myograph. (Cambustion Ltd, UK) The vessels were bathed in physiologic saline solution, and bubbled with 95%O_2/5%CO_2. Vessels were pre-tensioned to 100 mmHg and active tension recordings made. Vessels were maximally pre-constricted with 100 μM Prostaglandin F 2 alpha, and dose response curves to 1 μM–1 mM of testosterone (dissolved in water) were constructed

Results: Mean% dilatation (SEM) elderly vs young, was lower in the vessels from elderly animals, at all doses; 1 μM; +5.4 (1.9) vs −1.1(1.9) P = 0.012, 3 μM; +6.0(1.8) vs −1.9(1.6) P = 0.007, 10 μM; +2.8(2.2) vs −7.2(2.1) P = 0.007, 30 μM; −5.2(3.4) vs −19.6(3.9) P = 0.015, 100 μM; −29.9(5.7) vs −43.6(5.5) P = 0.06, 300 μM; −64.3(10.5) vs −74.9(4.5) P = 0.016, 1 milliM; −83.5(6.2) vs −100.8(6.1) P = 0.054.

Conclusion: Coronary arteries from elderly rats are significantly less sensitive to the vasodilatory effect of testosterone than those from younger animals.

P2163 17β-Oestradiol induces vasodilation in human coronary resistance arteries in vitro

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Estrogen directly induces vasodilation in the human coronary circulation. However, few studies have examined the effect that estrogen has on resistance coronary arterioles (CRA), and the mechanisms responsible for estrogen-induced vasodilation are poorly understood. The present study investigated the effect of 17 β-estradiol on endothelium-dependent and independent dilation of CRA *in vitro.*

Methods and Results. CRA (diameter: 79 ± 10 μ m) were isolated from the right atrial appendages of 20 patients [13 men and 7 postmenopausal women (mean postmenopausal interval: 10.7 years)] who underwent coronary bypass surgery. CRA were double-cannulated with glass micropipets and pressurized (40 mm Hg) in a no flow state. Concentration-response curves (CRC) for acetylcholine, substance P, and calcium were obtained before and 60 minutes after 17 β-estradiol (10^{-6} M) administration. Estrogen caused vessels to relax by 13 ± 4% of the control diameter. There were no differences in the responses to the agents between arterioles from male and female patients. The CRC of acetylcholine and substance P were not affected by 17 β-estradiol, however the CRC of calcium was shifted to the right by 17 β-estradiol. Estrogen receptors were not identified by immunohistochemical staining.

Conclusions. Estrogen affects vascular smooth muscle, and arterioles dilation is not mediated by nuclear estrogen receptors in human coronary resistance arterioles.

P2164 The migration of vacular smooth muscle cells in vitro is inhibited by abciximab via the avb3 integrin: a possible explanation for the inhibition of restenosis

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Brief i.v. administration of abciximab during angioplasty reduces revascularisation and coronary events long-term. Abciximab cross-reacts with the avb3 integrin on smooth muscle cells (SMCs). This integrin is upregulated following vascular injury, and is involved in cell migration, an important step in neointimal formation. Osteopontin (Opn) and vitronectin (Vn) are ligands for this integrin, and are present in injured vessels at increased concentrations.

Methods: Human vascular SMCs grown from primary explants were resuspended in DMEM+0.2% BSA. Their expression of avb3 was assessed by immunoprecipitation. Antibodies (c7E3, LM609 (anti-avb3) or control, 10 μg/ml) were placed in the upper chamber of a micro-Boydens chamber. The lower well contained DMEM ± Opn or Vn (20 microg/ml), or PDGF (10 ng/ml). The chambers were incubated at 6 hours at 37oC. The membrane was fixed, and cells on the upper surface were gently removed. Those on the lower surface were stained with prodidium iodide (20 microg/ml containing RNase 0.2 mg/ml). The number of cells per 5 high power fields was counted using a fluorescent microscope. The experiments were performed in triplicate.

Results: Vn and PDGF increased the migration of cells, whether they expressed avb3(avb3+) or not (avb3-). Opn only increased the migration of avb3+ cells. Migration of avb3- cells was not influenced by LM609 or c7E3. c7E3 inhibited migration of avb3+ cells to Vn by 39.2 ± 9.4% ($p < 0.0001$), to Opn by 70.9 ± 12.0% ($p < 0.001$) and to PDGF by 12.8 ± 10.7% ($p = 0.005$). LM609 also inhibited their migration, and there were no significant differences between the effects of LM609 and c7E3.

Conclusions: c7E3 and LM609 inhibit the migration of SMCs to a similar degree. The migration of SMCs not expressing avb3 was not affected by these antibodies, but these cells could still migrate to Vn and PDGF, implying other pathways are also involved.

P2165 Local delivery of antisence phosphorodiamidate compound – Restin-NG inhibits myointimal hyperplasia following balloon angioplasty

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Myointimal hyperplasia following percutaneous transluminal coronary angioplasty (PTCA) is a key component of the process of restenosis. The c-myc is a critical cell division cycle protein involved in the formation of neointima. We evaluated the long term impact of local delivery of Restin-NG upon myointimal hyperplasia following PTCA in a rabbit model. Twenty New Zealand white rabbits were anesthetized, transport catheter inserted in the iliac artery, and PTCA performed (8 atm for 30-seconds, three times; endoluminal delivery of saline (n = 10) or 500 mg. Restin-NG (n+10) to the PCTA site was at 2 atm via the outer balloon for two minutes. The diet was supplemented with 0.25% cholesterol for ten days before and sixty days after following treatment. Angiography was performed at harvest and vessels were fixed in formalin, processed and stained with Hematoxylin and Eosin, Movat's, smooth muscle cell actin and for PCNA. The area of intima and media was determined by planimetry. Data shown are mean area ± SD at sixty days.

	Control	Antisence	p value
Lumen (mm^2)	0.40 ± 0.11	1.32 ± 0.41	<0.05
Intima (mm^2)	1.43 ± 0.25	0.63 ± 0.36	<0.05

Histological analysis revealed that local delivery of antisence prevented balloon induced changes. We conclude that local delivery of Resting-NG inhibited myointimal hyperplasia following PTCA in a rabbit for up to 60 days.

P2166 Inhibition of vascular smooth muscle cell proliferation by adenovirus-mediated nitric oxide synthase gene transfer and biochemical characterization of the recombinant enzyme

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Background: Nitric oxide (NO) is synthesized in vascular endothelial cells by NO synthase isoform NOS-III. Experimental gene therapy using recombinant NOS (recNOS) has been applied to correct vascular pathology (e.g. restenosis), but full biochemical characterizations of the recombinant enzymes have not been published. However, many biochemical aspects of recNOS function and regulation are essential to assess its therapeutic potential and possible side effects. We report here a complete biochemical study of a recNOS-III expressed from an adenoviral vector.

Methods: Development of vector Ad5CMVNOS-III was done as described (PNAS 1998;95:9003). Targets were human endothelial (HUVEC) and vascular smooth (HUVSMC) cells from human umbilical veins. Biochemical NOS characterization followed published protocols.

Results: (1) Among 7 recombinant vector clones only one was fully functional, the others carried deletions. (2) The vector provided a gene transfer rate of >95% of target cells. (3) Immunoprecipitation showed a membrane-targeted recNOS-III protein of size 130 kDa with >85% of NOS activity localized in the membrane. (4) NOS activity reached a maximum on day 3, then decayed below the detection limit by day 15. (5) RecNOS-III was strongly dependent on Ca^{2+} (6.5% activity without), NADPH (inactive without), tetrahydrobiopterin (37% without), and flavins (65% without). (6) The influence of Ad5CMVNOS-III on cell proliferation is summarized in the table.

NOS-III gene transfer

Ad5CMVNOS-III	HUVEC	HUVSMC
–	100%	100%
+	−54 ± 7%	−34 ± 5%

Inhibition of human vascular cell proliferation by NOS-III gene transfer using the adenoviral vector Ad5CMVNOS-III

Conclusions: (a) The high rate of dysfunctional NOS-III vector mutants is very unusual (we have never seen it among 30 other transgenes cloned in this system) and could be a consequence of disturbance of the vector cloning procedure by recNOS expression itself, emphasizing the need for full characterization of NOS vectors. (b) Clone Ad5CMVNOS-III showed "physiological" regulation and co-factor dependency so that serious side effects are less likely. (c) Vector expression is self-limiting (<2 weeks) so that its strong antiproliferative effect should also be confined to this time interval.

P2167 Evaluation of the effect of oversizing on vascular injury, thrombogenicity and neointimal hyperplasia using the Magic Wallstent™ in a porcine coronary model

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Oversizing of a self-expandable coronary stent results in a continuous pressure on the stented vessel wall and has been considered as a continuous stimulator for neointimal growth.

Methods: Magic Wallstents (Schneider, Bulach) with a length of 24 mm were randomly implanted with either an oversizing of ± 50% (n = 28), or an oversizing of ± 100% (n = 28) in two coronaries of 28 crossbred pigs (weight 20–25 kg). The pigs underwent a control angiogram and were subsequently sacrificed at day 3 (n = 4), day 7 (n = 4), day 14 (n = 6), day 42 (n = 10) and day 84 (n = 4). Quantitative coronary analysis before, immediately after stent implantation and before sacrifice was performed using the semi-automated Polytron 1000® system. Morphometry was performed using a computerized morphometric program.

Results: Histopathology showed significantly more perivasculitis in the high oversizing group (1.08 ± 0.17 vs. 0.92 ± 0.16, $p < 0.02$). Morphometry showed a similar lumen area at day 3 and 7. At day 14 the lumen area in the high oversizing group was significantly smaller compared to the low oversizing group (4.70 ± 0.56 vs. 5.70 ± 0.64 mm^2, $p = 0.016$). At day 42 and 84, however, this difference became insignificant.

Neointimal hyperplasia was also significantly more pronounced at day 14 in the high oversizing group (1.94 ± 0.64 vs. 1.04 ± 0.66 mm^2, $p < 0.037$). At later follow-up neointimal hyperplasia remained increased at a non-significant level in the high oversizing group.

Conclusion: This study suggests that high oversizing results in an early neointimal overresponse, most probably induced by the higher vessel stretch, resulting in more perivasculitis and subsequently more neointimal hyperplasia. At longer follow-up, however, this continuous vessel overstretching did not result in a significantly more pronounced neointimal hyperplasia.

P2168 Evaluation of continuous oral or intravenous administration of beta-cyclodextrin tetradecasulfate (CDT) for the treatment of neointimal formation after angioplasty in normocholesterolemic swine

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Beta-cyclodextrin tetradecasulfate (CDT), a cyclic polysaccharide capable of binding basic fibroblast growth factors, inhibits smooth muscle cell proliferation and reduces intimal hyperplasia in small animal models. We hypothesised that CDT would attenuate neointima formation after balloon overstretch injury. CDT was started 2 days before coronary injury and continued until sacrifice, 14 days after angioplasty. 38 pigs were randomized into one of 3 groups: 1) Control, 2) Oral (300 mg CDT/kg/d) or 3) IV infusion (100 mg/kg/d given continuously through a jugular venous catheter connected to a peristaltic pump). Vessels were evaluated for the maximal intimal thickness (MIT) and the intimal area (IA) which was normalised to the injury index (II). 9 additional animals (6 arteries per group) were sacrificed at 5 days to determine cellular proliferation (medial cells exhibiting the proliferating cell nuclear antigen) and the extent of mural thrombus. (Morphometric analysis: see Table)

CDT also reduced cellular proliferation (Control 55 ± 18%, Oral 35 ± 7%, p = 0.03, IV 30 ± 12%, p = 0.01) and mural thrombus formation (Control 0.84 ± 0.4 mm^2, Oral 0.44 ± 0.14 mm^2, p = 0.04, IV 0.42 ± 0.09 mm^2, p = 0.03). Factor Xa inhibition as well as the activated clotting time were increased following IV administration.

Morphometric analysis

	Control (n = 22)	Oral (n = 22)	IV (n = 22)
MIT (mm)	0.42 ± 0.11	0.34 ± 0.15	0.29 ± 0.10‡
II	0.20 ± 0.06	0.21 ± 0.11	0.26 ± 0.13
IA/II (mm^2)	3.03 ± 0.75	2.31 ± 0.83*	1.67 ± 0.73‡

Mean ± SD; *p = 0.004 vs control; †p = 0.06; #p < 10^{-5} vs control.

Conclusion: Continuous oral administration and IV infusion of CDT reduces intimal hyperplasia significantly by 24% and 48% respectively. Reduction of cellular proliferation and mural thrombus formation and/or decreased factor Xa activity may be mechanisms by which CDT inhibits intimal hyperplasia.

P2169 Gene transfer in coronary arteries of a porcine animal model: comparison of three-vector systems

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To establish an animal model for vascular gene therapy we compared three different vector systems with LacZ as reportergene in a porcine model. We constructed an adenovirus and an adeno-associated virus containing the LacZ gene, and compared these two viral vectors with liposomal gene transfer in their expression efficacy, onset of expression and localisation of β-galactosidase activity after local delivery.

Application was performed with a microporous balloon (3 atm) and dwell time of 2–3 min with or without prior overstretch (10 atm). Adenovirus-mediated gene transfer (10^{11} pfu/ml) resulted in protein expression in the endothelial cell layer. With the lamina elastica interna as natural barrier, we found no gene expression in the media but in theadjacent myocardium. Adeno-associated virus as vector (10^8 tp/ml) led to a very low expression in the myocardium, no protein expression could be detected in the media. Liposomal gene transfer resulted in a low gene expression in the media of the coronary arteries.

With adenoviral gene transfer and adeno-associated virus as vector high expression (>90% of transfected cells) could be obtained in cultures of endothelial cell culture and smooth muscle cells, liposomal gene transfer only led to 5% of transfected cells. Expression efficacies results in cell culture can not predict the efficacy of vascular gene transfer in the intact animal. None of the vectors investigated in this study, yielded vascular gene transfer with the microporous balloon which appears appropriate for gene therapy of restenosis in an animal model. Neither adeno-associated virus, which theoretically seems to have advantages compared to other vector systems, nor adenovirus of this generation, nor liposomal gene transfer seem to be an appropriate system for catheter-mediated gene therapy of neointimal proliferation in coronary arteries after angioplasty.

P2170 Oral matrix metalloproteinase inhibition following balloon angioplasty in a non-atherosclerotic pig model

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Background: Previously, we demonstrated in an atherosclerotic model that inhibition of Matrix Metalloproteinases (MMPs) by intraperitoneal injection of Batimastat significantly reduced late lumen loss by inhibition of constrictive arterial remodeling. In the present study, the effect of an orally administered, clinically applicable, MMP-inhibitor, Marimastat, was tested in a non-atherosclerotic pig model.

Methods: Balloon angioplasty was performed in 33 femoral and internal iliac arteries in 11 pigs. Pigs were randomly divided into 4 groups: 1 control group (n = 6 vessels) and 3 groups in which Marimastat was administered for 2 weeks (n = 10 vessels), 4 weeks (n = 7 vessels) and 6 weeks (n = 10 vessels) respectively. Marimastat treatment was started one day prior to the intervention. Pigs were terminated 42 days after intervention. 30 MHz intravascular ultrasound was performed at all time-points. Data of the different Marimastat groups were pooled since no significant differences were observed among the groups.

Definitions: Late lumen loss = lumen post intervention–lumen at follow up, late vessel area loss = measure of remodeling: vessel area post intervention – at follow up, intimal hyperplasia (IH) = vessel area–lumen area at follow up.

Results: See table. Values are in mm^2, mean ± sd, *p < 0.001

MMP-inhibition and late lumen loss

	Lumen control	Vessel area control	Lumen marimastat	Vessel area marimastat
Pre	11.52 ± 4.18	11.52 ± 4.18	9.60 ± 4.50	9.60 ± 4.50
Post	18.89 ± 8.04	18.89 ± 8.04	14.40 ± 5.27	14.40 ± 5.27
Follow up	9.34 ± 3.16	11.60 ± 3.73	12.70 ± 5.69	15.60 ± 6.63
Late loss	9.55 ± 5.34	7.29 ± 5.23	1.70 ± 3.24*	−1.20 ± 3.37*
IH	2.26 ± 1.52		2.90 ± 2.26	

Conclusions: 1) Oral MMP inhibition by Marimastat reduces late lumen loss after balloon angioplasty 2) The reduction in late lumen loss is the result of blocking of constrictive remodeling by the MMP- inhibitor. Intimal hyperplasia is not inhibited.

P2171 Gender differences in isoproterenol induced myocardial hypertrophy in the rat

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Although several investigations confirmed that isoproterenol administration induced myocardial hypertrophy and damage in rats no data are available on the existence of a gender dependent effect. We tested the hypothesis that the response of the heart to 30 mg/kg of isoproterenol may differ in magnitude between males (M) and females (F). To this purpose 20 M and 16 F 2 months old rats, were injected for 3 consecutive days with 10 mg/kg and sacrificed the following day. Age and sex matched sham-operated rats (7 M and 8 F) were injected with vehicle. Additionally, the day before sacrifice all the animals were injected ip with bromodeoxyuridine (BrdU) (50 mg/kg). To test the influences of sex hormones the same treatment was performed in 7 M and 10 F castrated rats, fifteen days after surgery. After body weight determination, hearts were arrested in diastole with cadmium chloride and the weight of the right (RV) and left ventricle (LV) inclusive of the septum separately measured. A transverse slice of the ventricles was embedded in paraffin and 5 mm thick sections were obtained and stained with trichrome to measure morphometrically the amount of myocardial damage. Monoclonal antibody to BrdU was used to document DNA synthesis and in situ terminal deoxynucleotidyl transferase assay to detect apoptotic myocyte cell death on myocardial sections. In M, isoproterenol treatment induced a 36% (p < 0.0001) cardiac growth, 40% (p < 0.0001) in the LV and 23% (p < 0.001) in the RV. In F, the same treatment induced only a 24% (p < 0.0001) cardiac hypertrophy, 25% (p < 0.0001) in the LV and 20% (p < 0.005) in the RV. Interestingly, LV growth was enhanced following removal of sexual organs. In M LV hypertrophy was 50% (p < 0.0002), whereas in F was 37% (p < 0.0001). The amount of reparative tissue was similar among all groups of treated rats averaging less than 4% in the LV and 2% in the RV (ranging from 1 to 9%). These values were always higher than in untreated controls (p < 0.001). Myocardial damage was associated with apoptotic myocyte cell death detected in 98 myocyte nuclei/1000000 nuclei in M and 47 nuclei/1000000 nuclei in F. BrdU labeling was seen in 400 nuclei/1000000 nuclei in the LV of M rats and in 900/1000000 myocyte nuclei in F. Similar values were detected in castrated rats. In conclusion, beta adrenergic stimulation causes myocardial hypertrophy and damage with DNA synthesis and apoptosis in myocyte. The growth response of M heart is enhanced with respect to F and the absence of sexual hormones increases LV hypertrophy in both sexes.

P2172 Assessment of fractal dimension of regional myocardial blood flow heterogeneity of isolated rat heart by magnetic resonance imaging under various flow conditions

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Fractal dimension (D) of regional myocardial blood flow heterogeneity in the heart is usually evaluated using tracer microsphere technique. The aim of our study was to develop a method for the assessment of D with a high spatial resolution in isolated rat heart. We used our previously described NMR technique which determines alterations of perfusion without contrast agent from changes of 1/T1.

Methods: Five isolated rat hearts were studied (perfusion in the Langendorff mode, constant pressure of perfusion) in a 11.75 T Bruker system. Spins of one slice (2 mm thickness, short axis view) 4–6 mm below the valvular plane were inverted by an adiabatic 180° pulse. T1 maps were gained in this slice by 16 × Snapshot FLASH images (spatial resolution 140 μm in plane, TR = 3.6 ms) under different flow conditions in the range 5.4–20.0 ml/min. Local and global 1/T1 of the slice was considered as a function of flow. Fractal analysis was performed on 1/T1 maps inside 4–7 non-overlapping squares of 16 × 16 pixels (= 256 voxels) in the left ventricular myocardium.

Results: We observed that the relative dispersion (RD) of spatial distribution of flows is well described by the power law RD (N) = RD (N = 1) N^{D-1} where N is the number of voxels, RD (N = 1) is the intercept obtained by extrapolating to one voxel. The mean correlation coefficient was 0.95. D was in the range 1.096–1.205 and regression analysis D vs. mean perfusion revealed a negative relationship (mean R = −0.763, slope = −0.005 g min/ml, $P < 0.05$).

Conclusion: High resolution analysis of myocardial blood flow heterogeneity by NM imaging is feasible. These results indicate that the fractal behaviour of myocardial blood flow holds up to very low spatial dimensions and that D exhibits only a moderate dependence on flow.

P2173 Coronary vasodilation in microvascular beds by α_2-adrenergic stimulation in dogs with pacing-induced heart failure

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Background: It remains unknown how alpha-2 (α_2) receptor pathway in coronary microvascular beds is modulated in heart failure. We investigated the role of α_2 receptor pathway using coronary pressure-flow relationship (PF-R) during long diastole in rapid pacing-induced heart failure model.

Methods: In 18 dogs, a Doppler flow probe was placed around the left anterior descending (LAD) coronary artery, and atrio-ventricular node was completely blocked by injecting formaldehyde. PF-R was obtained by temporary cessation of ventricular pacing before and after rapid ventricular pacing at 240 bpm for 3 weeks, in which states hemodynamic study was also done. The slope of PF-R was evaluated as an index of coronary vascular resistance. Yohimbine (30 μg/kg) was administered into LAD for α_2-blockade. Propranorol (50 μg/kg), bunazosine (20 μg/kg) and norepinephrine (NE, 0.05 μg/kg) were injected to stimulate α_2-adrenergic receptor.

Results: After rapid pacing, heart failure was produced, but the slope of PF-R (1.46 ± 0.2 ml/min/100 g-LV/mm Hg) was not different from just before rapid pacing (1.23 ± 0.1, N.S.). α_2-blockade did not change the slope at both baseline state and heart failure state. On the other hand, α_2-stimulation significantly increased the slope only in failing state and this increase was abolished by N^G-nitro-L-arginine methyl ester (L-NAME, Nitric oxide synthase inhibitor) pretreatment. These slope changes corresponded coronary flow responses at given perfusion pressures tested.

slopes (before and after drug intervention): % changes

	Non-failing state		Failing state	
Resting state (n = 18)	100	to	119 ± 16	(N.S.)
α_2-blockade (n = 6)	100 to 96 ± 15	(N.S.)	100 to 104 ± 8	(N.S.)
α_2-stimulation (n = 6)	100 to 116 ± 11	(N.S.)	100 to 160 ± 17	(P < 0.05)
+ with L-NAME (n = 6)	100 to 105 ± 12	(N.S.)	100 to 105 ± 10	(N.S.)

Conclusion: These results suggest that α_2-stimulation exerts vasodilatory effect, presumably via augmentation of endothelium derived nitric oxide release in coronary microvascular beds in chronic heart failure.

P2174 Pericoronary nerves subserve a negative inotropic effect during coronary catheter balloon inflation in anaesthetized healthy pigs

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Intracoronary catheter balloon inflation may stimulate coronary mechanoreceptors and this, in turn, might reflexely affect left ventricular (LV) function, in addition to the ischaemia-induced haemodynamic depression. However, this hypothesis has not been tested.

Methods. LV pressure, LV dP/dt, and ECG were analyzed during catheter balloon inflation at the left anterior descending (LAD) coronary artery in α-chloralose anaesthetized pigs (30–40 kg; n = 24). All pigs were submitted to a 1-minute ballon inflation before and after each of the following treatments: denervation of the pericoronary nerves with topical phenol (n = 7), bilateral vagotomy (n = 6), or bilateral stellectomy (n = 11). The time course of the changes induced by the two balloon inflations were compared by the ANOVA test.

Results. LAD balloon inflation induced a significant ($p < 0.01$) decay in LV systolic pressure (LVSP) (105 ± 13 vs 86 ± 12 mmHg), peak LV (+)dP/dt (2952 ± 769 vs 1770 ± 549 mmHg/s) and LV (−)dP/dt (1569 ± 362 vs 1068 ± 288 mmHg/s), together with ST segment elevation (0.03 ± 0.06 vs 0.23 ± 0.13 mV). LAD pericoronary denervation significantly attenuated the drop in LVSP (17% vs 11% at 60 s; $p < 0.001$) and in LV (+)dP/dt (34% vs 28%; $p < 0.01$). Bilateral stellectomy attenuated the effects of balloon dilation on the decay of LV (+)dP/dt (41% decay vs 33%; $p < 0.001$), whereas bilateral vagotomy had no significant effect.

Conclusions. Coronary balloon inflation elicits a negative inotropic effect subserved by sympathetic pericoronary nerves, which acts in concert with the ischaemia-induced myocardial dysfunction.

PERIPHERAL CIRCULATION: MECHANISMS, DIAGNOSIS AND TREATMENT

P2175 Aortic viscoelastic properties in patients with essential hypertension, coronary artery disease and congestive heart failure

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In a perfectly elastic material, the stress/strain response occurs immediately or in a negligible time. If a constant tensile stress is placed on the aortic wall, it will continue to elongate (that is, the strain will increase) for some period of time until a new equilibrium is reached; this time dependence of the stress/strain response is called viscoelasticity. To describe the viscoelasticity of the aortic wall the gradual recoil, namely stress relaxation, was used to characterize this process.

Methods: The pressure-diameter relation was determined in the descending aorta in 120 subjects. Diameter was measured with a Y-shaped intravascular catheter using sonomicrometers in the same level with intra-aortic pressure measured with a catheter tip micromanometer. Aortic distensibility was estimated by the following formula: (2 × strain/pulse pressure). In one simple model ($D = D_d \times e^{-t/\tau}$), aortic diameter was fitted an exponential decay towards the diastolic dimension (D_d), and the time course of aortic wall relaxation was estimated by an exponential decay constant (τ).

Results: The study population consisted of 32 normal subjects (NLS), 28 hypertensive patients (HYPS) with moderate and severe hypertension, 49 patients with coronary artery disease (CAD) (13 with 1, 18 with 2, and 18 with 3 vessels disease), and 11 with congestive heart failure (CHF). The mean age ± SD was 56.9 ± 11.7 and there were 98 men and 22 women. Distensibility was different between the groups (NLS: 3.4 ± 0.7, HYPS: 1.4 ± 0.2, CAD: 1.2 ± 0.2, and CHF: 1.3 ± 0.2 $dyn^{-1}cm^2 10^{-6}$, ANOVA: $p = 0.000$). The constant τ was also different between the groups (NLS: 37.6 ± 8.5, HYPS: 52.6 ± 10.7, CAD: 74.0 ± 13.9, and CHF: 55.4 ± 10.2 ms, ANOVA: $p = 0.000$). In a multiple linear regression including all demographic and hemodynamic variables, distensibility was the best predictor, of strain variability ($b = 0.0390$, $p = 0.000$) and additionally pulse pressure added to the prediction of strain ($b = 0.0027$, $p = 0.000$); for all subjects τ and heart rate were associated in the same model with strain ($b = -0.0005$, $p = 0.000$ and $b = -0.0210$, $p = 0.048$, respectively).

Conclusions: In addition to the three-dimensional and nonlinear behavior of the aorta, an important time factor must be considered in the stress/strain response, called viscoelasticity. Aortic tissue rarely behave as a perfectly elastic material both in normal and pathological conditions.

P2176 Arterial stiffness in systemic sclerosis

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Background: Systemic sclerosis (SSc) is a generalized connective tissue disorder characterized by fibrosis and vascular changes of skin and multiple internal organs. No data are available on involvement of large arteries. Aim of the study was to evaluate anatomy and elastic properties of the great arteries in SSc.

Methods: Thirty normotensive women – 15 with SSc (disease duration: 6.4 ± 5.2 ys) and 15 healthy subjects (H) – matched for age, body mass index, clinical and 24-hour blood pressure (BP), underwent common carotid artery ultrasonography for assessing carotid intima-media thickness (IMT, mm), cross-sectional intima-media area (M-a, mm^2) and atheromatous plaques (n). As an index of arterial stiffness, pulse wave velocity (PWV, m/s) was calculated by simultaneous carotid and femoral pulse recording. Wilcoxon test, simple linear regression and binary logistic analysis were employed for statistical analysis.

Results:

	Age	24 h Sys BP	IMT	M-a	Plaque	PWV
SSc	55.8 ± 11.3	115.7 ± 9.02	0.7 ± 0.1	13.74 ± 3.1	6/15	9.2 ± 2*
H	57.9 ± 10.1	118.8 ± 7.27	0.67 ± 0.1	12.63.3 ± 2.1	4/15	7.6 ± 1.3

*$p < 0.05$

In a binary logistic analysis, PWV was the major predictor of the presence of SSc (odds ratio:5). PWV showed correlation with age, IMT, systolic, diastolic and mean BP ($p < 0.05$, $p < 0.01$, $p < 0.05$, $p < 0.05$ and $p < 0.01$, respectively).

Conclusion: Our data provide the first evidence of a peculiar involvement of large arteries in SSc, characterized by increased arterial stiffness in the absence of carotid wall thickening or plaque formation. The non invasive, easily determined evaluation of PWV may be of potential clinical and prognostic significance in SSc, predicting arterial damage and monitoring its progression.

P2177 Mechanism of ischaemia and pain in peripheral vascular disease: localization of endothelin-1 binding to femoral arteries

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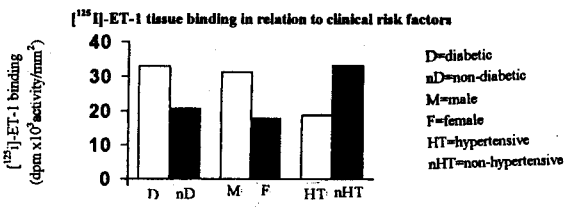
Raised circulating endothelin-1 (ET-1) has been found in peripheral vascular disease (PVD). ET-1 vasoconstricts by binding to ET_A and ET_B receptors on medial vascular smooth muscle cells. Binding to adventitial microvessels supplying perivascular nerves has also been described. The significance of these observations remains poorly understood.

Methods: Femoral arterial sections obtained from 9 patients undergoing aorto-femoral bypass grafting (5 men, 4 women, aged 54–77 y, 3 were diabetic and 5 hypertensive) were rinsed in saline, frozen in liquid nitrogen and stored at −70°C. ET-1 receptors were studied using *in vitro* autoradiography. Slide mounted sections were incubated in buffer containing [^{125}I]-ET-1 and receptor subtypes identified using [^{125}I]-PD131242 (ET_A selective) and [^{125}I]-BQ3020 (ET_B selective). Autoradiographs were generated on radiation sensitive film and receptor binding quantified by densitometric analysis. Microscopic localization of binding was achieved using nuclear emulsion and specific cells identified using immunomarkers.

Results: Both ET_A and ET_B binding in the tunica media was observed (ET_A 10.1 [2.8], ET_B 5.5 [2.8] mean [± SEM] dpm × 10^3 activity/mm^2). Autoradiography confirmed ET_A/ET_B binding on medial vascular smooth muscle cells and ET_B on vasa vasorum and vascular nerves. Claudication distance related to ET-1 binding ($r = 0.731$, $p < 0.05$) but not to ET_A or ET_B receptors. ET-1 and ET_B were higher in diabetics ($p < 0.05$). ET-1 and ET_A were higher in men ($p < 0.05$), ET_B receptors higher in women ($p < 0.05$). ET_A, ET_B and ET-1 concentrations were lower in hypertensives ($p < 0.05$). ET_A, ET_B and ET-1 were not inter-related.



[^{125}I]-ET-1 tissue binding in relation to clinical risk factors.

Conclusion: Medial ET_A and ET_B receptors are ideally situated to be affected by circulating ET-1. ET-1 binding to ET_A/ET_B receptors on vascular smooth muscle cells may be responsible for vasoconstriction causing ischaemia. Further, ET-1 may play a role in the mechanism of pain, by binding to ET_B receptors of microvessels supplying perivascular nerve.

P2178 Sympathetic tone and blood flow in vasovagal syncope

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The purpose of this study was to investigate the time course and relationship between cerebrovascular, peripheral blood flow and sympathovagal interaction in patients with vasovagal syncope (VVS).

Methods: 11 subjects with well documented VVS during tilting and 10 matched volunteers were studied at baseline and during 60° head-up tilt to the onset of syncope or at 30 minutes. Spectral analysis was applied to 5-minutes continuous recordings of ECG to assess autonomic function. Low frequency (LF) variations of the RR interval reflect both sympathetic and parasympathetic activity, whereas high frequency (HF) variations are an index of vagal tone and LF/HF ratio a measure of sympathovagal balance. Transcranial Doppler of the middle cerebral artery assessed systolic (Vs) and diastolic (Vd) velocities, with derivation of pulsatility (PI) and resistance indices (RI). Subcutaneous finger flow was measured by Laser Doppler flowmetry and blood pressure by Finapres.

Results: Immediately after tilt, LF (normalised units; nu) increased from 42.3 ± 7.1 to 66.5 ± 7.8 ($p < 0.01$), LF/HF ratio from 1.1 ± 0.4 to 3.4 ± 0.8 ($p < 0.01$) and HF (nu) decreased from 57.7 ± 7.1 to 35.6 ± 7.8 ($p < 0.01$) in normals suggesting shift of sympathovagal balance towards sympathetic predominance. However, in patients with VVS, LF increased from 53.4 ± 6.3 to 72.6 ± 9.6 ($p = 0.06$), LF/HF ratio from 1.6 ± 0.4 to 5.7 ± 2 ($p = 0.05$) and HF decreased from 46.6 ± 6.3 to 27.4 ± 9.6 ($p = 0.06$). Peripheral flow (measured as flux in arbitrary units) decreased immediately after tilt in normals from 245.7 ± 41.2 to 160.9 ± 35.2 ($p < 0.01$), whereas in patients this increased from 155.3 ± 39 to 194.9 ± 92.6 ($p = 0.24$). RI increased prior to syncope, Vs and Vd decreased after tilt, most markedly before syncope suggesting cerebral vasoconstriction, out of keeping with hypotension observed at syncope.

In conclusion, patients with VVS, in constrast to normals, respond to orthostatic stress by paradoxical peripheral vasodilation and cerebral vasoconstriction preceding onset of symptoms and hypotension.

P2179 A blunted nocturnal blood pressure fall is associated with greater carotid sinus stimulation responses in patients with essential hypertension

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Ambulatory blood pressure (BP) is correlated better with indices of hypertensive cardiovascular complications than office BP. Whether the absence of the normal nocturnal BP fall is related with the extent of carotid sinus stimulation responses (CSSR) remains to be established.

Methods: Towards this end, carotid sinus stimulation (with simultaneous recordings of the ECG and the BP sphygmomanometrically at the brachial artery) was performed in 81 untreated, newly diagnosed patients (pts) with stage I–II (JNC-VI) essential hypertension (aged 54 ± 10 years, office BP 154 ± 18/97 ± 12 mmHg; without a history of any cardiac or vascular disease or syncope). Cardionhibitory type CSSR was evaluated by calculating CSSR index which is defined as the ratio of the longest R-R interval on the ECG recording during stimulation to R-R interval at rest. By ambulatory BP monitoring the pts were classified into non-dippers (defined by a reduction in the night mean systolic and diastolic BP < 10% from day) and dippers (the remaining subjects). Results: In the entire study population, LVMI was 92.9 ± 19 gr/m^2, RWT was 0.48 ± 0.06, rest R-R interval was 0.79 ± 0.05 sec, max R-R interval was 1.36 ± 0.83 sec (ranged 0.68–4.84) and CSSR index was 1.74 ± 1.03. The two groups' non-dippers (34 pts) and dippers (47 pts) were matched for age, BSA, smoking status and plasma cholesterol level. Non-dippers compared to dippers had significantly increased office systolic and diastolic BP (159 ± 19 vs 150 ± 18 and 100 ± 15 vs 94 ± 8 mmHg respectively), 24 h systolic BP (140 ± 14 vs 132 ± 9 mmHg), 24 h ambulatory pulse pressure (54 ± 7 vs 48 ± 6 mmHg), 24 h systolic load (48 ± 30% vs 28 ± 18%), LVMI (100 ± 22 vs 90 ± 16 g/m^2), RWT (0.50 ± 0.06 vs 0.46 ± 0.05), max R-R interval (1.48 vs 1.29) and CSSR index (1.72 ± 0.8 vs 1.65 ± 0.8). In the entire study population, by a multivariate model including ambulatory BP parameters, only the 24 h systolic load was identified as a significant determinant of CSSR index.

Conclusion: The absence of normal nocturnal BP fall is associated with an impairment of CSSR in the setting of moderate essential hypertension. These findings may partly be accounted for the unfavorable prognosis of non-dipper hypertensives.

P2180 Intima-media thickness of the common carotid artery is related to plasma leptin and insulin resistance in normal weight and obese subjects

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We sought to investigate whether intima-media thickness (IMT) of the common carotid artery (CCA) is significantly associated with leptin (L) plasma levels. L, the satiety hormone expressed almost exclusively in adipose tissue, is a marker of body fat accumulation. Moreover, the thickening of the arterial intima-media complex is the initial sign of asymptomatic atherosclerosis.

Methods. We assessed fasting plasma L levels and the IMT of the CCA in 120 healthy subjects (52 men and 68 women), aged 18–45 years, and with a wide range of BMI. L concentrations were measured by radioimmunoassay and the IMT of the CCA was quantified by high resolution B-mode ultrasound imaging. Body fat distribution (measured by waist circumference and waist-to-hip ratio), smoking habits, blood pressure, insulin sensitivity (measured by the insulin tolerance test), and fasting plasma glucose, insulin and lipid pattern (cholesterol, HDL-cholesterol, triglycerides, LDL-cholesterol) were also measured.

Results. IMT of the CCA was positively correlated with L levels ($P < 0.001$ in men and $P = 0.004$ in women) and age ($P < 0.001$ in men and $P = 0.007$ in women) and negatively associated with insulin sensitivity in both sexes ($P = 0.04$ in men and $P = 0.004$ in women). IMT was also directly correlated with cholesterol and LDL-cholesterol in men ($P = 0.03$ and $P = 0.017$ respectively), and with mean blood pressure levels in women ($P = 0.03$). When a multiple linear regression model was used, the correlation between L and IMT was maintained in both men ($P = 0.008$) and women ($P = 0.048$), independently of age, KITT, smoking habits, mean blood pressure, fasting glucose, triglycerides, cholesterol, LDL-cholesterol and HDL-cholesterol.

Conclusions. L plasma levels show an independent relationship with the IMT of the CCA, suggesting that the increase of adipose tissue mass has an independent unfavorable influence on the development of atherosclerosis.

P2181 Morphological and functional markers of peripheral atherosclerosis in obstructive coronary artery disease

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Background and aim: Obstructive coronary artery disease (CAD) is a local manifestation of the advanced atherosclerotic process. Different vascular districts of patients (pts) with CAD have not been systematically evaluated for early morphological or functional markers of atherosclerosis, such as intimal-medial thickening (IMT) or endothelial dysfunction. The aim of our study was to find out to what extent the peripheral atherosclerosis is associated with these pts.

Methods: Using high-resolution 7.5 MHz linear phased-array transducer and a standard Acuson 128XP/10 system we studied IMT, as well as arterial diameter at rest and during endothelial-dependent (cold pressor test, CPT; hand-grip test, HGT; flow-mediated response, FMR) and endothelial-independent vasodilation (sublingual nitroglycerin 0.4 mg, NTG) of carotid, brachial and femoral arteries in 82 pts: in 47 pts with obstructive CAD (>50% diameter narrowing of at least one epicardial artery) and 35 control pts (angiographically smooth arteries). The mean pts age was 52 ± 14 years and female to male ratio 1:2.4.

Results (table): IMT was significantly ($p < 0.001$) increased in all target arteries in CAD pts as compared with controls. Atherosclerotic plaques were more often found in carotid (43% vs 3%) and femoral arteries (53% vs 9%) of CAD pts. Basal arterial diameters were significantly larger in carotid and brachial arteries of CAD pts but not in femoral arteries. Endothelial-dependent as well as independent vasodilation was significantly ($p < 0.05$-0.001) reduced in all target arteries of CAD pts. CAD pts with hypertension showed smaller brachial diameters ($p < 0.05$) while chronic ACE inhibition (>6 months) increased carotid diameters ($p < 0.031$). Statins improved endothelial-dependent vasodilation in brachial arteries of our CAD pts ($p < 0.05$).

Variables	Carotid artery		Brachial artery		Femoral artery	
	CAD	Controls	CAD	Controls	CAD	Controls
IMT (mm)	0.9 ± 0.2	0.6 ± 0.1*	0.6 ± 0.1	0.4 ± 0.1*	1.0 ± 0.2	0.6 ± 0.1*
Plaques (%)	20 (43%)	1 (3%)*	0 (0%)	0 (0%)	25 (53%)	3 (9%)*
Basal (mm)	6.6 ± 1.2	5.8 ± 0.7‡	4.4 ± 0.8	3.8 ± 0.7‡	8.0 ± 1.3	8.0 ± 1.3
CPT (%)	3.4 ± 3.3	8.7 ± 7.0*	4.8 ± 4.3	11.1 ± 8.5*	3.1 ± 2.7	5.6 ± 4.5‡
HGT (%)	4.6 ± 3.8	10.2 ± 5.7*	5.6 ± 4.3	13.5 ± 8.2*	3.8 ± 2.8	7.2 ± 4.0*
FMR (%)	–	–	8.1 ± 5.2	14.6 ± 5.7†-	-	
NTG (%)	7.0 ± 3.7	13.6 ± 5.7*	11.1 ± 6.4	21.2 ± 11.0*	6.7 ± 4.3	10.4 ± 4.0*

† < 0.05; ‡p < 0.01; *p < 0.001

In conclusion, increased IMT and substantial endothelial dysfunction of all examined peripheral arteries was invariably present in pts with obstructive CAD while atherosclerotic plaques were found in approximately half of their carotid or femoral arteries. CPT and HGT as well as FMR seems to be equivalent in the assessment of endothelial-dependent vasodilation in these pts.

P2182 Energetics of the human aorta: association with aortic elastic properties

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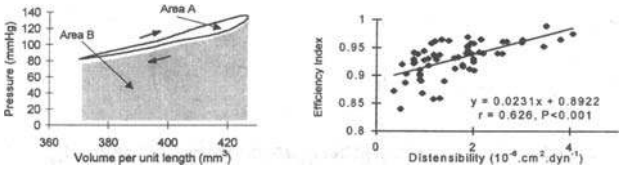
The aorta (Ao), by virtue of its elastic nature, stores a considerable amount of the LV power generated during cardiac systole, which is returned by Ao recoiling during diastole. To investigate the relation between Ao energetics and Ao elastic properties, we applied a technique developed in our institution for the in-vivo determination of the pressure-volume relation (Circulation 1995; 92: 2210–9) in 62 pts (age 56 ± 10 yrs). Ao diameter and volume per unit length were measured by an intravascular dimension catheter and Ao pressure was recorded simultaneously by a Millar catheter. The area under the systolic (ascending) portion of the clockwise loop (left fig., areas A + B) represents the energy stored by the Ao, the area under the diastolic (descending) portion of the loop represents the energy forwarded by the Ao (area B), whereas the area within the loop (area A) the energy dissipated by the Ao due to its viscosity.

Results: Efficiency index of the Ao (= energy returned/stored, i.e. area B/area A + B) had a positive correlation with distensibility (= 2 × [pulsatile change in Ao diameter]/[diastolic Ao diameter] × [pulse pressure], right fig.) indicating decreased energy loss with improved elastic properties.



Conclusions. Aortic energetics are closely associated with aortic elastic properties. This new insight into the performance of the aorta may provide a better understanding of the pathophysiology of the vessel.

P2183 The morbidity of peripheral arterial disease: a powerful and consistent clinical cardiovascular ischaemic risk

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Any clinical evidence of atherosclerosis identifies individuals at risk of cardiovascular ischemic events (IEs). Nevertheless, the relative predictive power of peripheral arterial disease (PAD) for such events is not widely recognized. Therefore, the CAPRIE study database was utilized to define this ischemic risk, as this trial is both the largest randomized trial of antiplatelet agents for the prevention of IEs, as well as the largest prospective evaluation of individuals with PAD.

Methods: CAPRIE prospectively evaluated 19,185 patients who presented with PAD (6452 patients), recent myocardial infarction (MI), or recent ischemic stroke (IS). Clinical evidence of PAD at study entry was recorded in all participants and included evidence of claudication, prior limb surgical revascularization, and/or amputation. Follow-up was for a mean of 1.9 years with evaluation of subsequent IEs. Multivariate analyses were performed using a reduced model of pertinent clinical factors to calculate relative risk ratios (RRs) for the event outcome cluster of MI or IS (fatal or nonfatal) in both the entire study cohort and in those presenting with PAD.

Results: All clinical markers of PAD served as potent predictors of subsequent MI or IS in the whole study cohort, including claudication (RR = 1.3, $p < 0.01$), prior surgical revascularization (RR = 2.2, $p < 0.001$), and amputation (RR = 2.2, $p < 0.005$). In those with PAD, increased risk of IEs was predicted by increasing age (RR = 1.3/10 yrs, $p < 0.001$) and diabetes (RR = 1.6, $p < 0.001$); by prior reversible ischemic neurologic deficit (RR = 2.3, $p < 0.001$) or IS (RR = 1.5, $p = 0.01$); by prior stable angina (RR = 1.7, $p < 0.001$) or MI (RR = 1.3, $p = 0.02$); or by prior surgical revascularization (RR = 2.5, $p < 0.001$). Current tobacco use or hypercholesterolemia did not predict subsequent IEs. The benefits of antiplatelet therapy with clopidogrel vs. aspirin were particularly profound in all individuals with PAD (by 22.9% [7.3%, 35.8%], $p = 0.006$).

Conclusions: PAD, whose presence is easily and inexpensively detected by medical history, examination, and the ankle–brachial index, increases the risk of IEs in patients with atherosclerotic syndromes. This risk is increased further by the presence of coronary or cerebrovascular symptoms. Ischemic event rates in PAD patients were preferentially reduced by clopidogrel compared with aspirin.

P2184 Sustained improvement in flow-mediated vasodilation after 30 minutes of submaximal constant work rate exercise in patients with chronic heart failure

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There is evidence that chronic exercise improves endothelial function (EF) in patients with chronic heart failure (CHF). However, it is not well defined whether a single bout of submaximal constant work rate exercise (SE) can improve endothelial function in the skeletal muscle vasculature. The duration of this potentially beneficial effect was also investigated.

Methods: Twenty patients with stable CHF due to ischemic heart disease were studied. A symptom-limited incremental cardiopulmonary exercise test was performed on a cycle ergometer to assess peak VO_2. Flow-mediated vasodilation in response to peak reactive hyperemia and the response to sublingual nitroglycerin (NTG) were evaluated in the right femoral artery (FA) of 20 patients with CHF. In 10 of them (group E) resting, peak hyperemic (PH) and post-NTG FA blood flow (BF) and diameter (D) were measured by a 2-dimensional and pulse Doppler ultrasonography at baseline and at 3, 24 and 72 hours after 30 min of SE on an electronically-braked cycle ergometer at an intensity of 60% of peak VO_2. Ten patients with CHF who did not exercise served as control group (C).

Results: No changes were observed in the C group. In the group E, resting BF was significantly increased after SE at 3, 24 and 72 hours (363 ± 35, 310 ± 28 and 288 ± 31 mL/min, respectively, compared with 153 ± 24 mL/min at baseline; $P < 0.01$ E vs C). Peak hyperemic BF and D were also increased at same times ($P = 0.01$ for both, E vs C), whereas no changes were induced by NTG. The changes in PHBF response after SE were correlated with peak VO_2 ($r = 0.76$; $P < 0.01$).

Conclusion: In patients with CHF, short-term SE selectively improves vascular endothelial function for at least 72 hours.

P2185 Is carotid and peripheral angiography beneficial during coronary angiography in patients with coronary artery disease?

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It is known that carotid disease (CD) or peripheral artery disease(PAD) is frequently associated with coronary artery disease (CAD). However, the incidence of these diseases in patients (pts) with angiographically documented CAD has not been clearly documented. This study was to determine the incidence of significant CD or PAOD in pts with CAD and the strategy of routine global vascular screening during coronary angiography can benefit the pts.

Methods: Between June 1996 and Nov. 1998, for 550 consecutive pts who was diagnosed to have significant CAD (>50% stenosis) by coronary angiography, we performed digital-subtraction angiography of carotid arteries and angiography of peripheral arteries from suprarenal abdominal aorta to femoral arteries in the same setting. Average amount of dye used were 28 ml for carotid and perpheral angiography, respectively. Significant CD was diagnosed if >50% luminal narrowing was present. Significant PAD was diagnosed as having total occlusion or >50% luminal narrowing with mean pressure gradient > 10 mmHg. Abdominal aortic aneurysm was included in PAD.

Results: There were 374 males (68%) and the mean age was 59 ± 10 (24–91) yrs old. Of these, 226 (41%) had 1 vessel-disease(VD), 160 (29%) had 2 VD, 164 (30%) had 3 VD. The incidence of significant CD including internal, external and common carotid arteries was 12.2% (66 pts). The incidence of significant PAD including aortic, iliac, femoral, and renal artery disease was 28.0% (154 pts). Carotid stenting was performed in 19 pts (3.5%), renal angioplasty in 21 pts (3.8%), femoro-iliac angioplasty in 28 pts (5.1%), aortic stent-graft in 8 pts (1.5%), bypass graft of femoro-iliac arteries in 2 pts (0.4%), and surgery of aortic aneurysm in 2 pts (0.4%). Excluding duplicate procedure in a pt, 74 pts (13.5%) were undertaken angioplasty or surgery detected by routine screening.

Conclusions: Routine carotid and peripheral vascular angiography at the same setting with coronary angiography in pts with significant CAD was beneficial in detecting pts with significant CD or PAD requiring treatment.

P2186 Oestrogen, but not antioxidant, treatment improve endothelial function in women with Raynaud's phenomenon secondary to systemic sclerosis

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We have recently shown that endothelial dysfunction is present in patients with Raynaud's phenomenon secondary to systemic sclerosis. It is not known if endothelial dysfunction in this setting is due to increased oxidative or other reasons.

Methods. Nine female patients with Raynaud's phenomenon and systemic sclerosis (age 58 ± 9 years) underwent ultrasound imaging of the right brachial artery for evaluation of flow-mediated dilatation (FMD < endothelium-dependent dilatation) and nitrate-induced dilatation (NID, endothelium-independent dilatation). Ten healthy women (age 58 ± 8 years) served as controls. Subsequently patients entered a crossover study and received conjugated estrogens (1.25 mg/day Premarin) for four weeks, placebo for four weeks and 2 g of ascorbic acid orally.

Vasoreactivity studies were repeated and the end of the 4-week period of estrogens or placebo and 2 hours after the oral administration of ascorbic acid.

Results. Baselin FMD was 2.1 ± 1.6% (controls 8.2 ± 3.2%, $p < 0.001$) and NID 17.6 ± 4.8% (controls 26 ± 8%, $p = 0.01$). FMD improved after 4-week treatment with estrogens to 6.6 ± 3.5% ($p < 0.05$), while NID did not change. No significant changes were observed after placebo treatment (FMD 1.5 ± 2%, NID 18.5 ± 7.6%, ns). No significant changes were observed after administration of ascorbic acid (FMD 2.6 ± 2%, NID 16 ± 7%, ns).

Conclusions. Antioxidant treatment does not improve endothelial function in Raynaud's phenomenon secondary to systemic sclerosis, indicating that oxidative stress is not implicated in the pathogenesis of endothelial dysfunction in this setting. The improvement observed after estrogen therapy indicates a possible upregulation of NO synthase.

DIVERSE NEW DEVELOPMENTS IN EPIDEMIOLOGY

P2187 Improved one year survival after acute myocardial infarction between 1986 and 1996

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During the last decade the treatment of patients with acute myocardial infarction (AMI) has changed dramatically. We set out to evaluate the effect of these changes on one-year mortality.

Methods and Results: All patients hospitalised for AMI in Reykjavik, Iceland during the calendar years of 1986 (n = 335) and 1996 (n = 351) were included in the study. Information on risk factors and medical therapy of each patient was obtained from medical records. All-cause mortality at one year after hospital admission was compared between years and related to risk factors and medical therapy at discharge and to interventional procedures within one year. Demographic characteristics did not change between 1986 and 1996. The one-year mortality decreased from 23.3% to 19.7% ($p < 0.05$). The recorded risk factors were not associated with one-year mortality. There was a significant increase in the use of aspirin (from 11% to 76%), beta blockers (from 48% to 62%) and thrombolytic agents (from 8% to 24%) between 1986 and 1996 and these drugs were associated with reduced one year mortality (table). The use of diuretics, digoxin and anti-arrhythmic agents did not change significantly but was associated with increased mortality. Calcium antagonists and ACE inhibitors had a neutral mortality effect. Although there was an increase in use of PTCA (from 7% to 23%) and CABG (from 4% to 11%) between years, these interventions were not associated with an imroved outcome.

	1986			1996		
	OR	95% CI	p	OR	95% CI	p
Aspirin	0.44	0.17–1.17	0.14	0.13	0.07–0.23	0.001
Beta blocker	0.28	0.16–0.49	0.001	0.36	0.21–0.64	0.001
Diuretic	3.18	1.89–5.36	0.001	3.55	2.01–6.27	0.001
Ca-antagonist	0.98	0.52–1.85	1.00	0.76	0.38–1.51	0.54
ACE-inhibitor	1.76	0.41–7.54	0.43	1.03	0.55–1.90	1.00
Digoxin	2.06	1.13–3.76	0.027	2.34	1.13–4.84	0.033
Anti-arrhythmic	3.61	1.18–11.1	0.025	2.92	1.27–6.73	0.017
Nitrates	0.74	0.44–1.21	0.31	0.95	0.54–1.69	0.99
Thrombolytic	0.37	0.11–1.26	0.16	0.27	0.11–0.64	0.001

Conclusions: The 6.6% mortality reduction during the last decade is mainly due to improved medical therapy.

P2188 Cancer risk and mortality in users of calcium channel blockers: cohort study

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It has been suggested that calcium channel blockers may increase the risk of cancer and promote the growth of tumours. Since calcium channel blockers are used extensively in the treatment of hypertension, ischemic heart disease and supraventricular arrhythmias, even a small excess risk may have major public health implications. On this background, we report the cancer specific risk and mortality in a Danish cohort of calcium channel blocker users.

Methods: We identified calcium channel blockers users in the prescription database of the County of North Jutland, Denmark. The study cohort was then linked to the files of the Danish Cancer Registry and the Danish Registry of Death, which collect information on all cases of cancer and death in Denmark. The follow-up period for cancer occurrence began at the date of first known prescription of calcium channel blockers and ended at the date of emigration, date of death, or 31 December 1995, whichever occurred first. The standardized incidence ratio was calculated as the ratio of the observed to the expected number of cancer cases. The observed number of deaths was likewise compared with the number of expected deaths.The statistical methods assume that the observed number of cases of cancer and death in any specific category followed a Poisson distribution.

Results: We identified 23 167 who had received more than one prescription, yielding 89 295 person-years of follow-up, with a mean follow-up period of 3.16 years.

	Cancers Observed	SIR	95% CI	Deaths Observed	SMR	95% CI
All causes of death				4123	1.47	1.42–1.51
All malignant neoplasm	945	1.04	0.98–1.11	653	0.97	0.89–1.04
Colon	82	0.86	0.68–1.06	65	0.96	0.74–1.22
Rectum	53	0.97	0.73–1.27	31	1.02	0.69–1.45
Breast	84	0.96	0.76–1.19	48	1.10	0.81–1.46

Observed number of cancers and deaths and standardized incidence rate (SIR) ratio for cancer, or standardized mortality ratio (SMR), occurring in calcium channel blockers users who received more than one prescription of calcium channel blockers (N = 23167)

Conclusion: Our study provides no evidence of an association between use of calcium channel blockers and cancer risk and mortality.

P2189 Naxos arrhythmogenic right ventricular cardiomyopathy: prevalence and clinical outcome

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Background: Naxos disease is a familial syndrome consisting of arrhythmogenic right ventricular cardiomyopathy, palmoplantar keratosis and curly hair. It originates from the Greek island of Naxos (population 20,000).

Methods: We traced all families with Naxos disease in the island (12 families) thanks to their stereotype phenotype (palmoplantar keratosis and curly hair). We found 25 pts (12 male/13 female, mean age 36 ± 17 years). The pts were assessed with clinical examination, 12-lead ECG, 2-D echo and 48 hour Holter monitoring and followed for a mean period of 9 ± 5 years.

Results: The prevalence of the disease in the island is about 1:800 (25:20,000). The mode of inheritance appears to be autosomal recessive. During the follow-up period, 7 pts (28%) developed heart failure and 8 pts (32%) died from cardiac causes (7 sudden, 1 right heart failure). The annual rate of sudden death was 3%. Five of 7 pts (71%) who died suddenly, as well as the patient who died of heart failure, were young (<35 years). Of all pts, 6 had a family history of sudden death (24%), 12 had syncope (48%), 7 developed sustained ventricular tachycardia (28%) and 6 developed morphological changes in both ventricles (24%).

Conclusion: Naxos disease is a progressive disease with high incidence of sudden death and heart failure. Patients who die suddenly are mainly young (<35 years).

P2190 Determinant factors of endothelial function in a Mediterranean population with a low prevalence of coronary artery disease

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Endothelial dysfunction is a key feature of atherosclerosis progression and appearance of coronary heart disease (CHD). Evidence is acumulating that coronary risk factors (CRF) differentially affect endothelium-dependent vasodilation, but its not clarify that CRF in european populations with low coronary risk affect to endothelial function (EF).

Methods: In a rural district of mediterranean population with low coronary risk (anual mortality for CHD < 70/100000 adjusted for age) 421 consecutive pts. (age 59 ± 16, 57% males) were recruited for echocardiography: 290 pts. with confirmed CHD and 131 without CHD or atherosclerosis complication (35 hipertensive patients). Flow mediated dilation (FMD%) and after nitroglicerin (endothelium-independent) were assessed in the brachial artery by high resolution ultrasound. A prognostic "score" indicanting risk of cardiovascular death or non-fatal MI was calculated according the Framingham model: age, gender, systolic blood pressure, total/HDL cholesterol, diabetes and smoking status. Others CRF were evaluated.

Results: Significant correlations were observed between FMD% and triglicerides (−0.23 p = 0.023), HDL-chol (0.41 p = 0.000), plasma glucose (−0.30 p = 0.002), fibrinogen (−0.46 p = 0.000), sistolicBP (−0.15 p = 0.046, age (−0.44 p = 0.000) and "risk score" (−0.51 p = 0.000) but not with total-chol, LDL-chol, diastolicBP. A stepwise multivariate regression incorporating laboratory data demostred HDL-chol independent predictor (β = 0.42 p = 0.004) with residual correlation (p = 0.013). After inclusion in model epidemiologic data only "risk score" influenced FMD% (β = −0.952 p = 0.000). Pts with CHD had significantly lower FMD% (0.10 ± 6.34 vs 9.29 ± 8.11 p = 0.042) and HDL-chol (46.2 ± 10.1 vs 65.1 ± 13.7 p = 0.034) and greater age (66 ± 11 vs 57 ± 15 p = 0.002) and "risk score" (2.78 ± 1.05 vs 1.47 ± 1.27 p = 0.000) without differences in others CRF or dilation endothelium-independent. Logistic regression showed "risk score" independent predictor of CHD (RR 5.45, p = 0.0183).

Conclusion: In populations with low coronary risk, the endothelial-function and appearance of CHD is associated a adverse risk factors profile depending principally of age and anormal metabolism of HDL.

P2191 Inhibition of post-injury neointima development by 17β-oestradiol and the phyto-oestrogens genistein and daidzein in non-toxic concentrations in vitro

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Phytoestrogens like Genistein and Daidzein have a beneficial influence on haemodynamics and lipid profile in vivo. Such effects have been shown for 17β-Estradiol before. The latter has anti-proliferative properties on the vessel wall as well. The aim of this in-vitro experiment was to establish non-toxic dosages of the three estrogens which inhibit the neointima formation after endothelial balloon denudation.

Methods: In situ endothelial denudation was performed in female rabbits by a 3 F Fogarty catheter. Segments of 5 mm were randomized in groups of n = 8 and held in culture. 17β-Estradiol, Genistein and Daidzein were applicated in concentrations of 20 μM, 30 μM, and 40 μM. Groups without hormonal treatment served as controls. The segments were histologically prepared and measured after 21 days. Afterwards, 3 further groups (n = 8) were held with the lowest concentration of hormones having been evaluated to inhibit the neointimal development. After 21 days of treatment these sections were held in medium only with 20% fetal calf serum (fcs) for another week to proof whether these segments were still able to proliferate.

Results: Compared to controls, 30 μM 17β-Estradiol, 20 μM Genistein and 40 μM Daidzein significantly inhibited neointimal development over 21 days. After another week of cultivation in medium with 20% fcs the amount of neointima formation was comparable to that of untreated controls after 21 days.

In conclusion, 17β-Estradiol, Genistein and Daidzein were able to inhibit post-injury neointima formation in non-toxic concentrations. This may have therapeutical consequences as the applicated phytoestrogen concentrations were only 10 fold higher than those found in humans consuming high amounts of soy products.

P2192 The effect of osmolarity and volume of fluid intake on the risk of fatal coronary heart disease. Findings from the Adventist Health Study

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Increased blood viscosity has been found to be directly assoicated with heart disease. Consumption of hyperosmolar fluids results in net secretion of water from the vascular system while hypo-osmolar fluids results in net absorption. We compared the effect of water, hypo- and hyper-osmolar fluid intake on the risk of fatal and non-fatal coronary heart disease (CHD) in participants of the Adventist Health Study.

Method: In 1976, 34,198 white, non-hispanic California Seventh-day Adventists enrolled in the Adventist Health Study, and were followed for 6 years. Extensive lifestyle information including diet and daily fluid intake was assessed at baseline. The risk of fatal CHD was analyzed according to self-reported daily intake of fluids among subjects without prevalent CHD, stroke or diabetes at baseline using Cox Proportional Hazards Model.

Results: Among the 26,938 persons analyzed, 124 males (1.1%) and 115 females (0.7%) experienced fatal CHD during follow-up. Fatal CHD showed an inverse dose-response relationship to daily intake of water and fluids hypo-osmolar to plasma after adjusting for age, smoking, education and BMI, fatal CHD (table).

Glasses /day	Water		Glasses /day	Hyposmolar Fluids (no coffee)	
	Male RR (95% CI)	Female RR (95% CI)		Male RR (95% CI)	Female RR (95% CI)
1 to 2	1.00	1.00	<2	1.00	1.00
3 to 4	0.61 (0.37–1.01)	0.56 (0.31–1.03	2 to <5.5	1.01 (0.49–2.10)	0.52 (0.22–1.24)
5+	0.40 (0.24–0.67)	0.60 (0.34–1.07)	>5.5	0.43 (0.20–0.092)	0.55 (0.24–1.27)
	Trend p = 0.0004	Trend p = 0.14		Trend p = 0.004	Trend p = 0.53

In females, intake of fluids hyperosmolar to plasma showed a direct relationship with risk of fatal CHD, RR (95% CI) 2.58 (1.19–5.59), Trend p = 0.01 for 4+ compared to <2 glasses/day.

Conclusion: Our data suggests that hypo-osmolar fluids are associated in a dose response fashion with reduced risk of fatal CHD in both males and females, whereas hyperosmolar fluids seem to increase the risk of heart disease in women.

P2193 Elite athletes with life-threatening arrhythmias: an update of a long term follow-up study

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Over the last decade a combined effort between Sport Physicians and Cardiologists has taken place with the intent of preventing severe sports related cardiac events, by identifying athletes with life threatening cardiac arrhythmias. The aim of this study is to present our updated results, until January 1999, regarding research of life-threatening arrhythmias and cardiac abnormalities in a cohort of International elite athletes (EA) studied for arrhythmias endangering their athletic careers.

Methods and results: From 1974 to January 1999, 1952 young (>35 yrs) competitive athletes, identified with arrhythmias, underwent an individualized arrhythmological non invasive and/or invasive study based on a codified clinical and instrumental protocol, 1937 males (m) and 315 females (f), mean age 21.4 yrs. 161/1952 (139 m, 28 f, average age 24.5 yrs) were EA including Italian, European, World and Olympic Champions. Of these 161 EA, 68 (42.2%) had cardiac abnormalities: arrhythmogenic right ventricular dysplasia (ARVD) in 12 (7.5%) mitral valve prolapse in 27 (16.7%), WPW in 15 (9.3%), Dilated Cardiomyopathy (DCM) in 3 (1.9%) one with sudden deah (SD), Hypertrophic Cardiomyopathy (HCM) in 1 (0.6%), mitral valve incompetence (severe) in 1 (0.6%), Aortic valve disease in 3 (1.9%), Myocarditis in 4 (2.5%), Atherosclerotic Coronary Artery Disease (ACAD) in 1 (0.6%) with SD, unknown Cardiomyopathy 1 (1.9%), with SD. Of these 161 EA 73(45.4%)were considered non eligible to participate in competitive sport activities and 18/73 (24.6%) are under antiarrhythmic treatment, 4 had a previously documented cardiac arrest (CA) (3 on field, one (WPW) at rest). Eleven had arrhythmic syncope. One with ACAD had SD at rest as first symptom. During the follow up 2 (with ARVD) ex EA required ICD implantation for refractory fast VT and high risk of SD; 2 experienced SD during sport activity, even though they had been declared non eligible. Six EA, with WPW at risk (including an alpine skier with CA) had successful RF catheter ablation (RFCA) of the accessory pathway, 2 with refractory recurrent atrial fibrillation/flutter had successful atrial RFCA with tridimensional non fluoroscopic approach.

Conclusion: EA with arrhythmias, previously considered eligible to compete, can have several arrhythmic events, at times life-threatening that are frequently consequence of an underlying heart disease or a "primary arrhythmic disease". This long term follow-up on EA can help us to explain and try to prevent drammatic cardiac events in the so called "apparently healthy subjects".

GENETICS AND PSYCHOLOGICAL INTERACTIONS

P2194 A comparison of psychosocial adaptation and acceptance in patients with pacemakers and implantable cardioverter-defibrillators

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Background: Implantation of a pacemaker (PM) or an implantable cardioverter-defibrillator (ICD) in a pt, at any time in life, by itself may result in a change in the body image, bringing along problems in psychosocial adaptation and acceptance. The aim of this study was to investigate the differences and similarities between the PM and ICD pts using validated tools of health status assessment.

Methods: 210 pts, aged 40 to 70 yrs, who underwent the first implantation of a PM or an ICD between 1993 and 1997 at the University Hospital of Zurich were included. All pts were asked to complete identical questionnaires mailed to them containing the Medical Outcomes Study SF36 and Hospital Anxiety and Depression (HAD) scale, both of which have accepted validity and reliability, and a specially designed device-related questionnaire to assess different aspects of an implantation, such as perceptions of an implanted device, technical concerns and individual needs of pts.

Results: 76 pts in the PM group (59 ± 10 yrs) and 76 pts in the ICD group (58 ± 13 yrs) returned the questionnaires. Sociodemographic properties of both groups were comparable. There was no difference between the 2 groups with respect to scores on any aspect of the SF36 and HAD. However, pts in the ICD group were more frequently aware of the physical presence of an implanted device, had increased preoccupation with their diseases and needed longer time to adapt ($p < 0.05$). ICD pts perceived the device as a 'source of anxiety', but also had a higher tendency to view it as a 'source of security' and 'life-extender'. Pts in both groups had little and similar degree of anxiety for battery failure or device-related technical problems (p = NS). 20% of PM pts and 33% of ICD pts wanted involvement in a support group.

Conclusion: Despite having distinct differences with respect to underlying heart disease and type of delivered therapies, pts with PMs and ICDs had similar performance on validated tools of health status assessment.

P2195 Heart rate variability and personality traits in acute myocardial infarction

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To define the possible correlation between the autonomic tone and the personality traits during acute myocardial infarction 24-h heart rate variability (HRV) by Holter monitoring (Remco-Cardioline) and personality by 16 Personality Factor Questionnaire(16 PF)of Cattell was evaluated before discharge. A Multicenter Italian study was conducted between genuary 1990 and december 1995: 455 patients were enrolled less than 70 years of age, mean 56 ± 8, 401 males. For this study 261 pts having both good quality recordings and 16 PF were selected. Following time and frequency HRV indices were computed from the two tracings: mean 24-h RR interval, standard deviation of all normal RR (SDNN), pNN50, r-MSSD, the mean of the 3 minutes RR standard deviation (SDRR), the standard deviation of the mean of the RR for all 3-minute segments (SDANN). Moreover, RR total power, VLF, LF, HF power, as well as LF/HF ratio, were computed.

The most significant correlations between time and frequency domain indices of HRV were those between SDNN and VLF power (r = 0.63) and SDNN and RR total power (r = 0.67).With regard to psychological dimensions, factors related to Anxiety negatively correlated with both time {SDNN: r = 0.15, PNN50: r = 0.18) and frequency (Total power: r = 0.16, HF power: r = 0.12) domain indices($p < 0.05$). These results suggest a possible link between psychological dimension and autonomic nervous system.

P2196 The impact of depressed mood on quality of life in patients after successful coronary angioplasty

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Background: Depressed mood is an important clinical problem in patients (pts) with coronary artery disease (CAD), present in 16–22% of cases. Previous data showed discrepancy between the morphological and functional success of coronary artery angioplasty (PTCA) and quality of life (QoL). However, data is spared on the effects of mood on QoL in pts after PTCA.

Purpose: The aim of the study was to evaluate the impact of mood on QoL in pts with CAD after successful PTCA.

Methods: 50 pts with symptomatic angina (CCS II–III) and optimal PTCA (quantitative coronary angiography (QCA) guided PTCA; residual stenosis – QCA < 30%) were included. The QoL was examined by the SF-36. Beck Depression Inventory (BDI) was used to assess depressed mood. All pts were assessed the day before and four weeks after the intervention.

Results: Four weeks after successful PTCA pts were significantly less depressed in comparison to day 1 (BDI = 8.5 vs 13.1, $p < 0.05$) and their QoL was also significantly better ($p < 0.05$). However, important differences were found between pts who were depressed (BDI > 10) the day before PTCA and those who were not (BDI < 11). In depressed pts, in contrast to non-depressed subjects, QoL did not improve after PTCA. The value of SF-36 was significantly lower in first ($p = 0.0003$) as well as in the second assessment ($p < 0.05$), in spite of optimal result of PTCA.

Conclusion: The depressed mood determinates the lack of improvement of QoL after successful PTCA.

P2197 Prevalence of dystrophin defects in male patients with dilated cardiomyopathy

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Dystrophin defects causing X-linked dilated cardiomyopathy (DCM) in patients (pts) with clinically dominant or exclusive cardiac involvement may be indistinguishable from other DCM, and dystrophin defects may be missed unless specifically investigated. This study was aimed at investigating dystrophin defects by screening consecutive DCM male pts

Methods: We screened dystrophin defects in 168 DCM males, aged 16 to 68, consecutively examined from 1995 to 1998; all pts underwent evaluation with invasive and non invasive methods, including endomyocardial biopsy (EMB) and biochemical investigation (muscle enzymes). Light and electron microscopy, and immunohistochemical studies of EMB samples were performed; 36 exons and muscle promoter were analyzed with 6 known multiplex polymerase chain reactions, and exon 9 and of muscle promoter-exon 1 were sequenced.

Results: Of the 168 pts, 11 (6.5%) were found to be affected by dystrophin defects; 6 were older than 20 and had performed a regular military service; 5 were younger. A mild, "myopathy" (dystrophin defects were missed) had been suspected in 3, and clinically diagnosed in 2 of the 7 older pts (2 were unsuspected), and in all 4 young pts. Family history was positive in 5 and not informative in 6. Light microscopy examination of EMB was non-informative; ultrastructural study showed multiple discontinuous membrane defects. Dystrophin immunostaining documented reduced, discontinuous or absent stain of the sarcolemma. Molecular analysis identified gene defects in 8 pts: 6 pts older than 20 (deletions of rod-domain exons) and 2 of the younger pts (deletions affecting both NH-terminus and rod-domain).

Conclusions: Although the prevalence of dystrophin defects in DCM clinical series is relatively low (6.5%), screening studies are justified by the need of subgrouping DCMs on their etiopathogenesis. Immunostain of endomyocardial biopsy and ultrastructural study of EMB allow the diagnosis; routine multiplex PCRs detect molecular defects in most cases.

P2198 The unique genetic variant in the beta 1-adrenoceptor gene and its evaluation in idiopathic dilated cardiomyopathy

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Genetic factors that underlie Idiopathic Dilated Cardiomyopathy (IDCM) have not yet been elucidated. Considering that beta 1-adrenoceptors are down-regulated in patients with IDCM and that beta-blocker therapy is consistently beneficial in this setting, we hypothesized that genetic variation in the beta 1-adrenoceptor might affect susceptibility to and/or severity of IDCM. As no intragenic polymorphism was available, a systematic screening of the gene was first performed. The organization and sequence of the human beta 1-adrenoceptor gene were established using polymerase chain reaction, single strand conformation polymorphism analysis and sequencing. The gene comprises 1434 bp and no intron was observed. We found a unique and frequent polymorphism (C1165G) which predicts an Arg389Gly substitution. The association of this polymorphism with IDCM was then analyzed using the PCR-restriction fragment length polymorphism method in the CARDIGENE population, a clinically homogeneous population of IDCM. Genotypic distribution was in agreement with Hardy-Weinberg equilibrium. There were no differences in the beta 1-adrenoceptor allele frequencies between IDCM (n = 426; C/G = 0.76/0.24) and age and sex-matched control subjects (n = 395; C/G = 0.78/0.22). Within the patient group, no association was observed with the severity of the disease. In conclusion, the genomic organization of beta 1-adrenoceptor is described here for the first time. We found a unique and frequent polymorphism in the coding sequence of the gene. No association was observed between IDCM and the genetic variant. Its possible involvement in other cardiac diseases related to the beta 1-adrenoceptor remains to be analyzed.

P2199 The response to short-term infusion of angiotensin II is not influenced by polymorphisms of the angiotensin AT_1- and AT_2-receptor genes in humans

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Objective: Angiotensin II (A II) is the most potent endogenous vasoconstrictor by the AT_1 subtype of angiotensin receptors (AT_1-R). The AT_2 receptor (AT_2-R) is believed to counteract some of the AT_1-R mediated effects. Polymorphisms of the AT_1R gene have been associated with arterial hypertension and left ventricular hypertrophy. This study was conducted to directly examine the influence of polymorphisms of the AT_1-R and AT_2-R gene on the immediate vascular and hormonal response to A II in humans.

Methods: We enrolled 122 male, white, young (mean age, 26 ± 3 years) subjects with normal or mildly elevated blood pressure (but never treated for that) into a cross-sectional study. Changes in mean arterial blood pressure (MAP; Dinamap, Germany), aldosterone levels (Aldo; radioimmunoassay), glomerular filtration rate (GFR; inulin clearance), and renal plasma flow (RPF; para-aminohippurate clearance) served as parameters for the response to A II (3.0 ng/kg/min over 30 minutes). The −2228 G/A polymorphism of the AT_1-R promoter and the intronic +1675 G/A polymorphism of the AT_2-R gene were determined by restriction digestion and single strand conformation polymorphism analysis after polymerase chain reaction amplification, respectively.

Results: Blood pressure, body mass index, and baseline aldosterone and A II levels were similar across the various genotypes. Infusion of A II resulted in an increase in MAP, Aldo, and GFR, and in a decrease in RPF (all $p < 0.001$). As depicted in the table, response to A II did not significantly differ across the various genotypes.

	All subjects	−2228 G/G	−2228 G/A	+1675 A	+1675 G
ΔMAP (mmHg)	+15 ± 7	+16 ± 8	+14 ± 7	+14 ± 78	+16 ± 7
ΔAldo (pg/mL)	+102 ± 70	+102 ± 73	+101 ± 64	+93 ± 69	+113 ± 70
ΔGFR (mL/min)	+4.6 ± 7.1	+4.4 ± 6.9	+5.1 ± 7.4	+5.9 ± 7.0	+3.2 ± 6.9
ΔRPF (mL/min)	−128 ± 67	−130 ± 70	−124 ± 61	−128 ± 65	−128 ± 70

Conclusion: Hormonal and vascular response to A II is not influenced by the −2228 G/A polymorphism of the AT_1-R promoter and the intronic +1675 G/A polymorphism of the AT_2-R gene. Thus, the examined polymorphisms did not influence the physiological response to A II.

P2200 Polymorphism in the high density lipoprotein paraoxonase gene M54L polymorphism and the risk of acute myocardial infarction in men: a prospective population-based cohort study

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The human serum paraoxonase (PON) is an antioxidative enzyme in high density lipoproteins (HDL), which eliminates lipid soluable radicals in the circulation. The missense mutation of A-to-T in codon 54 of the PON1 gene, producing M54L substitution, is associated with PON concentration and activity. We studied whether the MM genotype which leads to reduced PON activity is associated with an increased risk of acute myocardial infarction (AMI). The study population were 1263 male participants in the KIHD study who had no prior clinical coronary disease, aged 42–60 years at baseline. PON M54L genotypes were determined by PCR and Hsp92II digestion. Of the 1263 healthy men, 146 (11.6%) were MM homozygous. These men had both reduced PON activity and increased proportion of electronegatively charged LDL of total LDL in plasma ($p < 0.05$). 117 men had, based on MONICA criteria, an AMI during up to 13 years (mean 9 years) of follow-up.

The MM homozygous men had a 2.2-fold (95% confidence interval 1.4 to 3.5, $p < 0.001$) risk of AMI in a Cox model adjusting for 11 other strongest risk factors (including blood haemoglobin, diabetes, ischaemia in exercise test, serum apolipoprotein B, cigarette pack-years and serum ferritin). This relative risk was higher in smokers (3.4, 95% CI 1.6 to 7.2, $p = 0.002$) than in non-smokers (1.7, 95% CI 1.0 to 3.1, $p = 0.060$). The association of both smoking and high hair mercury content with AMI was stronger in MM homozygous than other men.

Our findings suggest a role for PON as a protective enzyme against coronary disease and provide thus evidence supporting the role of endogenous antioxidative systems. Also, these data show that the PON1 MM homozygosity is a risk factor for AMI. PON1 M54L is a good candidate for genetic screens of persons genetically predisposed to coronary disease.

THROMBOTIC FACTORS

P2201 Effects of anticoagulant and antiplatelet therapy on outcome during long-term follow-up in 427 patients with moderate to severe heart failure

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Current European and American guidelines do not recommend the use of anticoagulants and antiplatelets in patients with chronic heart failure (CHF). Recent data in patients with *mild* CHF, however, suggest that both treatments may possibly be beneficial.

Methods: We studied 427 patients (pts) with moderate to severe CHF (NYHA class III–IV, mean left ventricular ejection fraction (LVEF) 23%, 77% male), who were followed for 3.4 yr (range 2.0–5.2 yr). To study the effect of anticoagulation and antiplatelets on outcome, we performed univariate and multivariate analysis.

Anticoagulants were used in 288/427 (= 67%) pts. Use vs. non-use groups were similar for NYHA class, LVEF, and etiology of CHF. However, pts who used anticoagulants more often had atrial fibrillation (80% vs. 63%), and used fewer antiplatelets.

Antiplatelets were used in 74/427 pts (= 17%). Use vs. non-use groups were similar for severity of CHF, but pts on antiplatelets more often had ischemic CHF, and used fewer anticoagulants.

During follow-up, 221 pts died. A/ 51% of pts on anticoagulants died, compared to 54% of pts not on them. B/ 42% of pts on antiplatelets died, compared to 54% not on them. On multivariate analysis, both anticoagulants ($p = 0.01$, relative risk 0.65, 95% CI 0.46–0.90), and antiplatelets ($p = 0.03$, relative risk 0.62, 95% CI 0.40–0.96) were significantly related to a reduction in all-cause mortality.

Conclusion: The use of anticoagulants and the use of antiplatelets were both independently related to a reduction in mortality in pts with advanced CHF in the present study. These findings contrast with current guidelines for CHF, which do not advocate these agents.

P2202 Soluble P-selectin in patients presenting with chest pain : evidence for endothelial origin

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It has been reported that platelet expression and plasma levels of soluble P-selectin are increased in patients with unstable coronary artery syndromes and may serve as important diagnostic markers. However, the origin of soluble P-selectin remains unknown. We sought to determine whether platelet expression of P-selectin correlates with plasma levels in a population of patients presenting to the Emergency Department with chest pain.

Methods: Simultaneous soluble and platelet P-selectin levels were determined in 338 patients presenting with chest pain to the Emergency Departments of 3 different hospitals utilizing ELISA and whole blood flow cytometry, respectively.

Results: Using regression analysis no correlation ($R^2 = 0.055$) was found between soluble and platelet-bound P-selectin for the study population, including those patients with non-cardiac chest pain ($R^2 = 0.019$), unstable angina ($R^2 = 0.007$), acute myocardial infarction ($R^2 = 0.033$), congestive heart failure ($R^2 = 0.231$), and gastrointestinal illness ($R^2 = 0.020$).

In conclusion, the platelet expression of P-selectin is unrelated to the level found in plasma in patients with acute chest pain, irrespective of the etiology of chest pain. Dissociation between platelet and soluble P-selectin suggests prominent endothelial release of this molecule in this patient population.

P2203 Complex risk analysis of left ventricular thrombi in acute myocardial infarction

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We studied the risk factors of the development of left ventricular thrombi (LVT) detected by transthoracic echocardiography (TTE) in acute myocardial infarction (AMI).

Methods: We analysed data of 1200 non-selected patients, who had been treated during a 7-year period in our department with Q-wave AMI. TTE was performed in all cases in the acute phase of myocardial infarction (MI). We detected LVT in 118 patients (10%). The anticoagulant therapy was not different between the two groups of patients.

	AMI and LVT (n = 118)	AMI without LVT (n = 1082)	p value
Men (%)	66	63	NS
Mean age (years)	66 ± 10	64 ± 10	NS
MI in the family history (%)	3	8	0.05
Smoking (%)	24	34	0.05
Diabetes (%)	21	20	NS
Hypertension (%)	60	59	NS
Hypercholesterolemia (%)	36	45	NS
Recurrent MI (%)	16	12	NS
Anterior MI (ECG; %)	78	38	0.001
Time pbh < 24 hours (%)	17	49	0.001
Thrombolytic therapy (%)	8	19	0.01
LV dilatation (Dd > 60 mm; %)	28	18	0.05
LV aneurysm (%)	20	7	0.001
LV EF < 40% (%)	26	16	0.05

Conclusions: In cases of LVT in AMI the time passed before hospitalization (Time pbh) is often longer than 24 hours. The anterior MI, left ventricular (LV) dilatation, aneurysm and decreased ejection fraction (EF) make patients in AMI more susceptible to LVT. It's interesting that among patients who had AMI without LVT smoking and family history of MI was significantly frequent.

A seasonal fluctuation also can be observed in the incidence of LVT. We detected LVT most frequently in May (17%) and least frequently in August (5%, $p = 0.05$).

P2204 Association of fibrinogen plasma levels with lipid profile and haemostatic variables in 962 young adults

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Background: Several studies have shown the important role of high fibrinogen plasma levels to both plaque formation and manifestations of coronary artery disease in populations of mid and older age. However the association of high fibrinogen plasma levels with other conventional risk factors and haemostatic variables in younger age has not been investigated comprehensively.

Method: The study population consisted of 962 healthy subjects (685 males, 277 females) aged 18.5 ± 0.5 years old. For each participant, a questionnaire of medical history and life-style parameters was completed and lipid and haemostatic plasma variables were determined.

Results: The mean fibrinogen concentration was 263 ± 79 mg/dl. The study population was divided into two groups according to fibrinogen levels: Group A with fibrinogen levels ≥ 300 mg/dl (175 subjects, 18.2%) and group B with fibrinogen levels < 300 mg/dl (787 subjects, 81.8%). Comparisons between groups are shown in the table (values in mg/dl or percentage % as appropriate):

Variables	Group A	Group B	P
TC	187 ± 34	178 ± 37	0.01
LDL	114 ± 33	104 ± 45	0.005
Lp(a)	19 ± 15	15 ± 12	0.015
VII	104 ± 19	98 ± 17	<0.00005
VIII	108 ± 23	103 ± 27	0.046
X	92 ± 10	90 ± 8	0.002

Conclusion: High fibrinogen plasma levels are found rather frequently in healthy young adults. They are associated with an adverse lipid profile and high levels of haemostatic variables, suggesting existence of a tight link between atherogenesis and thrombogenesis.

DIABETES

P2205 Increased late mortality and heart failure in diabetics after revascularization is not matched by more repeat interventions

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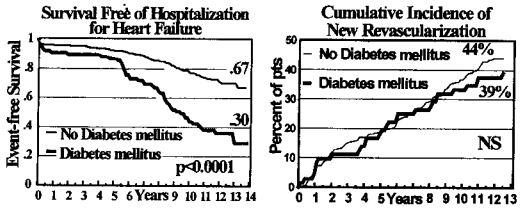
Background: Following revascularization (Rev) diabetics have a higher mortality and more heart failure and a more vigorous policy of re-intervention may be required. We examined the incidence of repeat Rev in a long-term cohort study.

Methods: Cohorts of 80 diabetics and 285 non-diabetics treated by angioplasty or bypass surgery in one center in 1984–6 had structured telephone interview and records review over 12–14 yr. Analysis used Kaplan-Meier and cumulative incidence curves.

Results:



Conclusions: 1. Late mortality and heart failure were increased in diabetics vs non-diabetics after Rev. 2. There was no similar increase in late repeat Rev. 3. The data suggest that progression of CAD may be insidious or diffuse in diabetics hindering further Rev or heart failure in diabetics may have non-coronary causes.

P2206 Heart failure and prognosis in diabetic and non-diabetic patients after previous revascularisation; 8-year follow-up

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Survival is poorer in diabetic than non-diabetic patients (pts) with coronary disease despite revascularization. Heart failure is a strong predictor of poor survival. We studied the need for hospitalization for heart failure (HHF) and its prognostic implications in diabetic and non-diabetic pts over 8 years after revascularisation by bypass surgery.

Methods: 380 pts revascularized by bypass surgery were studied. Survival was assessed in all pts from records and HHF from patient or family interview is available to date in 334 (87.9%). Analysis used Kaplan-Meier survival curves.

Results: Diabetics and non-diabetics were of similar age (59 ± 10 vs 57 ± 12 yrs; p = NS). Prior to revascularization a similar proportion had myocardial infarction (46/77, 60% vs 144/257, 56%; p = NS) and multivessel disease (72% vs 64%; p = NS). Diabetic had worse 8 yr survival than non-diabetics (50% vs 78%; p < 0.001), worse survival free of HHF (33% vs 60%; p < 0.001), worse subsequent survival after first HHF (38% vs 68%; p < 0.05) and worse survival free of further HHF (21% vs 58%; p < 0.05).

Conclusion: In pts with diabetes mellitus undergoing coronary revascularization long-term survival was reduced, hospitalization for heart failure was more common and hospitalization for heart failure had a more ominous prognosis, than in non-diabetic pts.

P2207 Maternally transmitted susceptibility to non-insulin-dependent diabetes mellitus and left ventricular hypertrophy

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It is suggested that non-insulin-dependent DM (NIDDM) has a strong genetic basis, and that some maternally transmitted DM is associated with mitochondrial DNA mutations, which can cause LV hypertrophy (LVH). DM is also known to be associated with LVH. Hence, LVH in NIDDM may be related to some genetic factors of DM.

Methods: We consecutively investigated the family history of DM and the prevalence of LVH using echocardiography in 324 patients (pts) with NIDDM. Pts with valvular heart disease or CAD were excluded.

Results: Of the 324 pts, 59 had diabetic mothers, 40 had diabetic fathers, and 4 had both. On the echocardiograms, LVH (wall thickness ≥ 12 mm) was found in 31 pts. The prevalence of LVH was higher in pts with diabetic mothers (17%) than in those with non-diabetic mothers (8%) (p < 0.05), whereas it was similar in pts with diabetic fathers (5%) and those with non-diabetic fathers (10%). Compared with 261 pts with non-diabetic mothers (group M–), 63 with diabetic mothers (group M+) were younger (61 ± 9 vs 64 ± 9 yrs, p < 0.05) and had the earlier onset of DM. The percentage of pts having diabetic siblings was higher in group M+ (40%) than in group M– (17%) (p < 0.001). However, there was no difference in sex, body mass index, DM duration, blood glycemic levels and blood pressures. Hypertension was present in 33% of group M+ and 47% of group M–. Group M+ had greater LV wall thickness (9.3 ± 1.4 vs 8.9 ± 1.2 mm, p < 0.02) and greater LV mass (149 ± 44 vs 139 ± 33 g, p < 0.05) than group M–. In multivariate analysis, the family history of DM in mothers, DM duration and hypertension were each significantly associated with LVH, but the family history of DM in fathers was not.

Conclusion: LVH in pts with NIDDM was associated with maternal transmission of DM. Some genetic factors of DM, such as mitochondrial DNA abnormalities, may be contributing to the development of LVH in maternally transmitted NIDDM.

P2208 Endothelium-dependent microcirculation vasomotion is not improved by lowering LDL in poorly controlled diabetes

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Cutaneous microangiopathy is suspected to play a role in the pathogenesis of diabetic foot ulcer. Microcirculatory flow is in part regulated by the endothelium and hyperlipidemia has been shown to adversly affect endothelium-dependent relaxation in several vascular beds. We sought to determine if abnormal microcirculatory flow in the foot in patients with Type 2 diabetes and hyperlipidemia is improved by lipid lowering therapy.

Methods: We used laser Doppler techniques in conjunction with iontophoresis to measure endothelial dependent and independent microcirculation in 13 diabetic pts with LDL cholesterol > 130 mg/dL (12 F, 1 M). Patients were randomized to receive 40 mg of simvastatin (7 pts) or placebo (6 pts). Characteristics of these two groups were not statistically different at baseline (Table 1). Lipid profile and endothelial function were followed monthly. Endothelial and non-endothelial dependent vasomotion were assessed respectively by 1) response to local heating to 44°C and to iontophoresis of acetyl choline (Ach) and 2) to iontophoresis of sodium nitropruside (SNP). Although lipid profile improved significantly in the simvastatin group, endothelial function did not improve at 3 months (Table 2).

Table 1

	Age (years)	BMI (kg/m^2)	HbA1C %	TChol mg/dl	TG mg/dl	LDL mg/dl	HDL mg/dl
S	61 ± 6	33 ± 5	9.3 ± 1.7	256 ± 34	155 ± 17	177 ± 35	48 ± 10
P	60 ± 5	32 ± 5	9.1 ± 2.5	242 ± 32	137 ± 89	160 ± 24	54 ± 14

BMI: Body Mass Index, TChol: total cholesterol; TG: triglycerides

Table 2

	TChol mg/dl	TG mg/dl	LDL mg/dl	HDL mg/dl	HbA1C %	ΔHeat	ΔAch	ΔSNP
S	175 ± 29	124 ± 25	100 ± 25	51 ± 8	9.4 ± 2	1 ± 20	−0.7 ± 1.8	−9 ± 8.5
P	234 ± 35*	153 ± 125	146 ± 23*	56 ± 14	8.7 ± 1.6	0 ± 15	0.7 ± 1.4	−2.5 ± 2

ΔHeat, ΔAch and ΔSNP: Variation of normalized responses to heating, Ach and SNP between 3 months and the beginning of follow-up. *$p < 0.007$

Conclusion: In this population of patients with poorly controlled diabetes, LDL lowering by itself is not effective as a way to improve endothelial function. Further studies should assess the benefit of optimal control of diabetes, in conjuction with lipid lowering, on endothelium-dependent microcirculation vasomotion in patients with Type 2 diabetes.

P2209 Spontaneous baroreflex sensitivity in diabetic patients after pancreatic islet transplantation

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Pancreatic islet transplantation may improve the carbohydrate metabolism and delay the development of diabetic complications. The aim of this study was to analyze the baroreflex sensitivity (BRS) in the resting supine position and after standing up in patients (pts) with insulin-dependent diabetes mellitus (IDDM) after islet cell transplantation (Tx).

Methods: 10 Tx pts (age: 43.7 ± 2.6 years, duration of IDDM: 26.4 ± 2.7 years, graft function: 9.6 ± 1.0 years; mean ± SEM), 17 non-transplanted (n-Tx) IDDM pts (age: 46.9 ± 3.8 years, duration of IDDM: 23.5 ± 3.1 years) and 15 healthy controls (age: 46.0 ± 1.7 years) were studied. The blood pressure was measured continuously with a *Finapres 2300* instrument (Ohmeda). The ECG signal was detected with a *Sirecust 730* (Siemens) electrocardiograph. The ECG and plethysmographic signals were fed through an analog-digital converter into a computer. The data were analyzed off-line. The spontaneous BRS was calculated in the supine position and after standing up.

Results: Both in the n-Tx and in the Tx group, the BRS was decreased in the supine position and also after standing up relative to the control value. In the Tx pts, the BRS values were elevated as compared with those for the n-Tx group. In the control group, the BRS was decreased after standing up in comparison with the resting position. In both the n-Tx and Tx groups, there was no significant difference between the BRS values measured in the supine and standing positions.

	Control	n-TX	TX
BRS in supine position (ms/mmHg)	8.7 ± 0.9	*3.2 ± 0.6	†*5.5 ± 0.7
BRS after standing up (ms/mmHg)	‡5.3 ± 0.5	*2.0 ± 0.4	†*3.6 ± 0.8

*$p < 0.05$ vs control, †$p < 0.05$ Tx vs n-Tx, ‡$p < 0.05$ standing vs supine position

Conclusions: 1) In long-standing IDDM, a severe impairement of the cardiovascular adaptation was found. 2) The BRS was less diminished in the transplanted patients relative to the non-transplanted group. 3) Pancreatic islet transplantation may decrease the progression of diabetic autonomic neuropathy.

P2210 Impaired aortic elastic properties in patients with coronary artery disease: impact of non-insulin diabetes mellitus

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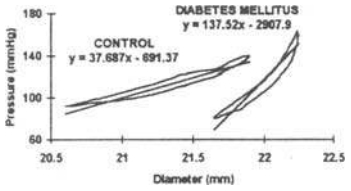
Deterioration of arterial elastic properties may be an early feature of vascular dysfunction. Patients (pts) with diabetes mellitus (DM) are at high risk of cardiovascular disease. This study investigated aortic elastic properties in pts with coronary artery disease with non-insulin dependent DM and matched control pts.

Methods: Fourteen patients with non-insulin dependent diabetes mellitus (DM) and 66 pts without DM were studied. All pts suffered from coronary artery disease. Instantaneous aortic diameter (D) was measured by an intravascular catheter developed in our institution and previously validated. Instantaneous aortic pressure (P) was measured simultaneously at the same aortic level with a catheter-tip micromanometer. Thus, aortic P-D loops were obtained and slope, and intercept were calculated. Also, aortic distensibility was calculated by = (Pulsatile change in aortic D)/(Diastolic D × Pulse Pressure).

Results: Age and heart rate were similar in the 2 groups. The pulse D was greater in the control group (1.27 ± 0.42 vs 0.92 ± 0.45 mmHg). The distensibility was less in DM pts (1.65 ± 0.95 vs 0.94 ± 0.48 dyn^{-1} cm^{-2} 10^{-6}, $p < 0.01$). Also, the slope (109.12 ± 118.4 vs 19.6 ± 3.3 mm^{-1}, $p < 0.004$) and the intercept was less in DM pts (−2257.39 ± 2579.7 vs −338.7 ± 93.1, $p < 0.005$).



Conclusions: In pts with non-insulin dependent DM, aortic elastic properties are deteriorated. These results may contribute to the unfavorable outcome of pts with DM suffering from coronary artery disease. Further studies in DM pts with pharmacologic agents that affect the elastic properties of the aorta are currently undergoing.

P2211 Protective effect of cicletanine on renal function in uninephrectomized diabetic spontaneously hypertensive rats

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Diabetic spontaneously hypertensive rats (SHR/D) develop renal functional alterations similar to those observed in human diabetic nephropathy associated with hypertension. Microalbuminuria is a predictive marker of renal disease in this case. Cicletanine is a new antihypertensive agent with an original structure that provides cardiovascular and renal protection and it uniquely stimulates prostacyclin production. Its effect on renal dysfunction during hypertension and diabetes is unknown. the present study was designed to assess whether the orally active cicletanine affects progressive renal dysfunction in a diabetic and hypertensive rat model of renal damage.

Methods: Uninephrectomized SHR/D (n = 18) were subdivided in three groups: SHR/D, SHR/D + 10 mg/kg body wt/day of cicletanine and SHR/D + 50 mg/kg body wt/day of cicletanine. Age-matched untreated Wistar Kyoto rats serve as control. The cicletanine treatment began one week after diabetes induction and was maintained on 6 weeks. Microalbuminuria and proteinuria have been evaluated throughout the treatment. At the end of the treatment, kidney histology and creatinine clearance were studied.

Results: Treatment with cicletanine did not affect significantly systolic blood pressure and hyperglycemia in animals. Cicletanine, at its two dosages, decreased significantly the elevated microalbuminuria of SHR/D in a dose related manner ($p < 0.01$ vs. SHR/D). These effects were similar for proteinuria and occurred after one month of cicletanine treatment. Renal histology analysis was not significantly different from Wistar Kyoto rats without signs of glomerular hypertrophy and sclerosis. Altered creatinine clearance was normalized at the higher cicletanine dose (4.2 ± 0.6 vs. 3.6 ± 0.7 ml/min./g of kidney).

Conclusion: The main finding of this study is that the orally active cicletanine has a nephroprotective effect on the progression of renal disease, probably blood pressure-independent, in a hypertensive and diabetic rat model.

P2212 Comparison of coronary stenting and coronary angioplasty in diabetic patients

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Background: Most of studies have demonstrated excess morbidity and mortality in diabetic patients treated with coronary angioplasty (PTCA) and have suggested superior outcomes with coronary by-pass (CABG) surgery. Coronary stents (S) have reduced the restenosis rate compared to PTCA in the global population. But there are some questions coronary stenting in diabetic patients still unanswered.

Methods: We designed this study to compare the results of coronary stenting and PTCA in native coronary vessels with diabetic patients. We retrospectively evaluate 404 patients undergone PTCA. There were 63 (15.6%) diabetics and 341 (84.4%) non-diabetics. We prospectively evaluate 185 patients undergone coronary stenting. There were 36 (19.5%) diabetics and 149 (80.5%) non-diabetics. There were no differences in clinical and angiographic characteristics between PTCA and S groups. PTCA and S were performed to single coronary artery in all patients. We took 8 months clinical follow-up data for our study.

Results: There were no significant differences in procedural and clinical success and in-hospital major complications between PTCA and S groups. In 8 months clinical follow-up, in PTCA group incidence of untoward cardiac events was significantly higher than S group.(38% vs 13.9%, p = 0.02)Rates of mortality(3.2% vs 2.8%), nonfatal myocardial infarction(AMI)(3.2% vs 5.6%) were similar in both groups. Rates of revascularization (37.1% vs 5.6%, p = 0.005) were higher in PTCA group.

Conclusion: Diabetes is a risk factor for restenosis. Cardiac events and revascularization rates were significantly higher in patients who underwent PTCA alone at 8 months of follow-up. Coronary stenting is more suitable than PTCA in diabetic patients.

P2213 Low job-control and prevalence of diabetes: results from the Belgian "Belstress study" baseline data

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Several epidemiological surveys have shown a positive association between stress at work and incidence of cardiovascular diseases. A current method, for measuring stress at work, consists in using "Job Stress Scales", based on the "Job Content Questionnaire", developed by R. Karasek: "Psychological Demands (PD), "Decision Latitude, or Job Control (JC)", "Job Strain" (a combination of high PD and low JC) and "Social Support at Work (SSW)". In the Belstress prospective study, we verified the association between stress at work, defined as either high PD, low JC, low SSW and Job Strain, with coronary risk factors (CRF) in 16335 male and 5084 female volunteers, aged 35–59 years old and working in 24 companies. They completed a questionnaire and underwent a clinical screening examination at the beginning of the study. Diabetes, based on a positive answer at the question "Did a physician ever told you that your blood sugar was to high?", was considered as a major CRF. The overall diabetes prevalence was 2.8% in males and 2.1% in females. After excluding the insulinodependent cases, we still found respectively 2.6% and 2.0% of subjects, having answered positively to the question. Comparison of crude means showed no differences in diabetes-prevalence between the PD-quartiles and SSW-quartiles and between Jobstrain groups, neither for males nor for females. An inverse, statistically significant, association was observed between JC and diabetes prevalence, in male as well as in female subjects. After adjustment for age, educational level (EL), Body Mass Index (BMI), SSW and Depression, we still found an Odds Ratio (OR) of 0.52 (CI: 0.38–0.71)*** between the highest JC quartile and the lowest JC quartile for the male population. An OR of 0.47 (0.26–0.85)* was found for females, independently of age, EL and BMI; after adjustment for SSW and Depression, the OR is 0.78 (0.40–1.55) (Not Significant). In females OR of diabetes between highest and lowest quartile of SSW is 0.63 (0.41–0.96), independently from age, EL and BMI.

Conclusion: A consistent inverse association is observed between JC and diabetes prevalence; we are unable to show a causality in a cross-sectional analysis; however, we have to consider the hypothesis that diabetes is one of the mediatory CRF, explaining the relationship between low JC at work and coronary heart disease as observed in several prospective studies.

P2214 Assessing diabetic autonomic neuropathy: how many tests are necessary?

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When diabetic autonomic neuropathy is assessed a battery of 5 tests are often used, but the number of tests required has not been investigated empirically.

Purpose: To evaluate the relative importance of 5 clinical tests using heart rate variability (HRV) as the gold standard.

Methods: In a random population based sample of 135 diabetic patients a group of 3 mainly parasympathetic tests (E/I-ratio (A), 30:15-ratio (B) and Valsalva-ratio (C)) and 2 mainly sympathetic tests (Ortostatic-BP (D) and sustained handgrip (E)) were carried out. After log-transformation of A, B and C the results of all 5 tests were standardised to units of SD. To evaluate combinations of tests the mean of the standardised readings were used. A 24-h Holter recording (Tracker) was edited manually on the Path-finder 700. Spectral analyses of the first 5 min each hour were performed in the RR-Tools programme. The mean log power of the Low Frequency band in the daytime expressed the sympathetic function and the nighttime mean log power of the High Frequency band the parasympathetic function. The mean sum of squares (Mssq) of the HRV explained by each test or combination of 2 tests in regression analysis was compared to the combination of each group of tests and to all 5 tests using an F-test (*P*, table).

	P	Mssq	*r*	*P*
Nighttime mean lnHF				
A	NS	61.9	0.57	NS
B	<0.001	40.1	0.46	0.01
C	<0.001	37.0	0.44	0.003
AB	NS	65.2	0.58	NS
AC	NS	67.9	0.60	NS
BC	NS	55.1	0.54	NS
ABC	→	71.4	0.61	NS
ABCDE		61.6	0.57	←
Daytime mean lnLF				
D	NS	46.1	0.51	<0.001
E	<0.001	9.64	0.14	<0.001
DE	→	41.5	0.48	<0.001
ABCDE		101.2	0.75	←

Results: All 5 tests were significantly associated to HRV ($p < 0.01$). The E/I-ratio had the highest correlation to HRV and no combination of the 5 tests explained a significantly larger part of the variation in HRV. The Valsalva- and 30:15-ratio were significantly poorer than their combination with E/I-ratio. The sympathetic tests were poorer than the combination with the parasympathetic tests (table).

Conclusion The E/I-ratio is the superior of the 5 tests assessed, it may be used alone or in combination with another parasympathetic test. Adding the ortostatic BP or handgrip test does not provide further information.

P2215 Influence of the presence and type of diabetes mellitus on the initial and long-term outcome after coronary stenting

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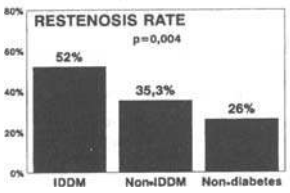
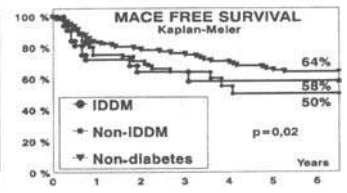
Data regarding the evolution after coronary stenting (CS) of insulin-dependent diabetes mellitus (IDDM) and non-IDDM patients are scant and controversial.

To assess the initial and long-term efficacy of CS in diabetics we compared the evolution of 35 IDDM patients (pts) with the outcome of 92 non-IDDM pts and a control group of 856 non-diabetic stented pts of a series of 983 consecutive pts treated with CS. Patients with IDDM were more often female (40%), and had a higher rate of previous heart failure (14%) and lower reference diameter ($p < 0.05$, compared with non-IDDM and non-diabetic pts). Hypertension was more frequent in non-IDDM pts than in the other two groups (52% vs 46% vs 37%, $p < 0.05$). No other clinical, angiographic or procedural differences between groups were found. Clinical follow-up was completed for 94% of pts (3.1 ± 1.4 years, range: 1.8–6.5).

Clinical success at one month (angiographic success without major events) was similar among the three groups (IDDM: 93%, non-IDDM: 94%, non-diabetic: 94%). Angiographic restenosis rate was significantly higher in IDDM pts. Major adverse cardiac events (death, re-PTCA, CABG or admission for myocardial infarction or unstable angina) (MACE) during follow-up were significantly higher among diabetics, without differences between IDDM and non IDDM-pts (figures)





Thus: 1) initial outcome of diabetics is similar to that of non-diabetic pts but angiographic restenosis occurs more often in IDDM pts; 2) diabetics have a worse clinical long-term evolution without differences related to the type of diabetes.

P2216 Cardiovascular autonomic neuropathy in the diabetic population: more prevalent in insulin-dependent diabetes mellitus compared to non-insulin-dependent diabetes mellitus

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Only a few population based studies on cardiovascular autonomic neuropathy (CAN) in diabetes is available and differences between IDDM and NIDDM has not been explored.

Purpose To estimate the prevalence of CAN in the diabetic population and compare the frequencies in IDDM and NIDDM.

Methods To delineate the diabetic population in the municipality of Horsens, Denmark, data from all prescriptions of antidiabetic medicine were registered in 8 months. A random sample of 120 users of insulin and 120 users of oral hypoglycaemic agents between 40 and 75 yrs were recruited. IDDM was registered if f-C-peptide was below 0.30 nmol/l, the remaining had NIDDM. From a standard ECG recorded at 50 mm/sec the longest RR-interval in expiration and the shortest during inspiration in each of 3 consecutive cycles of deep breathing at 6 breaths/min were measured and their mean ratio calculated (E/I-ratio). A 24-h Holter recording (Tracker) were obtained and after manual editing on the Pathfinder 700 the number of differences in successive RR intervals exceeding 50 msec ($sNN50_{24\text{-}h}$) were computed. The power in the High Frequency band (0.15–0.4 Hz) the first 5 min each hour during nighttime (HF_{night}) was calculated in the RR-Tools programme. After log-transformation the age dependent 5-percentile was established for all 3 methods in a random sample of 173 non-diabetics. CAN was registered in diabetics with values below these limits.

Prevalence of CAN, %

Method	IDDM	P	NIDDM
E/I-ratio	31.3	0.04	17.4
$sNN50_{24\text{-}h}$	34.3	0.03	19.6
HF_{night}	35.8	<0.001	7.6

Results 178 diabetics responded and readings by all 3 methods were obtained in 159. 67 had IDDM (age: 40–75 yrs, males: 63%) and 92 NIDDM (age: 43–75 yrs, males 52%). A significantly higher prevalence of CAN was found in IDDM compared to NIDDM (Table) by all 3 methods. The difference was especially pronounced when the degree of CAN was expressed by HF_{NIGHT}, which may be the more sensitive method.

Conclusion Cardiovascular autonomic neuropathy in the 40 to 75 yr old diabetic population is more prevalent in IDDM compared to NIDDM.

P2217 Improved outcome of diabetic patients with acute myocardial infarction in the thrombolytic era

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Several studies performed in the prethrombolytic era (PTE) consistently showed that diabetic (DM) pts with AMI have a higher in-hospital and post-discharge mortality. Data comparing the outcome of DM pts in the PTE and the thrombolytic era (TE) are scarce. We compared the incidence and short- and long-term outcome of DM pts with AMI in the TE and the PTE.

Methods: A prospective, nationwide survey of 4317 consecutive pts admitted with AMI in all CCUs in Israel during Jan.–Feb. of '92, '94, and '96 (TE), compared with a previous Israeli study of 5839 AMI pts (SPRINT Registry) in 1981–83 (PTE).

Results: DM pts in the TE (n = 1093) were older and had a worse risk profile than those without DM. DM in the TE was independently associated with increased 30-day (15.9 vs. 9.3%; OR = 1.27; 95% CI 1.00–1.61) and 1-yr (25.3 vs. 14.0%; HR = 1.42 1.42; 95% CI 1.20–1.68) mortality. The incidence of DM was higher in the TE (25 vs. 21%, p < 0001). DM pts in the TE were slightly older (65 ± 11 vs. 64 ± 9; p = 0.01) and had prior MI more often (30 vs. 25%; p = 0.01), but Q-wave MI (74 vs. 86%; p < 0.0001) and prior angina less often (39 vs. 55%; p < 0001). The crude and multivariate adjusted 30-day (15.9 vs. 22.4%; OR = 0.55; 95% CI 0.42–0.73) and 1-yr (25.3 vs. 31.4%; HR = 0.67; 95% CI 0.56–.80) mortality rates of DM pts were significantly lower in the TE than in the PTE.

Conclusions: Pts with DM in the TE had a better short- and long-term outcome than counterparts in the PTE, probably reflecting the better management of AMI pts in the TE. However, the mortality of DM pts with AMI in the TE remains high despite recent improvement in management.

EPIDEMIOLOGY: INFECTION AND INFLAMMATION

P2218 High prevalence of IgG antibody to Chlamydia pneumoniae in patients with proven coronary artery disease in a western Galilee population

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Objectives. To evaluate the association between chronic infection with Chlamydia pneumoniae (C. pneumoniae), as measured by a high titer of IgG antibody, and coronary artery disease (CAD). Our study was designed to explore the relationship between seropositivity to C. pneumoniae and serious coronary events, and to assess whether or not there may be additional association between established cardiovascular factors and infection with this organism.

Background. Previous work has suggested an association between C. pneumoniae infection and CAD. The infection was demonstrated by titers of antibodies – enzyme linked immunosorbent assay (ELISA) or immunofluorescence (MIF), PCR and by the findings of C. pneumoniae in the atherosclerotic plaque.

Methods. The serum of 130 patients with proven CAD was tested for the presence of IgG antibodies to C. pneumoniae using an ELISA test (SeroCP-Savyon Diagnostics). A titer greater than or equal to 1: 64 using the MIF method, the recognized "gold standard", correlates with a positive result when using the ELISA method. The mean age was 57 (40 to 65), 82% male and 18% female. The patients had either myocardial infarction (n = 109) or unstable angina (n = 21) six months before the investigation (range 3–24 months). The serum for the control group was obtained from 98 blood donors from the same area matched for age 52 (40 to 58) and sex.

Results. In the CAD group 75% of patients were positive for C. pneumoniae. In the control group 33% were positive (P = 0.001). No increased correlation could be demonstrated between traditional risk factors and C. pneumoniae infection, except in those patients with diabetes mellitus. We found out that in diabetes subgroup there was low prevalence of IgG antibody to C. pneumoniae, comparing with other subgroups. (p < 0.006)

Conclusions. These results suggest that chronic C pneumoniae infection may be a significant risk factor for the development of coronary artery disease.

P2219 Periodontitis as a potential risk factor for coronary heart disease

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Some recent studies have suggested that an association could exist between chronic oral infections, such as periodontitis, and coronary heart diseases: the periodontal pockets could serve as reservoirs of Gram-anaerobic bacterias and their toxins, and be in relation with the development of atherosclerotic events and their acute complications.

Methods: The periodontal status of 107 heart patients (52 AMI, mean age 61.2 y; 55 CCHD, mean age 60.3 y) and of 39 controls (mean age 60.3 y) was determined. Blood samples were taken to assess various biological parameters and, in some cases, to investigate the periodontitis-associated endotoxemia: for 34 AMI and for 8 CCHD patients, 10 ml of blood were taken before and 10 ml after a gentle standardized mastication; for 28 CCHD patients, 10 ml of blood were collected without chewing. All these patients had a moderate to severe periodontitis.

Results: Both groups of heart patients exhibited an extremely high prevalence of periodontitis when compared with the controls: respectively 96%, 87% and 66% of AMI, CCHD and controls had a periodontitis, which was severe in 69% of AMI, in 60% of CCHD but only in 36% of controls. In addition, the mean number of pockets by patient was 18.5 for AMI, 16.5 for CCHD and 5.9 for controls. There were 60% of AMI patients versus 16% of CCHD patients who exhibited an levated blood level of fibrinogen. Among these AMI patients, 27.3% showed a positive and significative endotoxemia after mastication. On the other hand, 51.5% of AMI patients versus 8% of CCHD patients had an elevated blood level of CRP. 21% of these AMI patients showed a positive and significant endotoxemia after chewing. As a whole, a significant endotoxemia was found in 11.7% of AMI patients before mastication, whereas 35.3% of these patients had a post-mastication positive endotoxemia. Among CCHD patients, no one showed a positive endotoxemia before mastication when 25% of them became positive after chewing.

Conclusions. The severity, extent and prevalence of periodontitis were higher in both heart patient groups than in controls. In addition, AMI patients had more often a severe periodontal disease than CCHD patients. Our results also show that an endotoxemia can occur after a gentle mastication in periodontitis-affected heart patients. Nevertheless, wether or not periodontal disease plays an etiological role for cardiovascular diseases deserves further studies.

P2220 A role for Chlamydia pneumoniae and cytomegalovirus infections in coronary artery disease in Polish population

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Background: Chlamydia pneumoniae (CP) as well as Cytomegalovirus (CMV) are common pathogens found in about 50% of healthy western population. Many studies suggest their adverse influence on development and course of coronary artery disease (CAD). So far no reports investigated relationship between infectious agents and CAD in Polish population, which has higher incidence of CAD than western European countries.

The aim of our study was to evaluate a possible role of CP and CMV infections in both CAD development and course of the disease in patients (pts) undergoing percutaneous coronary angioplasty (PTCA).

Methods: We enrolled 73 consecutive pts (mean age 54.8 years, 55 males) admitted for PTCA and 63 healthy controls (mean age 47.25 years; 31 males). The study subjects were evaluated for presence of CP specific IgG antibodies (microimmunofluorescence MIF test – Pointe Scientific; titre > = 1/8 regarded as positive) and CMV specific IgG antibodies (ELISA Eti-Cytok-G PLUS – Dia Sorin). Pts were sampled at the time of PTCA. In 68 pts available for follow up presence of CAD symptoms was assessed by angina questionnaire 7 months (mths) after the procedure.

Results: CP IgG antibodies were detected in 33 pts (45.2%) and in 14 subjects (22.2%; $p < 0.05$) from control group. In 29 out of 68 pts (42.6%) CAD symptoms were observed 7 mths after PTCA. No significant correlation was found between anti-CP IgG presence in symptomatic and non-symptomatic pts. There was no significant difference in anti-CMV IgG titre between study and control groups. Mean anti-CMV IgG titre in the symptomatic group tended to be higher than in non-symptomatic group, respectively 5.11 ± 2.67 vs 4.65 ± 3.91.

Conclusions: Our study results suggest a significant correlation between CP but not CMV infection with CAD prevalence. We did not find a positive association of CAD symptoms 7 mths after PTCA with markers of either CP or CMV infection.

P2221 Antibodies to Chlamydia pneumoniae do not predict subsequent coronary heart disease in the Scottish Heart Health and MONICA studies

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Evidence associating the respiratory bacterial pathogen Chlamydia pneumoniae and coronary heart disease (CHD) is accumulating. Archived serum from participants in the Scottish Heart Health Study (1984–1987) and the MONICA risk factor surveys (1986–1995) is a valuable resource, useful for investigating new coronary risk factors. Follow-up of the study participants for both fatal and non-fatal coronary events is continuing. For this study, 252 case-control pairs with adequate stored serum were identified. Control subjects, with no evidence of coronary heart disease, were chosen from within the study populations and were matched for age, sex and locality. The average time period between the collection of blood in the original survey and the coronary event was 3.9 years.

IgG, IgA and IgM antibodies to C. pneumoniae were estimated using Savyon (Ashdod, Israel) ELISA kits. Specimens from the CHD cases and their matching controls were randomly analysed on each microtitre plate. The manufacturer's cut-off values were used to evaluate the absorbance data obtained.

Antibody	Number of positive specimens			
	Controls		Cases	
	n	%	n	%
IgG	188	75	193	77
IgA	124	49	134	53
IgM	9	4	8	3

The table shows a high prevalence of both IgG and IgA antibodies to C. pneumoniae but no case-control differences. In these subjects, antibody status is not predictive of coronary events occurring some years later. However these data do not rule out active C. pneumoniae infection having a role in the precipitation of coronary events.

P2222 Correlation of components of the metabolic syndrome with C-reactive protein: a sensitive marker of systemic inflammation

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The metabolic syndrome (MS) is closely related to coronary heart disease (CHD) risk. Inflammation plays a crucial role in atheropathogenesis and features of the MS, like elevated levels of serum VLDL-cholesterol, glucose, fibrinogen and PAI-1 were linked to an ongoing acute phase response.

We correlated C-reactive protein (CRP), a sensitive marker of inflammation – with components of the MS. Total cholesterol (Chol), HDL-cholesterol (HDL), triglycerides (TG), fasting blood glucose (Gluc), uric acid (UA) and body mass index (BMI) were determined in a total of 747 men and 956 women aged 18–88 years participating in the VERA study which was carried out in 1987/88. Participants were drawn from a random sample representative for the population in West-Germany. Persons with acute and chronic diseases were excluded. Chol, HDL, TG, Gluc and UA were determined by routine laboratory methods. CRP was measured by means of a sensitive immunoradiometric assay. Prevalence of arterial hypertension (AHT) was assessed by a standardized interview.

Spearman correlation analyses yielded a statistically significant positive crude correlation between CRP and Chol ($r = 0.19$), TG ($r = 0.29$), BMI ($r = 0.32$), Gluc ($r = 0.11$) and UA ($r = 0.14$). A negative correlation was found between CRP and HDL ($r = 0.13$). After clustering subjects with 0–1, 2–3 and >4 features of the MS, age-adjusted geometric means of CRP values were calculated across groups. CRP values increased appreciably with increasing features of the MS. The values were 1.06, 1.24 and 2.0 mg/l respectively.

The MS is closely associated with a systemic inflammatory response. This may be a further pathogenetic mechanism for the increased CHD risk in those subjects.

EPIDEMIOLOGY: RISK FACTORS, PROGNOSIS AND TIME TRENDS

P2223 Longitudinal trends in cardiovascular risk factors in the Czech population

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The Czech Republic, unlike the other former East Bloc countries, has seen a decrease in total, and cardiovascular (CV) mortality in particular; still CV disease accounts for 56% of total mortality.

Methods: Three cross-sectional surveys of CV risk factors were conducted within the WHO MONICA Project in six Czech districts in 1985 (n = 2570), 1988 (n = 2768), and 1992 (n = 2342). In 1997/98, another population survey (a 1% random sample, aged 25–64, mean age 45 years) was performed in the six original districts (n = 1990) and in three other districts (n = 1219). The respondence rate was 64.4%.

Results: Over a 12-year period, there was a statistically significant decrease in the prevalence of smoking in males (from 49.2% to 36.8%, $p = 0.001$) and no change in smoking habits in females. Body mass index did not change in either sex, and obesity is still highly prevalent in the Czech population, especially aged 45+. A significant reduction, both in SBP (from 133.6 ± 20.2 to 127.8 ± 17.5 mmHg; $p < 0.001$) and DBP (from 84.1 ± 11.3 to 81.5 ± 10.1 mmHg; $p < 0.001$), was achieved. There was also a decreased prevalence and improved control of hypertension. A remarkable drop in total cholesterol was seen in both sexes (males: from 6.21 ± 1.29 to 5.65 ± 1.15 mmol/l; $p < 0.001$; females: from 6.18 ± 1.26 to 5.53 ± 1.21 mmol/l; $p < 0.001$). The 1997/98 survey showed a better lipid profile and lower diastolic blood pressure in the six original MONICA districts.

Conclusions: The remarkable improvement in CV risk factors documented in a 12-year follow-up period may contribute to the decrease in CV and total mortality, contrary to the trend in the other post-communist countries.

P2224 Standard risk factors continue to be under-recorded in patients discharged following an admission with acute coronary syndrome

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Ischaemic heart disease is multifactoral, but published reports suggest that documentation of risk factors has been poor. The European Society's Coronary Risk Chart enables easy identification of risk level but requires, as a minimum, levels of blood pressure, total cholesterol and smoking. We wanted to ascertain if increasing awareness of cholesterol had led to improvements in risk factor documentation generally.

Method: Patients admitted with symptoms suggestive of acute myocardial infarction (MI) during 6 months of 1996 and 2 months of 1998 were identified from a heart attack register. We reviewed, for those discharged with a cardiac diagnosis, the documentation of risk factors from their medical records.

Results: 2116 patients were admitted in 1996 and 1547 were discharged with a cardiac related diagnosis. For 1998 the figures were 920 and 783. For the total cohort, documentation of blood pressure increased from 70% to 96%, smoking from 76% to 90%, diabetes from 73% to 96%, family history from 48% to 94% and lipids from 23% to 41%. For discharge diagnoses of confirmed MI, suspected but unconfirmed MI and severe angina after a previous MI, similar improvements in the recording of risks other than lipids were seen. For patients with a confirmed MI, lipid recording improved from 27% to 61%, but for the largest group – those with suspected but unconfirmed MI – the improvement was less, from 22% to 37%. The ability to determine a patient's overall European risk score was only possible in 37% of all patients, due largely to the continued under-recording of lipids. Patients with a confirmed MI did slightly better- all three risks were recorded in 23% in 1996 and this had increased to 56% in 1998. Risk recording was less complete for women than for men. Women were half as likely in 1996 and still one third less likely in 1998 to have all 3 risks recorded. Patients identified as being diabetic (206 in 1996 and 114 in 1998) fared little better than the total cohort. 55% of the diabetic patients with a confirmed MI, and 46% of the entire 1998 cohort, had all 3 risk factors documented.

Conclusions: Despite recent improvements in documentation, greater efforts are still required particularly pertaining to lipids. Women remain less likely to have risks documented compared to men. Being diabetic, and so at high risk, does not mean that other risks are more likely to be recorded.

P2225 Trends in prevalence of cardiovascular disease risk factors in a working Bulgarian population, 1986-1997

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Background: Bulgaria is experiencing epidemic rates of coronary heart disease and stroke mortality. Few data exist on prevalence of risk factors, and no data exist for trends in risk factors.

Methods: We compared data from two cross-sectional surveys of male transport workers ages 30–59, conducted in 1986 (n = 1146) and in 1996/7 (n = 638). The men were recruited during their annual physical examination. A structured interview was conducted and measures of anthropometry and resting blood pressure were obtained.

Results: Mean age of investigated men was 47.7 y in the 1986 study, and 43.7 y in the 1996/7 study, respectively. Hypertension prevalence (SBP > 140 mmHg and/or DBP > 90 mmHg) decreased across surveys (75% in 1986, 64% in 1996/7; age-adjusted p = 0.009). Prevalence of more severe hypertension (SBP > 160 mmHg and/or DBP > 95 mmHg) did not change (42% in both surveys). For SBP, the increase with age was steeper in 1996/7 than in 1986 (age by survey interaction, p = 0.004). Mean BMI was 27.6 kg/m^2 and 27.3 kg/m^2 (age-adjusted p = 0.16); prevalence of overweight (BMI > 25 kg/m^2) was 73% and 68% in 1986 and 1996/7, respectively. The prevalence of ever-smoking increased from 56% to 80%, reflecting increase in both current smoking (49% to 59%) and former smoking (7% to 21%). Among current smokers, the proportion smoking >15 cigarettes/day decreased from 76% to 68% (p = 0.01), probably reflecting the deteriorating economic situation. 5.9% of employees in the 1986 survey and 3.8% of employees in the 1996/97 survey reported parental history of myocardial infarction prior to age 60 y, respectively (p = 0.06).

Conclusion: Traditional risk factors were highly prevalent in 1986 and have remained widespread in this 10-year period. In the absence of major lifestyle changes, morbidity and mortality rates are unlikely to decrease in the near future.

P2226 Continuing burden of heart disease: mortality trends in Olmsted County, Minnesota

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Age-adjusted heart disease mortality rates have declined since the 1960s. However, trends may have differed in women and the elderly. We examined age- and sex-specific heart disease mortality (ICD9 codes 390–398, 402, 404–429) in Olmsted County, MN, between 1979 and 1994. The total number of heart disease deaths was 3095, 1578 (51%) occurred in women, and 1980 (64%) in persons ≥ age 75. Most heart disease deaths (77%) were coronary disease deaths (ICD9 410–414). Age-adjusted heart disease mortality rate declined from 123 per 100,000 (95% CI 102, 144) in 1979 to 81 (67, 95) in 1994. However, Poisson regression analyses indicated that the trends differed according to sex and age. For women, the risk ratio (RR) of heart disease death in 1994 compared to 1979 was 0.69 vs 0.53 for men (P = 0.06). This equates to a decline in heart disease mortality of 2.5%/yr in women or 32% over the study period and 4.2%/yr in men or 47% over the time period. The decline in heart disease mortality was also less pronounced as age increased (P < 0.001). For 60-year-old women, the RR for 1994 compared to 1979 was 0.59, whereas for 80-year-old women, the RR for 1994 compared to 1979 was 0.77. For men, the RR for 1994 compared to 1979 was 0.61 for 80-year-old men vs 0.45 in 60-year-old men.

Thus, between 1979 and 1994, in Olmsted County, the decline in heart disease mortality was of lesser magnitude in women and in the elderly. This reflects the shift of the burden of disease towards women and older age groups and underscores the necessity to carry out age- and sex-specific analyses of heart disease mortality time trends as such trends are incompletely described by adjusted analyses.

P2227 Characteristics, resource use, and outcomes in Latin-American patients with acute coronary syndromes

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Background: Practice patterns and resource use for managing patients (pts) with coronary disease vary in different geographic regions.

Objectives: To describe the characteristics, resource use, and outcomes in Latin-American (LA) pts treated for acute coronary syndromes in the PURSUIT trial, a randomized comparison of eptifibatide versus placebo.

	Non-LA (n = 10363)	LA (n = 585)
Median age, y	64	60
Male sex, %	65	63
Hypertension, %	55	62
Diabetes, %	23	24
Prior MI, %	32	35
Baseline MI, %	46	32
ICU admission, %	74	85
Angiography, %	61	46
Percut. intervent, %	24	18
Bypass, %	14	11
Median ICU stay, d	3	5
Total hosp stay, d	8	9
Composite rate, %	14.7	15.4

Methods: Baseline characteristics and resource and outcomes data were collected prospectively for 585 pts in 8 LA countries. The primary endpoint of PURSUIT was a composite of 30-day death or nonfatal MI.

Results: LA and other trial patients had similar baseline risk. LA pts were admitted more often to an ICU and stayed longer. The rate of the composite endpoint did not differ between groups, but mortality alone was significantly higher (6.8% for LA pts; 3.4% for other trial pts; p < 0.001).

Conclusion: LA pts had less invasive treatment and longer hospital stays for acute coronary syndromes. The death/MI composite did not differ, but mortality alone was higher. Future studies are needed to elucidate the relationship between resource use and outcome in this population.

P2228 Does heart rate predict cardiovascular mortality in a low risk population?

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Elevated heart rate is considered an indicator of increased sympathetic nervous system activity, which can favour the occurrence of both severe hypertension and serious arrhythmia. Epidemiological studies demonstrated a direct association between elevated heart rate and hypertension, hypercolesterolemia and hyperglicemia, a pattern already known to be a risk factor of cardiovascular and total mortality. The purpose of this analysis is to verify the independent role of heart rate in the prediction of both cardiovascular and all-cause mortality.

Methods: Within the MATISS Project, an Italian population-based observational study, heart rate was measured from electrocardiograms in 1996 men, aged 40–69 years, screened from 1984 to 1987. Serum cholesterol, fasting blood glucose, blood pressure, pulmonary function, body mass index, smoking habits and physical activity were collected, following standardized procedures. Men were classified according to 5 groups of heart rate (= 90 beats/min). Vital status, mortality and causes of death were recorded until Dec 1997. Causes of death were coded using the WHO-ICD 9th revision.

Results: In 10 years of follow-up, 377 fatal events were recorded, 144 (38%) due to cardiovascular diseases. Age-adjusted death rates in the 5 classes of heart rate showed an increasing trend. The relative risks between the extreme classes were about threefold for both cardiovascular (3.0) and total mortality (2.7). The independent role of heart rate as predictor of cardiovascular and total mortality was investigated using the Cox proportional hazards model. Adjusting for confounders, the estimated coefficients of heart rate achieved significant level for both end-points. The adjusted relative risks for 20 beats/min heart rate increment were 1.63 (95%CI: 1.28–2.13) for cardiovascular mortality and 1.51(95%CI: 1.28–1.78) for total mortality.

Conclusions: In the free-living Italian male population, heart rate proved to be an independent predictor of mortality. These findings suggest a link of heart rate to subsequent incidence or mortality, probably, from cumulated cardiovascular conditions.

P2229 Flavonoid intake and the risk of coronary heart disease

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Background: Flavonoids are polyphenolic compounds found in tea, vegetables, fruits and wine. In experimental studies flavonoids have been shown to be effective free radical scavengers, metal chelators and antithrombotic agents. However, of the few epidemiologic studies only two have suggested an inverse association between flavonoid intake and the risk of cardiovascular diseases.

Methods and Results: The study population consisted of 25,372 male smokers, aged 50–69 with no previous myocardial infarction. They were participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study which was a randomized, double-blind, placebo-controlled trial with daily supplementation of alpha-tocopherol and/or beta-carotene. Men completed a validated dietary questionnaire at baseline. Flavonoid intake was the sum of quercetin, myricetin, kaempherol, apigenin and luteolin intake. After 6.1 years of follow-up, there were 1,122 non-fatal myocardial infarctions and 815 coronary deaths. In the multivariate model, for men in the highest quintile of intake (median 18 mg/day) compared to men in the lowest (median 4 mg/day), the relative risk (RR) of non-fatal myocardial infarction was 0.78 (95% confidence interval (CI) 0.64–0.95, p for trend 0.02). The respective RR for coronary death was 0.99 (95% 0.79–1.26, p for trend 0.71). Wine drinkers had a lower risk of nonfatal infarction (RR 0.82, 95% CI 0.68–1.01) and coronary death (RR 0.74, 95% CI 0.57–0.98) as compared to those who did not drink wine.

Conclusions: Total flavonoid intake infarction had a modest, but statistically significant inverse association with non-fatal myocardial, whereas there was no association with coronary death.

P2230 Haptoglobin polymorphism as a risk factor for coronary heart disease mortality

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Background: In the biomedical literature, several reports have dealt with the haptoglobin polymorphism as a potential risk factor for cardiovascular disease. However, since these results were obtained from cross-sectional studies in clinical series of young coronary patients, no formal statement regarding the independent etiologic nature of the haptoglobin polymorphism can be made.

Methods: Within the framework of the longitudinal part of the Belgian Interuniversity Research on Nutrition and Health survey, a nested case-control study was performed with the aim of evaluating the independent role of the haptoglobin polymorphism as a risk factor for coronary heart disease (CHD) mortality. In the large cohort with baseline measurements gathered in the 80s, 107 deaths from CHD, occurring within a follow-up period of 10 years, were matched for age (mean = 64.9 yrs) and gender (36.5% women) with three controls, and in the resulting 428 subjects the haptoglobin polymorphism as well as the haptoglobin concentration was determined.

Results: The distribution of the haptoglobin polymorphism (Hptype) was found to be in Hardy-Weinberg equilibrium (Hptype 1-1: 15.0%; Hptype 2-1: 50.4%; Hptype 2-2: 34.6%). At baseline, no differences were found between the three subgroups regarding age, sex, lifestyle characteristics, cardiovascular risk factors or prevalent CHD; only the haptoglobin concentration was significantly associated with the Hptype, with highest values in the Hptype 1-1 group (1.50 g/L) and the lowest in the 2-2 individuals (1.18 g/L). Conditional logistic regression analysis for matched sets, revealed that the haptoglobin polymorphism was significantly associated with CHD death. Rather surprisingly, the finding was that 1-1 individuals were at doubled risk for CHD mortality compared to the others, the odds ratio being 2.09 (95%CI: 1.22–3.60). The association was independently from other classical CVD risk factors and the haptoglobin concentration, and of comparable size between men and women. Moreover, evaluating the interaction term in a multiplicative model, showed that the Hptype did not play a synergistic role on the prognostic value of established CVD risk factors or the haptoglobin concentration.

Conclusion: In contrast to the findings from cross-sectionally based studies, the results from this longitudinal study show that Hptype 1-1 individuals are at elevated risk for CHD mortality.

P2231 Visceral fat accumulation and conditional probabilities of coronary heart disease: a community-based study in Porto, Portugal

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Background: Obesity has been one of the more inconsistent cardiovascular risk factors. Body fat distribution probably mediates the relationship between CHD and weight excess.

Methods: One hundred sixty one individuals older than 39 years (77 M, 84 F), without evidence of coronary heart disease (CHD) according to the Rose questionnaire and ECG, were selected from the community by random digit dialing, with a participation rate of 70%. Body fat distribution was assessed by computed tomography (CT) at the level of the 4th lumbar vertebra. The attenuation interval of adipose tissue was defined between −50 and −250 Hounsfield Units. Visceral fat (VF), subcutaneous fat (SF) and total fat (TF) areas were quantified. Coronary risk profile was obtained according to the updated Framingham equations, including measurements of total and HDL-cholesterol, SBP, presence of diabetes mellitus, cigarette smoking and LVH as measured by ECG.

Results: Total point score (TPS) of conditional probabilities of CHD according to Framingham equations correlated with VF ($r = 0.43$, $p < 0.0001$) and VF/SF ratio ($r = 0.42$, $p < 0.0001$) and was not related to SF ($r = 0.06$). These correlations were significant in both sexes (VF-TPS: $r = 0.44$, $p < 0.001$, VF/SF-TPS: 0.36, $p < 0.01$ in females and VF-TPS: $r = 0.42$, $p < 0.001$, VF/SF-TPS: 0.50, $p < 0.0001$, in males). When two classes of participants were considered, the first one with a total punctuation ≤ 20 and the other with > 20 points, the former group has lower VF compared to the latter (121.0 ± 62.2 cm^2 Vs 148.9 ± 73.2 cm^2, $p < 0.02$), and there were significant differences between the two classes in VF/SF and VF/TF ratios ($p = 0.04$). There were no significant differences between classes in SF ($190.7.0 \pm 90.3$ cm^2 Vs 196.3 ± 99.3 cm^2, $p = 0.81$) and TF (311.7 ± 129.7 cm^2 Vs 345.2 ± 142.5 cm^2, $p = 0.17$).

Conclusion: Visceral fat accumulation determined by CT is associated with increased conditional probabilities of CHD in asymptomatic individuals randomized from the community.

P2232 The control of multiple risk factors for coronary artery disease causes the change in the carotid arterial wall elasticity prior to the change in wall thickness

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It has been reported that the initial change of the vascular atherosclerosis is the thickening of the vascular wall by plaque deposition with compensatory enlargement of the lumen (vascular remodeling) We tested clinically if the vascular wall elasticity (E) changed prior to the vascular wall thickning and if the correction of risk factors resulted the normalization of E even in subjects with no change in thickness.

Methods: In the population of the Tohoku Electric Company who underwent annual health examination, the subjects (n = 176) **with normal wall thickness** at the carotid arterial wall was divided into two groups; the group without any risk factors of smoking, myocardial hypertrophy, diabetes mellitus, hypercholesterolemia, lower HDL cholesterol and hypertension (normal group, n = 56), and the group with one or more risk factors (risk group, n = 120). The magnitude of the risk for myocardial infarction in each subject was quantified using 10-year probability (risk index) by the equation of multiple risk (Framingham study 1991). The vascular wall thickness (Tkn, intima-media thickness) and the instantaneous change of Tkn at the common carotid artery was measured by the recently developed high sensitivity doppler technique of phase tracking method. (IEEE. 1997, see below). The elasticity of the vascular wall is calculated as (pulse pressure of the brachial artery)/ΔTkn.

Results: There were no significant difference in blood pressure, pulse pressure, and wall thickness between two groups. However, the slope of the relationship between elasticity and age showed significant ($p < 0.01$) difference as $E = -0.9 + 0.05^*$ age ($r = 0.86$) in normal and $E = -1.5 + 0.08^*$ age ($r = 0.89$) in risk group. The risk index from the multiple risk equation and E showed linear relation as $E = 0.99^*$ risk index + 8.2, $r = 0.79$, $P < 0.01$. In eight subjects we could follow at one year interval, the change in risk index resulted no change in Tkn but change in the wall elasticity.

Conclusion: This wall elasticity changed with risk factors even in those with normal wall thickness. The demonstration of this sensitive change in E at daily clinical practice would be of use in educating such subjects with risk factors but no realistic image of the future serious disease. (Development of this novel doppler method was awarded in 1996 and 1998 by Japan Society of Ultrasonics in Medicine).

EPIDEMIOLOGY: TRIALS AND CLINICAL PRACTICE

P2233 Impact of disease history on subsequent ischaemic event rates in actual practice versus the clinical trial

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In a previous analysis, we demonstrated that patients receiving ASA after an ischaemic event in actual practice are at much higher risk of subsequent events than those randomized to the ASA arm in CAPRIE. In this paper, we examine our patients' disease history, compare it to the baseline characteristics of the trial patients and assess subsequent event rates in the actual practice patients with and without history of additional disease.

Methods: The presence of ischaemic stroke (IS), TIA, diabetes, hypertension, hypercholesterolemia, angina, MI, congestive heart failure, atrial fibrillation or PAD prior to an index diagnosis of MI, IS or PAD was evaluated using the health records of 12,931 residents of Saskatchewan, Canada. All patients were prescribed aspirin after an index diagnosis between 1990–1995 – diagnostic history was examined between 1980 and the date of index event. The distribution of baseline characteristics in actual practice was compared to those observed for patients in the aspirin arm of the CAPRIE trial. Further analysis determined the rate of subsequent MI, IS, death or combination of endpoints for patients with prior disease and those without.

Results: Health records were available for 12,881 patients in the actual practice cohort. Rates of additional disease in actual practice ranged from 7% for atrial fibrillation to 74% for hypertension versus 4% to 51% for similar histories among patients in the trial. Patients in actual practice who had any disease history were 35% more likely to experience a subsequent ischaemic event (MI, IS, vascular death) following their index diagnosis.

Conclusion: Patients in actual practice have a higher prevalence of additional disease than the patients selected for the clinical trial. In turn, this helps explain the higher risk manifested in actual practice.

P2234 Are the West of Scotland Coronary Prevention Study (WOSCOPS) results for pravastatin generalizable to other populations?

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In 1996, the West of Scotland Coronary Prevention Study (WOSCOPS) demonstrated for the first time a substantial reduction in the risk of cardiovascular disease (CVD) with the use of pravastatin among hypercholesterolemic men with no previous history of CVD. Until then, direct data on the outcomes to be obtained by using statins were lacking. However, because the WOSCOPS trial population was comprised of Scottish men – which as a group demonstrate one of the highest worldwide risks for coronary heart disease – the generalizability of the results to other populations has been questioned. The legitimacy of this concern was examined, using Belgium as a case study.

Methods: Risk equations that allow prediction of the transition from health to CVD have previously been derived based on the WOSCOPS trial data. While it is unlikely that the nature of cardiovascular risk factors varies markedly between populations, the prevalence and clustering may. An epidemiologic study with information on the prevalence of these risk factors in a representative sample of the Belgian community was identified (Belgian Interuniversity Research on Nutrition and Health) and men that would have qualified for participation in WOSCOPS (i.e., 45–64 years with high total cholesterol) were selected. The probability of CVD was estimated separately for each individual by entering the corresponding risk factor data in the regression equations and then the distribution and the mean risk were derived for the cohort.

Results: In contrast to prevailing beliefs, the risk distributions were shown to be remarkably similar across populations in this study (mean 5-year risk of 14.62% in WOSCOPS versus 14.47% in Belgium). Based on two reasonable assumptions – the implications of the risk factors for baseline risk are the same in Scotland and Belgium, and no other important unmeasured factors affect the baseline risk in Belgium – our findings suggest that the pravastatin results in the WOSCOPS trial can indeed be generalized to other populations.

P2235 Practice patterns for unstable angina and MI without ST-segment elevation: UK prospective registry of acute ischaemic syndromes (PRAIS-UK)

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Background: The acute coronary syndromes (ACS) of unstable angina (UA) or myocardial infarction (MI) without ST elevation on the admitting ECG are important and frequent causes of admission in UK hospitals. Little is known about their treatment and investigation in the UK.

Methods: We conducted a prospective cohort registry of patients with ACS in 56 UK hospitals. Twenty consecutive eligible patients were enrolled in each centre. In hospital data are available for 950 patients of a planned sample of 1000.

Results: Mean time from pain onset to admission was 8.2 hours, standard deviation 15. First admission location was 36% to a Coronary Care Unit (CCU), 48% to an acute admissions ward, 13% to a general medical ward and 3% to another location. Median length of stay in hospital was 4.5 days (inter-quartile range 2–7). Median length of stay in CCU was 2 days. On admission, 63% were on aspirin (ASA), 31% beta blocker (BB), 39% on calcium antagonists (CA), 53% on nitrates, 10% potassium channel openers (PCO). In hospital 86% received ASA, 50% BB, 53% CA, 85% any nitrate (30% IV nitrate). At discharge 85% were prescribed ASA, 47% BB, 47% CA, 69% nitrates, and 19% PCO. In hospital IV unfractionated heparin was used in 33% (median 2 days) and subcutaneous low molecular weight heparin in 43% (median 3 days). Neither treatment was used in 29% of patients. Glycoprotein GPIIb/IIIa inhibitors were used in 1%. About 40% of participating hospitals had facilities for angiography. At hospital discharge 13% of patients had undergone stress testing (1% with thallium), 10% angiography, 4% PTCA and 2% CABG. Troponin was measured in 5% of patients.

Conclusion: About 30% of patients admitted to a broad group of UK hospitals with unstable angina and MI without ST elevation are not treated with an effective heparin regimen and in those who receive heparin, the duration of treatment may be too short. Rates of investigation in-hospital appear low. Data on practice patterns for the 6 month follow-up will be available for presentation.

P2236 α-Tocopherol and β-carotene supplementation and chronic heart failure: incidence and prognosis

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Purpose: To study the effects of long term α-tocopherol (vitamin E) and β-carotene supplementation on incidence of chronic heart failure, and on mortality in subjects with heart failure

Methods: Subjects were participants of the ATBC Cancer Prevention Study, i.e. male smokers aged 50–69 at study entry. 27 654 men reported no heart failure at baseline evaluations, nor did they have right for refundable medication for chronic heart failure according to registers of the Social Insurance Institution. These same registers were then used for identification of new cases of chronic heart failure during follow-up.

1479 participants had either self-reported heart failure or the right for refundable medication for the disease at baseline. They were followed up through national mortality statistics for total mortality, cardiovascular and cardiac mortality.

Participants of the ATBC Study had been randomized to either 50 mg/d α-tocopherol, or 20 mg/d β-carotene, or both, or placebo, and they were followed up for a median of 6 years.

Results: There were no differences in baseline variables across supplementation groups. Of participants initially free of heart failure, 675 received the right for refundable medication for chronic heart failure during follow-up (excluding the first year). Risk for chronic heart failure did not differ across supplementation groups (RR; 95% CI): α-tocopherol 0.97 (0.78–1.20), β-carotene 1.02 (0.83–1.26), both 0.92 (0.74–1.14) compared to placebo. Multivariate adjustments had no significant effects on the results.

Among participants with heart failure at baseline, 448 died during follow-up. The risk for total, cardiovascular, or cardiac mortality did not differ significantly across the supplementation groups.

Conclusion: α-tocopherol and β-carotene supplements did not affect incidence or prognosis of chronic heart failure.

P2237 Multivariate analysis of risk factors for coronary artery disease in Jordan

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Objectives: to describe the distribution of risk factorss and and analyse them in patients of both sexes treated at the coronary care unit, Jordan University Hospital, and compare the data produced with data in western countries.

Methods: The blood of 835 patients with documented acute myocardial infarction, 693 male (mean age 54.11 yrs) and 1142 female (mean age 62 yrs) was tested for serum cholesterol, triglycerides, low-density lipoproteins (LDL), high-density lipoproteins (HDL), fasting blood sugar, uric acid and serum creatinine. Systolic and diastolic blood pressure and cigarette smoking were included in the analysis. Student's "t" test distribution, standard method of correlation and multiple regression analysis were used.

Results:

Sex	Chol	Hdl	Ldl	Trig.	FBS
Male	205.7	37.2	135.4	152.6	145
Fem	214.8	40.1	137.1	163.8	191.9
"P"	0.09	0.03	0.738	0.267	0.0001
Male	SBP	DBP	U. acid	S. Creat	SMK/P/Y
	124.1	8.7	6.28	1.49	3.36
Fem	13.2	81.6	5.74	1.89	5.32
"P"	0.01	0.475	0.249	0.570	0.0001

Conclusion: 33% have SBP > 140; 38% have DBP > 90; 55% have Diabetes; 67% are smokers 58% have S. (Chol) > 180; 74% have Ldl > 90; 78% have hdl < 40. Classifcation of risk from s. Lipoprotins level in Jordan

	Mild	Moderate	Severe
s. chol.	140–180	181–200	200
s. trig	<100	100–150	150
ldl-c	90–120	120–150	150
Hdl		40-30	<30

SYSTEMIC ASPECTS OF HEART FAILURE

P2238 Digoxin impairs endothelium-dependent and -independent relaxations in isolated arteries

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Digoxin (DIG) is widely used in treatment of patients with moderate to severe heart failure (CHF). High DIG-concentrations (10^{-6} M) constrict isolated arteries. It is not known whether DIG in therapeutic concentrations ($3*10^{-9}$ M) alters endothelium-dependent or -independent relaxations in isolated arteries.

Methods: Ring preparations of pig coronary arteries (PCA) and human internal mammary arteries (IMA; obtained during surgery) were mounted into organ baths and were preconstricted with prostaglandine $F_{2\alpha}$ (10^{-6} to $3*10^{-6}$ M) or norepinephrine (10^{-6} M). Rings (n = 5–10) were subsequently exposed to endothelium-independent vasodilator nitroglycerine (NTG; 10^{-9}–10^{-6} M). In IMA we used endothelium-dependent vasodilator acetylcholine (ACh; 10^{-8}–10^{-5} M), and respectively in PCA substance P (SP; 10^{-11}–10^{-9} M). Relaxations to different substances are analysed in the abscence (–DIG) and presence (+DIG) of DIG in percentage of preconstriction.

Results: In PCA DIG impairs significantly ($p < 0.05$) relaxations to NTG and SP, in IMA only relaxations to NTG are significantly reduced. Table summarizes maximal relaxations for agonists.

	PCA		IMA	
	–DIG	+DIG	–DIG	+DIG
NTG	98.7 ± 2.3	92.0 ± 6.1*	93.1 ± 10.3	81.9 ± 19.8*
ACh			67.3 ± 19.5	66.0 ± 17.9
SP	100 ± 0	65.8 ± 26.2*		

(mean ± SEM; *$p < 0.05$)

Conclusions: 1. DIG impairs in therapeutical concentration endothelium-independent and -dependent relaxations in PCA, and endothelium-independent relaxations in IMA. 2. Further investigations are needed to evaluate whether these findings have therapeutic consequenses in treatment of patients with CHF.

P2239 Mechanical thrombectomy in patients with deep venous thrombosis : immediate and short-term results

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Purpose: Currently available techniques for the treatment of venous thrombosis have limitations. We report our early experience with mechanical thrombectomy in patients with deep venous thrombosis (DVT).

Materials and Methods: The Amplatz Thrombectomy Device (ATD) is an 8F catheter terminating in a double inverted helix, encapsulated and rotating at 150,000 revolutions per minute. Eighteen patients (8 male and 10 female) aged 37.6 ± 16.1 (17–74) were treated. The estimated mean age of the thrombi was 11.3 ± 6.9 days (4–28); the average length of the thrombosed segment was 16.9 ± 9.1 cm (5–40) and the mean thrombus diameter was 15.9 ± 4.3 mm (8–20). The thrombi were located as follows: iliac and femoral veins (3), inferior vena cava (5), inferior vena cava and iliac vein (10). The approach used was the ipsilateral (10) or contralateral (5) femoral vein, or the popliteal vein (3). All procedures were performed under cover of a temporary caval filter.

Results: Successful recanalisation was achieved in 15/18 patients (83.3%). The percentage of thrombus removed using the ATD, estimated angiographically, was 63.9 ± 30.9%. For the 5 floating caval thrombi, 78.0 ± 22.8% of the thrombotic material was removed and 70.0 ± 31.8% for all the caval thrombi (n = 15). At the iliofemoral level, 54.6 ± 36.4% of the thrombotic material was removed. Complementary interventions were performed in 7 patients: balloon angioplasty (5), stenting (2), thrombo-aspiration (2), permanent filter (2). No serious complications occurred but 38.9% of the patients had episodes of arterial desaturation per procedure. At follow-up, obtained in 13/15 patients, 12/13 succesfully treated vena cava and 6/11 succesfully treated iliac veins were patent.

Conclusion: Thrombectomy using the ATD is a rapid and effective procedure which may be a useful therapeutic option for patients presenting with recent proximal deep venous thrombosis with iliac and/or caval clot. Further studies are needed to evaluate the effects of this technique to prevent the occurrence of complications of DVT.

P2240 Hyperinsulinaemia augments muscle lactate production during exercise in patients with chronic heart failure

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Introduction: Patients with chronic heart failure are resistant to the metabolic effects of insulin and develop compensatory hyperinsulinaemia. Insulin resistance correlates with exercise intolerance in patients with chronic heart failure. The mechanism of this interaction has not been explained. Exercise testing is usually performed in the fasting state when insulin levels are at a minimum and does reproduce the usual metabolic state of the patient.

Aim: To examine the effect of hyperinsulinaemia on skeletal muscle metabolism and blood flow during isometric forearm exercise.

Methods: We have employed a forearm model of muscle metabolism. 10 male patients with stable (NYHA II-III) chronic heart failure were studied on two occasions. Patients performed a series of forearm exercises at increasing workloads (5 seconds contraction, 5 seconds rest for 5 minutes at 7, 14 and 21 kg) with the right arm. The left hand was placed in a heated box for sampling of arterialised blood samples. Blood was sampled from veins draining the exercising forearm muscles for measurement of blood gases, lactate and ammonia before and after each bout of exercise. Forearm blood flow was measured in the right arm at rest and after each exercise. On one visit patients received a hyperinsulinaemic glucose clamp to maintain a steady state plasma insulin of ~250 mU/l. On the other visit the insulin was replaced with a saline placebo.

Results: Hyperinsulinaemia led to a marked increase in muscle lactate efflux during exercise (Area under the curve 2.5 ± 0.5 v 1.5 ± 0.5 p = 0.02, Peak lactate 2.18 ± 0.97 v 1.63 ± 0.75 mmol/l p = 0.01). There was no significant difference in ammonia production, oxygen extraction or blood flow during the hyperinsulinaemia.

Conclusion: Insulin infusion has a profound effect on muscle metabolism during submaximal exercise in the absence of any change in muscle blood flow or oxygen extraction. Insulin promotes glucose metabolism and inhibits utilisation of fat, which accounts for the increase in muscle lactate production during exercise. This may in part explain the relationship between insulin resistance, hyperinsulinaemia and symptoms in patients with chronic heart failure.

P2241 Apoptosis and atrophy in rat slow skeletal muscles in chronic heart failure: differences with fast muscles

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Background: Congestive heart failure (CHF) is characterized by a skeletal muscle myopathy with muscle bulk loss. The mechanisms responsible for these changes are not clear at present.

Objectives: We have investigated the role of apoptosis in the rat "slow" Soleus muscle during the development of heart failure induced by monocrotaline and compared it with the "fast" Tibialis anterior.

Methods: CHF was induced in rats by injecting 30 mg/kg monocrotaline. We looked at the time course of apoptosis studying animals at day 0, 17, 24 and 30 days.

Results: We found a decreased expression of anti-apoptotic protein Bcl-2 (969 ± 10 AU 1893 ± 481 ($p < 0.002$ 0 vs 30 days)), accompanied by a rise of pro-apoptotic caspase-3 (2490 ± 36 AU 1335 ± 67 ($p < 0.001$ 0 VS 30 days)). Ubiquitin did not change (2460 ± 284 vs 2813 ± 48) while circulating TNFα was increased (5.0 ± 1.8 AU day 0, 5.16 ± 0.7 day 17, 3.5 ± 1.7 day 24 48.3 ± 30.2 day 30 $p < 0001$ ANOVA). DNA nick-end labeling showed an increased number of apoptotic nuclei both in myofibres and interstitial cells when heart failure occurs both in the soleus (0.015 ± 0.015 day 0 vs 0.062 ± 0.03 day 30 $p < 0.001$ for myofibers) and in the Tibialis Anterior (0.0025 ± 0.05 day 0 vs 0.19 ± 0.05 day 30 $p < 0.0001$ for myofibers). At 30 days, when CHF is overt, in the fast Tibialis Anterior muscle the magnitude of apoptosis is therefore significantly higher ($p < 0.05$) than in the slow Soleus. There was no appearance of muscle atrophy as measured by the muscle weight/body weight in the Soleus (0.47 ± 0.1 vs 0.48 ± 0.2 day 0 vs 30 p = NS), while in the Tibialis Anterior there was a significant decrease of this index (1.78 ± 0.02 vs 1.63 ± 0.02 $p < 0.001$ day 0 vs 30).

Conclusions: The present findings suggest that in rats with CHF TNFα induces apoptosis in skeletal muscle via activation of the caspase-3 system and that muscle bulk loss is not secondary to TNFα-ubiquitin dependent protein waste activation. Slow muscles are less prone to develop apoptosis than fast muscles. Muscle atrophy appears earlier in these latter ones.

P2242 Insulin resistance in patients with idiopathic dilated cardiomyopathy assessed by fluorodeoxyglucose positron emission tomography imaging: implications for metabolic intervention?

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Insulin resistance may reduce glucose uptake in dysfunctional myocardium in patients with idiopathic dilated cardiomyopathy (IDC). Therefore myocardial glucose uptake might be influenced by metabolic imaging conditions.

Methods: Myocardial glucose uptake with 18-Fluorodeoxy-glucose (FDG) positron emission tomography imaging was studied in 12 consecutive IDC-patients during hyperinsulinemic euglycemic glucose clamp (clamp) and compared to 17 IDC-patients who underwent FDG imaging with oral glucose loading (load).

Results: Age (46 ± 15 vs 46 ± 14) and left ventricular ejection fraction (LVEF) (27+10% vs 34+15%) were not statistically different in both groups (load and clamp resp.). In load a positive correlation was observed between FDG-uptake and LVEF ($r = 0.37$, $p = 0.15$), while in clamp a negative correlation was demonstrated ($r = -0.38$, $p = 0.22$). Regression lines of load (FDG = 0.82 LVEF + 30.5) and clamp (FDG = −0.50 LVEF + 76) were significantly different by ANOVA ($p = 0.03$). For patients with LVEF < 30% a trend to higher myocardial glucose uptake was observed in clamp (46.7+18.7 vs 64.9+19.9 mmol/min/100 g, $p = 0.07$, load and clamp resp.).

Conclusion: In IDC-patients myocardial FDG-uptake is influenced by metabolic imaging conditions. Difference between load and clamp can be explained by insulin resistance predominantly present in IDC-patients with lower LVEF. With clamp, insulin resistance was circumvened and preserved glucose uptake was demonstrated in dysfunctional myocardium. These results suggest a basis for tailored metabolic intervention in IDC-patients.

P2243 Insulin resistance in chronic heart failure is not due to peripheral vascular dysfunction

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Background: Chronic heart failure is a syndrome of haemodynamic dysfunction and neurohormonal disturbance. Chronic heart failure is an insulin resistant, hyperinsulinaemic state. Insulin is a vasoactive peptide that gives rise to skeletal muscle vasodilatation. In other insulin resistant states failure of insulin mediated vasodilatation has been demonstrated, and is thought to be at least in part responsible for insulin resistance.

Aim: To explore the role of peripheral vascular dysfunction in the aetiology of insulin resistance in patients with chronic heart failure.

Methods: Ten patients with stable chronic heart failure (NYHAII-III) and nine age matched healthy controls were studied. Subjects underwent a hyperinsulinaemic euglycaemic clamp at insulin levels of ~100 and ~250 mU/l for 90 minutes each. Whole body glucose metabolism (M) was calculated during the last 30 minutes of each clamp as a measure of insulin sensitivity. Heart rate (HR), mean arterial pressure (BP), cardiac output (CO), superior mesenteric artery flow (SMAF) and forearm blood flow (FBF) were measured non-invasively at baseline and after 30 and 60 minutes at each insulin level.

Results: The patients with heart failure were insulin resistant compared to the controls (M 3.7 ± 0.7 vs. 6.1 ± 0.8 at plasma insulin ~100 mU/l; $p < 0.05$). Despite insulin resistance the insulin infusion led to a significant increase in FBF in the patients (Peak 0.73 ± 0.14 ml/dl/min; $p = 0.002$) and the controls (Peak 0.60 ± 0.21 ml/dl/min; $p = 0.037$). There was also a significant fall in SMAF in both groups but no change in cardiac output or systemic vascular resistance. There was no difference in the haemodynamic response to insulin infusion between the groups.

Conclusion: Despite insulin resistance the haemodynamic actions of insulin are preserved in patients with chronic heart failure. Insulin resistance is not due to peripheral vascular dysfunction in this population. The significance and aetiology of insulin resistance in these patients merits further study. Furthermore, insulin should be investigated as a unique skeletal muscle vasodilator in the treatment of heart failure.

P2244 Physical training in warm water – a new method to improve function in older patients with congestive heart failure

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Conventional physical training has been associated with improved function in patients with congestive heart failure. Rehabilitation programs using training in warm water have been used for patients with rheumatic and other disabling disorders. However, immersion in warm water in combination with physical activity has been considered potentially dangerous in patients with cardiac disorders.

Method: In order to test the applicability of water training, 14 patients with chronic heart failure (NYHA III, age 71 ± 6.4) were randomised to 8 weeks of training in warm water (33–34°C) (n = 8), or to control (n = 6). Exercise capacity and muscle strength was tested before and after the training/control period.

Results: The training program was well tolerated, and there were no adverse events. Patients in the water training group improved their maximal exercise capacity more than patients in the control group (+2.1 vs. −8.2 Watt, p = 0.03), maximal VO_2 (+0.5 vs. −2.6 ml/kg/min, p = 0.086) and the six minute walking test (+34 vs. 5.7 m, $p < 0.02$). Further, the patients in the training group improved significantly their muscle strength in shoulder flexion and abduction, as well as in performance of heel-lift. There was no significant improvement in isometric and isokinetic strength and endurance in knee extension.

Conclusion: Physical training in warm water was well tolerated and associated with significant improvement in maximal exercise capacity in patients with chronic heart failure. This new method might be useful for many elderly patients and for patients with heart failure in combination with other disorders that impede mobility.

P2245 Loss of the normal coupling between the anaerobic threshold and insulin sensitivity in chronic heart failure

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The anaerobic threshold (AT) is a measure of the balance between aerobic and anaerobic metabolism. Given that glucose, insulin action and oxygen are involved in this process, we considered that: a) in healthy individuals, the AT might be related to whole-body insulin sensitivity (S_I); and b) that this relationship might be altered in patients with chronic heart failure (CHF) – a condition characterised by an imbalance aerobic and anaerobic metabolism.

Methods Healthy individuals (n = 20) and patients with CHF [n = 36, aged 59.1 ± 2.0 yrs (mean ± SEM), NYHA class I–IV, AT = 11.8 ± 0.7 ml/kg/min, radionuclide LVEF = 26 ± 2%], underwent measurement of S_I (intravenous glucose tolerance test and minimal model analysis) and assessment of AT, derived from measurement of oxygen comsumption and carbon dioxide output during maximal treadmill exercise tests.

Results Whilst AT correlated positively with S_I in healthy controls [$r = 0.72$, $p < 0.001$], no such relationship was observed in patients with CHF. In stepwise multiple linear regression analyses of variables in healthy individuals, S_I emerged as the only predictor of AT (standardised coefficient = 0.72, $p < 0.001$), whilst fasting insulin, incremental insulin area and total body fat (dual photon X-ray absorptiometry) failed to enter into final models (joint $R^2 = 0.52$, $p < 0.001$).

Conclusions This is the first demonstration that, in healthy individuals, whole-body S_I is related, or 'coupled', to the AT. The absence of such metabolic coupling in patients with CHF provides further evidence of disturbed cellular metabolism in patients with this condition.

P2246 Expression of FAS in peripheral muscle biopsies from heart failure patients

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It has been suggested that skeletal muscle changes may have pathophysiological significance for the progression of congestive heart failure (CHF). Apoptosis has been described in the heart of CHF patients, but is not known if apoptosis in skeletal muscles plays a role in CHF. We hypothesized that cells within the skeletal muscles might become predisposed to apoptotic cell death by expression of the "death receptor" FAS. The purpose of this study was to examine if FAS (APO1, CD95) is expressed in skeletal muscle biopsies of heart failure patients.

Biopsies from skeletal muscle (quadriceps) of 21 patients with CHF, aged 59 years, were obtained under approved protocols; all patients had ejection fraction < 35%. Paraffin blocks were obtained and sectioned at 5 microns. Immunohistochemistry with a monoclonal antibody to human FAS (clone CH11) detected highly reactive leukocytes within vessels and between fasciculi in all samples. In some biopsies, heavily immunoreactive endothelial cells also were observed within vessels interspersed throughout the fasciculi. The muscle fibers surrounding the vessels showed no reactivity with anti-FAS antibodies. These data suggest that FAS is expressed by microvascular endothelial cells and leukocytes within the skeletal muscle vascular bed in patients with CHF. They also raise the possibility that FAS-induced apoptosis in the vessels supplying skeletal muscle might contribute to the mechanism for the peripheral muscle changes observed in patients with congestive heart failure.

P2247 Apoptosis in heart failure: the link between skeletal muscle atrophy and exercise capacity limitation?

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Background In CHF exercise capacity (EC) is limited by fatigue and dyspnea. These symptoms are in part due to skeletal muscle abnormalities such as a shift from the slow fatigue resistant aerobic Myosin Heavy $Chain_1$ (MHC_1) to the fast MHC_{2a} and MHC_{2b}. The contribution of atrophy to the decreased EC is still debated, as well as the link between changes in fibers type and muscle waste. We have investigated whether apoptosis (A) plays a role in the development of the skeletal muscle myopathy in patients with CHF.

Patients and Methods We studied 9 patients with severe CHF due to ischemic heart disease (IHD) and evidence of hibernating myocardium who underwent CABG. Five subjects with no history of cardiovascular disease and normal ECG and echo represented the control group. On surgical biopsies taken from the vastus lateralis (VL) of the right leg, the electrophoretic pattern of MHCs, the fibers cross sectional area (CSA), the number of total, myocyte, and interstitial A nuclei with TUNEL method, and tissue levels of caspase-3, bcl-2 and ubiquitin were determined.

Results VL of CHF patients showed a significant increase of MHC_{2a} and MHC_{2b} ($p < 0.0001$ and $p < 0.0013$) and a significant decrease of MHC_1 ($p < 0.0001$). There was also an increased number of TUNEL positive A nuclei ($p < 0.021$ for myocyte and $p < 0.0013$ for interstitial). Tissue levels of Bcl-2 were decreased ($p < 0.0001$), while levels of Caspase-3 and ubiquitin were increased ($p < 0.0001$ and $p < 0.0001$). CHF patients showed a much higher degree of fibers atrophy as demonstrated by the decreased fibers CSA ($p < 0.0001$). We found a statistically significant correlation between the number of A nuclei and fibers CSA ($p = 0.004$ for myocyte and $p = 0.0015$ for interstitial). There was no correlation between% distribution of MHCs and number of TUNEL positive cells. The number of A cells was correlated with peak VO_2 ($p < 0.003$), but not with any of the other indices of severity of CHF. There was only a trend for peak VO_2 to correlate positively with MHC_1 and negatively with MHC_{2a} and $_{2b}$. We found a significant correlation between peak VO_2 and fibers CSA ($p = 0.0015$).

Conclusions In CHF the magnitude of myocyte A correlates with EC limitation. A causes muscle atrophy. The reduced EC in severe CHF can be explained both by the increased% of fast MHCs and by the A-related fibers atrophy.

P2248 Excessive ventilation in patients with cardiac cachexia and chronic heart failure: the role of skeletal muscle

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Abnormal skeletal muscle may contribute to excessive ventilatory response to exercise in chronic heart failure (CHF). Patients with cardiac cachexia show major metabolic abnormalities. We hypothesised that CHF patients with cachexia, with abnormalities of muscle quantity and muscle quality (impaired strength per unit muscle) also have highly elevated ventilatory response to exercise. We investigated 114 CHF pts (age: 59 ± 9 yrs, LVEF: 23 ± 11%; NYHA: 2.7 ± 0.7; 31 cachectics [cCHF]: dry, documented weight loss > 7.5% of previous normal weight in >6 months) and 83 non-cachectics [ncCHF]), and 30 controls (age 60 ± 9 yrs). cCHF (NYHA 3.0 ± 0.6) and ncCHF (NYHA 2.6 ± 0.7) had similar age and LVEF. The regression slope relating minute ventilation to carbon dioxide (VE/VCO_2 slope) was used as an index of the ventilatory response to exercise. We also assessed muscle mass (DEXA scan) and muscle function (quadriceps isometric muscle strength and fatigue).

Results: cCHF showed higher VE/VCO_2-slope vs ncCHF and controls (47.1 ± 16.7 vs 35.1 ± 9.9. vs 26.8 ± 3.9, respectively, $p < 0.0001$ in all comparisons). Reflecting CHF severity, VE/VCO_2-slope correlated with peak VO_2 ($r = -0.51$), NYHA class ($r = 0.46$, both $p < 0.0001$), and LVEF ($r = -0.27$, $p < 0.01$). However, presence of cachexia predicted an increased VE/VCO_2-slope, independently of these clinical variables ($p < 0.01$). Neither peak VO_2 nor muscle function (maximal strength and 20-min fatigue) and muscle mass correlated with the VE/VCO_2-slope in controls. Only in cachectic patients lean leg tissue mass ($r = -0.66$, $p < 0.01$), and quadriceps strength ($r = -0.64$, $p < 0.01$) correlated with VE/VCO_2 slope. In multivariate analysis the major determinants of VE/VCO_2 were muscle mass and strength in cCHF patients and NYHA class and peak VO_2 in ncCHF patients.

Conclusions: Muscle atrophy and impaired skeletal muscle strength are the strongest predictors of an excessive ventilatory response to exercise in CHF patients who develop cachexia. The study confirms the role of skeletal musculature in the generation of symptoms in CHF patients.

P2249 Skeletal muscle biomechanical inefficiency in heart failure measured by cardiopulmonary exercise testing

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Background: CHF results in marked skeletal muscle changes with a decrease in efficient Type I fibers and an increase in inefficient Type IIb fibers. Reduced skeletal muscle biomechanical efficiency (BioEff) has been reported with skeletal muscle magnetic resonance spectroscopy, but has not been reported during cardiopulmonary exercise test (CPET).

Methods: We measured BioEff during peak ramp exercise (30 CHF and 15 age/sex/weight matched controls) and during 6 minutes of 35 Watt steady state exercise (15 subjects in each group) with CPET. For SS and ramp exercise, Gross (zero VO_2 baseline), Net (rest VO_2 baseline) and Work (unloaded pedaling VO_2 baseline) BioEff were calculated using the O_2 debt measured during the recovery VO_2 after exercise, rather than the estimated O_2 deficit.

$$\text{Net BioEff (\%)} = \frac{\sum(\text{Watts during exercise} \times 1435)}{\sum(VO_2 \text{ during exercise and recovery above the resting } VO_2) \times k.}$$

where k = calories/VO_2 (l/min) = 3,840 + 1,180 × RER for SS exercise and k = 5,000 calories/l of VO_2 for ramp exericse. Statistics by unpaired t-test.

Results: see table below.

CPET-CHF vs Controls

Mean ± SEM	CHF	Controls	% Change	p Value
Steady State 35 Watts				
VO_2 (ml/min)	988 ± 49	829 ± 36	+19%	0.014
Gross BioEff (%)	10.3 ± 0.5	12.6 ± 0.5	−18%	0.005
Net BioEff (%)	16.0 ± 1.0	19.3 ± 1.0	−17%	0.032
Work BioEff (%)	21.4 ± 1.5	33.2 ± 2.9	−36%	0.001
Ramp Exercise				
VO_2 at 50 Watts (ml/min)	1,027 ± 40	883 ± 34	+16%	0.024
Gross BioEff (%)	13.0 ± 0.4	17.8 ± 0.5	−27%	0.0001
Net BioEff (%)	18.7 ± 0.7	21.1 ± 0.6	−11%	0.019
Work BioEff (%)	22.9 ± 0.7	24.9 ± 0.7	−8%	0.039

Conclusions: CHF patients have an increase in VO_2 (16–19%) at matched workloads (35 Watts steady state and 50 Watts ramp exercise). This increase in VO_2 translates into a decrease in biomechanical efficiency during both steady state (−17 to −36%) and ramp (−8 to −27%) exercise. The biomechanical inefficiency in CHF measured by CPET is probably due to alterations in skeletal muscle fiber type and may relate to CHF symptoms.

P2250 Cardiac troponin I is a predictive marker of left ventricular impairment after high-dose chemotherapy

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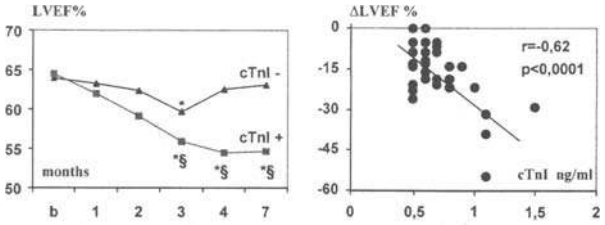
Patients with advanced cancer stage are often treated with high dose chemotherapy (HDCT) which efficacy is someway blunted by cardiac toxicity. As cardiac impairment may become clinically relevant weeks or months after the end of treatment, the availability of an early marker of cardiac injury, able to predict late ventricular dysfunction is an actual need. The role of serum cardiac Troponin I (cTnI) in this setting has never been investigated before. We measured cTnI value (immunoenzymometric assay, Stratus II, Dade; normal value < 0.5 ng/ml) in 109 patients (21 men, 88 women; age 45 ± 10 years, mean ± SD) affected by aggressive malignancies, before and after i.v. administration of potentially cardiotoxic HDCT [epirubicin, cumulative dose (CD) = 600 mg/mq; cyclofosfamide, CD = 12 gr/mq; etoposide, CD = 900 mg/mq; idarubicin, CD = 45 mg/mq, singly or in association]. Left ventricular ejection fraction (LVEF) was measured in all patients by echocardiography before treatment (b) and 1, 2, 3, 4 and 7 months after HDCT. In 39 cases (35%) cTnI increased after HDCT (cTnI+; 0.62 ± 0.25 ng/ml; range 0.5–1.5 ng/ml). * = $p < 0.05$ vs. baseline value. § = $p < 0.05$ vs. cTnI−.



Conclusions: 1) cTnI increased in 35% of patients treated with HDCT; 2) in cTnI+ patients a greater and more persistent LVEF reduction is observed. cTnI is an early and sensitive marker able to identify patients developing late ventricular dysfunction.

P2251 Pulse oximetry and left ventricular failure in the acute phase of myocardial infarction

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The continuous monitoring of oxygen saturation (SaO_2) by pulse oximetry (PO) is a current practice in coronary care units in patients with acute myocardial infarction (AMI) but its usefulness and its correlation with cardiac failure (CF) has not been established.

Methods: With this objective, 118 consecutive patients with AMI were studied prospectively during the first three days, registering daily data from physical examination (Killip classification), chest x-ray film (Battler score) evaluated by two observers and baseline SaO_2. The later parameter was measured when the patient was awake, selecting the steadiest value after discontinuing oxygen therapy for 30 minutes. Patients with cardiogenic shock (Killip IV) were excluded due to technical problems with PO.

Results: A total of 354 simultaneous registers were obtained for analysis, 74% Killip I, 18% Killip II and 8% Killip III. There was a good correlation between SaO_2 and physical examination (Killip/SaO_2): I/ 95 ± 3%, II/ 93 ± 3% and III/ 87 ± 6% (R-0.64, $p < 0.001$) and with x-ray film (Battler/SaO_2): 0/ 96 ± 2%, 1/ 95 ± 2%, 2/ 93 ± 3%, 3/ 91 ± 2%, 4/ 83 ± 3% (R-0.62, $p < 0.001$) although a better correlation was found between Killip and Battler score (R 0.78). Defining true CF by the association of Killip ≥ 2 and Battler ≥ 1, a SaO_2 < 94% correctly predicted CF with a sensitivity of 80%, specificity of 68%, and a test accuracy of 71%.

In conclusion, SaO_2 determination by pulse oximetry is a good predictor of cardiac failure in patients with AMI and may be an early sign of this complication. Pulse oximetry must be considered in the routine evaluation of these patients.

P2252 A comparison between rapid access chest pain clinics for the diagnosis and management of patients with new onset exertional angina

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Introduction: Rapid and accurate diagnosis of exertional angina is important in view of the significant morbidity and mortality associated with this condition. Rapid Access Chest Pain Clinics (RACPC) have been set up to address this, and the outcomes of 4 clinics are compared.

Methods: 4 RACPC's have been opened in 4 different areas serving 4 different populations under the same research group. General Practitioners (GP) and casualty doctors were invited to refer all patients presenting for the first time with exertional chest pain considered to be angina. (At Hillingdon and Southampton hospital patients over 70 years and those from casualty were not seen). Patients were seen on the day of referral and had a history and examination, resting ECG, blood tests and exercise testing where appropriate.

Results: see table

Hospital	Southampton	Hillingdon	Bromley	Charing Cross
Study duration	21 months	18 months	18 months	3 months
Population size	192,000	155,000	295,000	157,000
No. of referrals	467	370	2137	149
Referral rate (/1000/month/pop)	0.12	0.13	0.40	0.32
Ethnic minority	2%	15%	8%	24%
Diagnoses (%)				
Non-anginal pain	58	72	67	70
Possible angina	13		7	7
Exertional angina	23	25	21	19
Unstable angina	1	1	1	0
Acute M.I.	5	2	4	4
Angiography referrals (%)	–	38	47	42

Conclusion: Different RACPC's have provided rapid diagnosis and appropriate management of new onset exertional angina in different populations. The diagnoses in all RACPC's are similar and illustrates the same extent of diagnostic misclassification in the community. When a RACPC is offered to all patients of any age there is a 3 fold increase in patients assessed for chest pain.

ASSIST DEVICES, HEART AND LUNG TRANSPLANTATION

P2253 Partial left ventriculectomy improves functional capacity during long-term follow-up: relation to left ventricular shape

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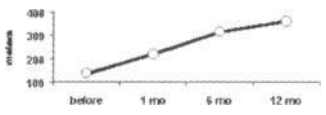
Several series of partial left ventriculectomy (PLV) patients have been reported recently. However, data are scarce regarding functional capacity and left ventricular function during long-term follow-up.

Methods: PLV was performed in 38 patients with end-stage idiopathic dilated cardiomyopathy enrolled in our prospective study, with mean follow-up of 19 months (range 2–28). Mean age was 52 years (range 2–71 years) and there were 6 women. In 29 patients mitral valve was repaired, while it was replaced in the remaining 9 patients. Tricuspid valve repair was done in 16 patients. Long and short axis of the left ventricle were measured by contrast ventriculography. Six-minute walking test distance was determined before, 1 month, 6 months, and 1 year after surgery.

Results: Thirty-day, 6-month, 1-, and 2-year survival were 81%, 67%, 64%, and 62%, respectively. After the initial 3-month period, patients had a stable outcome. Six-minute walking test distance increased significantly at each successive measurement (Figure). Diastolic long to short axis ratio (sphericity index) increased from 1.34 ± 0.15 before surgery to 1.66 ± 0.22 at 1 month, and 1.57 ± 0.22 after 6 months ($p < 0.05$ for both).



Changes in six-minute walking test.

Conclusion: Functional capacity improved in surviving patients during 1 year following PLV, which was paralleled with beneficial changes in left ventricular shape.

P2254 Anaesthetic strategy for partial left ventriculectomy

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Background: Surgical remodeling of the left ventricle using partial left ventriculectomy (PLV) is an attempt to reduce diameter of the left ventricle (LV) and consequently to decrease wall stress (WS). The goal is to improve LV efficiency proportionally to reduction of the afterload. Dynamic intraoperative changes in the load due to PLV and mitral valve repair (MVR) might influence left ventricular function. Therefore, haemodynamic evaluation of the patient during this procedure, as well as maintenance of anesthesia represents a challenging work and requires exceptional skill.

Methods: During two years, 38 patients (pts) (age 2–71 years) had been operated. PLV was coupled with mitral valve repair (29 pts), or valve replacement (9 pts). The modified technique for mitral valve repair and ventricular closure was used. Premedication with 0.5 mg atropine and 0.1 mg/kg midazolam was used. Induction and maintenance of anesthesia was performed with midazolam, fentanil and pancuronium. Arterial, central venous and pulmonary artery pressures were monitored continuously while transesophageal echo (TEE) was performed at the beginning and at the end of the procedure, as well as after the weaning of the bypass. Oxygen profile was measured in 20 pts after the induction, at the end of the procedure, 6 and 14 hours after operation

Results: In all pts who underwent PLV haemodynamic indexes improved at the end of the procedure. Cardiac index (CI) increased from 2.06 L/min/m^2 to 2.75 L/min/m^2, ($p < 0.05$). LVSWI was also improved (20.43 vs. 25.82 g-m/m^2). The average EF on TEE increased from 23.9% to 40.7% ($p < 0.05$). Oxygen consumption (VO_2) increased 34% (131 vs. 176 ml/min/m^2) while oxygen delivery (O_2 T) increased 10.9% (329 vs. 360 ml O_2/min). The weaning from bypass was successful using inotropic and vasodilator support which was necessary in all pts. There were no operative deaths.

Conclusion: This procedure involves reduction of left ventricular volume, correction of mitral regurgitation and eventual impairment of myocardial contractility with dynamic changes of the load intraoperatively. Continuous haemodynamic monitoring with TEE and oxygen profile provided sufficient data for proper intraoperatve treatment and maintenance of anesthesia.

P2255 Indicators of recurrent life-threatening ventricular tachyarrhythmias in cardioverter-defibrillator patients awaiting heart transplantation

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Background: Patients with advanced heart failure awaiting heart transplantation (HTX) are threatened by ventricular tachyarrhythmias (VT). Examination of stored electrograms (EGMs) in patients awaiting HTX with documented symptomatic VT and implanted cardioverter-defibrillator (ICD) was done to improve risk stratification and to identify subgroups at increased risk for arrhythmia recurrence.

Methods: During the study period (7/1994 to 8/1998) 1484 patients have been selected for HTX in the German Heart Institute Berlin including 106 Patients with an ICD. In 64 patients only incomplete information about VT episodes was available. EGMs of 42 patients could be classified after a mean follow-up time of 9.79 ± 7.46 months. Arrhythmia detection and therapy delivery of all stored episodes have been analysed retrospectively in detail and classified individually as adequate or inadequate. Clinical, echocardiographic and hemodynamic characteristics have been examined for possible influences on time and frequency of VT episodes.

Results: During the first month of observation 14/42 patients (33%) experienced an adequately detected and terminated VT episode while 28/42 (67%) remained event-free. Groups with and without ICD therapy did not differ at this point of follow-up in baseline LVEF, LVEDP, PCW, HZV, LVEDD, LVESD, heart rate, blood pressure or NYHA-class. Patients with atrial tachyarrhythmias (AT) suffered significantly more frequent from VT episodes ($p = 0.02$). From the second to the 6th month 7/26 patients (27%) had new VT episodes. Actual values of LVEDD and LVESD did not differ significantly, but there was a strong influence of LVEDD increase during the first 6 months on new occurrence of VT episodes ($p = 0.01$). Low blood pressure at 6 months was also an indicator of VT episodes (103 ± 11 mmHg vs. 133 ± 23 mmHg, $p = 0.03$).

Conclusions: Presence of AT is correlated with more frequent early occurrence of VT episodes in patients with advanced heart failure and an implanted ICD. It is not possible to stratify the risk of recurrent VT episodes by one point hemodynamic or echocardiographic measurement, but progressive LV enlargement and hypotension are indicators of recurrent life-threatening ventricular arrhythmias.

P2256 Impact of changes between serial stress echocardiography, coronary angiography and intravascular ultrasound on clinical outcome after cardiac transplantation

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Coronary angiography (CA), intravascular ultrasound (IVUS) and dobutamine stress echocardiography (DSE) are used for surveillance of allograft vasculopathy after heart transplantation (HTX). In this study, the impact of changes between annual tests with these methods on the clinical outcome was compared.

Methods: 83 patients (P) were studied serially (40 ± 37 months after HTX and 12 months later) by DSE (5–40 μ/kg/min; assessment of wall motion abnormalities) (WMA) and CA. IVUS (analysis of intimal index) was done in 65 P. An increase in WMA in ≥1 segment or new WMA were regarded as deterioration by DSE. Any luminal changes by angiography and an increase of mean intimal index ≥ 5% (absolute change) were defined as deterioration. The incidence of subsequent cardiac events (infarction, heart failure, Re-HTX, revascularization, cardiac death) was compared with changes between preceeding studies.

Results: 2/50 P (4%) without and 9/31 P (29%) with DSE deterioration had an event (relative risk, 7.26; p = 0.0014); in 2/83 P, the second DSE image quality was not adequate for evaluation. 2/56 P (3.6%) with unchanged serial CA and 10/27 P (37%) with worsened CA had events (relative risk, 10.37, p < 0.0001). By combined IVUS and CA, 2/25 P (8%) without changes and 9/51 P (17.6%) with deterioration by IVUS and/or CA had an event (relative risk, 2.21, n.s.).

Conclusion: Worsening of serial DSE and of serial CA predicts subsequent events in a considerable number of patients. The chosen IVUS parameter (increase in intimal index by IVUS ≥ 5%) did not improve the prognostic value of CA. Unchanged DSE findings at serial testing, and unchanged serial CA both indicate a very low risk of subsequent events. Thus, serial DSE allows for a reliable noninvasive risk stratification after HTX and may safely help to avoid invasive procedures.

P2257 The protective effect of labetalol on myocardial function in brain-dead pigs is associated with attenuated increase in myocardial microdialysis concentrations of adenosine and lactate

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Heart transplantation programs are partly limited by Donor hearts dysfonction of poorly understood mechanisms. Recently, altered myocardial oxygen supply/demand as a consequence of uncontrolled activation of the sympathetic nervous system (SNS) has been documented following brain death. The aim of this study was to investigate a potential protective role of pharmacological α-, β-adrenergic blockade on myocardial function, as well as its mechanisms, in brain-dead pigs.

Ten anesthetized pigs divided into two groups, GI as brain-dead animals and G2 as brain-dead animals receiving 10 mg/kg of labetalol at brain death induction, were involved in the study. Heart rate (HR), left ventricular dP/dt (LVdP/dt), coronary blood flow (Q LAD), mean aortic pressure (MAP), and cardiac output (CO) were recorded. Myocardial interstitial adenosine and lactate concentrations were assessed using microdialysis probes. Experimental brain death was obtained by an acute increase in intracranial pressure. Hemodynamic and biological parameters were recorded for 3 hours. At the 3rd hour, a volume expansion protocol was performed.

Following brain death, a transient increase in heart rate (HR: from 90 ± 11 to 158 ± 12 beats/min), left ventricular dP/dtmax (from LVdP/dt: 1700 ± 210 to 5030 ± 480 mmHg.sec^{-1}), cardiac output (CO: from 2.5 ± 0.3 to 3.4 ± 0.6 l/min), a limited increase in coronary blood flow (Q LAD: from 43 ± 6 to 70 ± 9 ml/min) was observed in G1. A significant 2 to 3 fold increase in adenosine and lactate myocardial dialysate concentration was observed, followed by a slow decline, reaching basal values after 2 hours. On the contrary, hemodynamic parameters and adenosine and lactate dialysate concentrations remained stable in G2. Following volume expansion, labetalol treated animals exhibited a significant increase in CO, dP/dt, and MAP, whereas G1 brain dead pigs exhibited decreased LVdP/dt values and only moderate increase in CO.

In conclusion, in brain-dead pigs, pharmacological α-, β-adrenergic blockade attenuates the myocardial dysfunction due to uncontrolled activation of the SNS. The protective effect of α-, β-adrenergic blockade is probably mediated by attenuation of the imbalance between myocardial oxygen supply and demand as suggested by the attenuated increase in myocardial interstitial concentrations of adenosine and lactate.

P2258 Relationship between macrovascular and microvascular changes in graft vessel disease of transplanted hearts

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Based on assessment of vascular function by flow-velocity measurements it has been suggested that there might be no correlation between microvascular and macrovascular graft vessel disease (GVD) in the transplanted heart. The study tests the correlation of macrovascular morphological parameters evaluated by intracoronary ultrasound (ICUS) with histological findings.

Methods: We studied 20 patients (three women, 17 men, mean age at HTx 54 ± 11 years), who underwent HTx due to terminal heart failure. All patients had cardiac catheterization including ICUS and right ventricular biopsies for diagnosis of GVD. Maximal plaque diameter, Stanford class (SC) of most severe lesion, local plaque geometry and distribution of macrovascular disease were assessed from ICUS. The paraffin-embedded biopsy samples were immunohistologically investigated with α-actin (smooth muscle cells, SMCs) and factor VIII (indicator for membrane injury of endothelial cells). Computer based quantitative morphometry and qualitative evaluation of H & E staining was performed at ×200. All data were analyzed using Mann-Whitney test.

Results: 1. Prominent endothelial cells in qualitative histologigal examination were associated with a higher amount of α-actin positive microvessels (p = 0.04) and with increased macrovascular plaque thickness (p = 0.03) as diagnosed by ICUS. 2. A higher count of α-actin positive microvessels was correlated with concentric local lesions (p = 0.04) and a diffuse distribution of macrovascular disease (p = 0.01). 3. Membrane injury of endothelial cells as indicated by an increased amount of factor VIII positive vessels in the biopsies were associated with a higher stage of macrovascular disease as assessed by the SC (p < 0.01).

Conclusion: According to our results macrovascular GVD is associated with pathologic changes in the terminal vascular system. Endothelial membrane injury and smooth muscle cell proliferation seem to be involved in the pathogenesis of this disease.

P2259 The relation of HLA-, gender- and CMV-matching to myocardial function assessed by dobutamine stress echocardiography

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HLA compatibility is related to survival and morphologic evidence of allograft vasculopathy in patients (pts) after heart transplantation (HTX) as shown by intravascular ultrasound measurements (IVUS) and coronary angiography in previous studies. Another method for surveillance of allograft vasculopathy is dobutamine stress echocardiography (DSE). The aim of this study was to evaluate the impact of HLA-, gender- and CMV-matching on myocardial function assessed by DSE in pts after HTX.

Methods: 104 pts (24 f, 80 m) undergoing DSE (5–40 μg/kg/min) were matched for HLA-A, -B and -DR compatibility (0–6 mismatches), donor/recipient CMV and gender status. By DSE, regional wall motion abnormalities (WMA) were assessed (16 segment model), systolic wall thickening (SWT) of septum and posterior wall was quantified and compared to previously defined normal values. A DSE score (1 = normal WMA and SWT, 2 = WMA or SWT path., 3 = WMA and SWT path.) was attributed to all pts. HLA-Typing was performed using lymphocytotoxicity technique (-A, -B) and PCR (-DR).

Results: The mean number of mismatches (MM) was 4.3. Pts were divided into a group A (<4 MM, 26% of all pts) and B (>3 MM, 74% of all pts). The mean DSE score was 1.8 in group A and 2.2 in group B with a significant difference (p = 0.038). Pts with a male donor (69.7%) had a mean DSE score of 2.3, whereas pts. with female donors (30.3%) had a mean DSE score of 1.8 (p = 0.032). A difference was also noted in recipient male/female sex (female rec. 2.0, male rec. 2.2), but did not reach statistical significance (p = 0.12). No differences in DSE score were found according to CMV-status of donor/recipient.

Conclusion: A lower number of HLA-mismatches and donor female sex is associated with fewer functional abnormalities assessed by DSE. This corresponds to previous IVUS and angiographic studies and indicates the clinical relevance of DSE.

P2260 A prospective study of changes in plasma nitrate levels following human heart transplantation: relevance to rejection and myocardial dysfunction

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Expression of iNOS and release of nitric oxide (NO) into the circulation has been linked to acute rejection in animal studies and NO has been shown to depress myocardial function. However its role in acute rejection in humans has not been adequately defined. We prospectively studied the relationship between plasma nitrate (breakdown product of NO), biopsy proven acute rejection and ventricular function (both systolic and diastolic) after transplantation.

Methods: Biopsies were performed weekly and then fortnightly up to 12 weeks after heart transplantation in 37 patients. On clinical indication of rejection additional studies were performed. Plasma nitrates were obtained on the morning of each biopsy (total 341). An echocardiogram was performed immediately prior to each biopsy in which the systolic parameters ejection fraction (EF) and fractional shortening (fs) and the diastolic parameters isovolumetric relaxation time (IVRT), mitral valve Pressure Half Time (MVPHT), mitral valve deceleration time (MVDT), peak a and e wave, e:a ratio and a wave duration were measured.

Results: Mean plasma nitrate rose significantly by a mean of 14.6 ± 7.4 μmol/L ($p < 0.005$) when rejection developed compared to a mean change of −2.6 ± 2.2 μmol/L between non rejecting biopsies. Plasma nitrate level showed no correlation with the systolic parameters ejection fraction EF or fs. There was a significant correlation between plasma nitrate and mitral valve peak a wave ($p < 0.001$), but no correlation with other diastolic parameters.

Conclusions: Nitrate level increases during acute rejection and could be a useful diagnostic marker. In this group of patients changes in plasma nitrate appear to be associated with diastolic but not systolic dysfunction.

P2261 Cytokine genetics and cardiac allograft vasculopathy: impact of tumour necrosis factor-α and -β gene polymorphisms

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Tumor necrosis factor (TNF) represents one of the most important pro-inflammatory cytokines, mediating immunological reactions in organ transplantation. Biological activity is influenced by several genetic polymorphisms.

To assess a possible impact of genotype on actuarial development of cardiac allograft vasculopathy (CAV) after heart transplantation (HTX), we analyzed two different TNF-gene-polymorphisms (TNF-α, position-308 and TNF-β, intron 1, NcoI-RFLP) in a large cohort of heart transplant recipients (n = 146, 1–12 years after HTX). Genotypes were correlated to the development of advanced CAV, as assessed by serial angiography (luminal obstruction $\geq$ 50%).

Allelic frequencies (TNF-α: GG = 71.2%, GC = 26.7%, CC = 2.1% and TNF-β: GG = 89%, GC = 9.6%, CC = 1.4%) were comparable to the normal population. Genotype dependent differences could be shown for the unstimulated serum activity of TNF-α (4.9 ± 1.8 pg/ml in the GG-genotype as opposed to 4.1 ± 1.7 pg/ml in carriers of the C-allel, $p = 0.05$) and were not interpretable for TNF-β (values below the detection threshold). However, freedom from CAVD was not found to differ significantly, neither between the TNF-α nor the TNF-β genotypes (TNF-α $p = 0.97$, TNF-β $p = 0.86$; kaplan meier analysis, log rank test).

It is concluded that the biological activity of TNF-α is influenced by the genotype. However, TNF-α as well as TNF-β polymorphisms fails to identify as a genetic risk marker for the development luminal obstruction in cardiac allograft vasculopathy.

P2262 Association between restoration of autonomic modulation in the native sinus node (SN) after cardiac transplantation and haemodynamic improvement

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We recently showed that there is a clear increase in both low-frequency (LF) and respiratory-related high-frequency (HF) power in the heart rate power spectra of the native sinus node in cardiac transplant (HTX) patients from about 4–6 months onwards post-HTX, clearly exceeding pre-HTX values, suggesting a restoration of (normal) autonomic modulation post-HTX. In this study possible relations of this new technique with multiple hemodynamic and biochemical parameters were assessed.

Methods: 389 intracardiac (i) recordings (rec) were made every 1–3 mths. post-HTX in 124 HTX pts, mostly starting from an index rec 0–1 mths. post-HTX or a pre-HTX rec. i-HRV of the native SN and HRV of the donor heart were calculated in LabVIEW, as described. An expert system in SPSS, with multiple hemodynamic and biochemical parameters, obtained at the same time-points as i-HRV, was developed to validate possible correlations with these indices and with future outcome of the patients.

Results: A clear increase in the spectral content was present in the consecutive recordings from 4–6 mths. onwards for both LF ($p < 0.001$) and HF($p < 0.001$), confirming previous results. The increases of LF and HF power were highly significantly correlated (all $p < 0.001$) with right ventricular pressure (RVP; rsp = −0.51, and −0.51 resp), right a. pulmonalis pressure (APP) (rsp = −0.53, and −0.50 resp) and right atrial pressure (RAP; rsp = −0.50, and −0.59 resp), and with total bilirubin (rsp = −0.67 and 0.61 resp). There was no relation with the rejection biopsy grading of the right ventricle.

Conclusions: The restoration of autonomic modulation in the native SN seems to be associated with the improvement of cardiac hemodynamic indices such as RVP, RAP and APP. There was no relation with rejection histology. This suggests that HRV of the native SN could have an important clinical application in the routine follow-up of HTX patients.

P2263 Skin cancer in heart transplant recipients: frequency and risk factor analysis

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The frequency of skin cancer is increased among organ transplant recipients, but the predisposing risk factors are controversial. It is also unclear whether heart transplant (HT) patients face an increased risk compared to recipients of other organs, e.g. kidney transplants (KT). We performed multivariate analysis of risk factors for skin cancer in 272 HT recipients (aged 54 ± 14 years, 233 male, mean follow-up 4.7 years, range 1 month–12 years) and in a control series of 242 KT (mean age 35 ± 15, 164 male, mean follow-up 4.5 years, range 1 month-22 years) followed up at a single Center. An extensive dermatological examination was carried out; baseline features, type of immunosuppression, number of rejection episodes requiring increased immunosuppression (3A ISHLT score), extent of sunlight exposure, skin type were recorded. Multivariate analysis (Cox multiple regression) included: age at transplant, sex, skin type, presence of warts, type of organ (heart vs. kidney), immunosuppressive regimen (double vs. triple therapy), number of Methylprednisolone I.V. boluses, sunlight exposure. During follow-up skin cancer was more common among HT patients (40, 15%) than in KT (18, 7%, $p = 0.01$). The prevalence of squamous cell carcinoma was 400 times higher than normal for Mediterranean countries. The cumulative incidence of skin cancer by life table analysis increased from 13% after 5 years to 28% after 10 years in HT patients and from 5% to 16% in KT ($p = 0.003$) (log-rank test). However, by multivariate analysis, age at transplant ($p = 0.0006$), skin type ($p = 0.03$) and sunlight exposure ($p = 0.03$), but not organ type were significant risk factors. In conclusion, age at transplant, skin type and sunlight exposure, but not organ type, are associated with increased risk of skin cancer in HT. Chronic immunosuppression may be implicated in the progressive increase of cancer frequency during follow-up. Prospective studies are warranted.

P2264 Prognostic modelling for cardiac events after heart transplantation using intravascular ultrasound in a large patient cohort

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Previous studies have shown that cardiac allograft vasculopathy (CAV) as assessed by intravascular ultrasound (IVUS) may predict cardiac events in patients after heart transplantation (HTx). These results were limited by the statistical approach and by sample size. Additionally, there is controversy about the optimal IVUS-parameter. We therefore sought to determine the prognostic impact of a suitable IVUS parameter on cardiac events in a large patient cohort.

Methods: 203 patients were studied by IVUS after HTx at two transplant centers. As potential predictors for cardiac events, we included four IVUS-parameters, the presence of angiographic CAV and various clinical characteristics. The analysis was performed in two steps. First, the IVUS-parameter with the highest predictive value was selected using deviance comparison. Second, all significant predictors were determined and relative rates (RR) with 95% confidence intervals (CI) were calculated using the Cox proportional hazards model.

Results: During a 6-year follow-up period, 37 events were observed. The maximal intimal index was found to be the most effective IVUS-predictor for cardiac events. In the bivariate analysis, various variables were significantly associated with the outcome. However, in the multivariate analysis, only the presence of angiographic CAV (RR 18.2, CI 6.5–50.7), maximal intimal index > 30% by IVUS (RR 12.0, CI 3.4–42.2) and body mass index (RR 5.6, CI 2.2–14.4) were identified.

Conclusion: We demonstrated that IVUS provides additional prognostic information to angiographic findings. This is important in patients with a normal coronary angiogram. Among all clinical parameters, body mass index has an independent prognostic impact. This may help to reduce costs and the need of invasive procedures in low-risk subgroups.

P2265 Coronary flow reserve is bi-directionally regulated by myocardial inducible nitric oxide synthase after cardiac transplantation – a longitudinal follow-up in 45 cardiac transplant recipients

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Objective: We followed 45 cardiac transplant recipients over one year and determined the potential relationship between myocardial iNOS and endothelial constitutive NOS (ecNOS) gene expression and coronary vasomotor function 1 and 12 months post-HTx.

Methods: iNOS and ecNOS gene expression was determined in endomyocardial biopsies 1, 6 and 12 months (Mo) after HTx by reverse transcriptase PCR followed by computerized densitometric analysis. Coronary flow velocity reserve (CFVR) was measured by doppler flowire in response to endothelium dependent (Acetylcholine (Ach); 30 μg/min/5 min) and independent (Adenosine (Ade); 160 μg/min/5 min) stimuli 1 and 12 months after HTx. Blood samples rom the aortic root and coronary sinus (CS) were used for measurement of nitrite (μM) and TNF-a (pg/ml) levels.

Results: iNOS and ecNOS gene expression was detected in all patients and did not differ over time (iNOS: 1 Mo: 1.9 ± 0.5 vs 6 Mo: 1.85 ± 0.6 vs 12 Mo: 1.0 ± 0.2, p = n.s.; ecNOS: 1 Mo: 15.2 ± 7 vs 6 Mo: 9.8 ± 2.1 vs 12 Mo: 8.7 ± 2.8, p = n.s.) Endothelium dependent CFVR increased in 56% over the first year (2.4 ± 0.1 vs 3.7 ± 0.17, p = 0.0001) wherea in 44% a decrease was noted (2.8 ± 0.18 vs 2.2 ± 0.22, p = 0.03). Increase in CFVR over time in response to Ach was associated with higher gene expression of iNOS (r = 0.68, p = 0.02 and with CS nitrite levels (r = 0.66, p = 0.008) at one year post HTx. In contrast, transcardiac nitric oxide production (nitrite levels in aorta: 34.7 ± 4.1 vs 40.6 ± 4.2, p = 0.0001) observed one month after HTx correlated with transcardiac production of TNF-a only in patients with impaired CFVR (r = 0.42, p = 0.02). However, this was not observed after 6 and 12 months.

Conclusions: These data in line with experimental evidence suggests a bi-directional role of iNOS activation in humans contributing to endothelial dysfunction early after HTx in association with inflammatory mediators (TNF-a) and improvement of CFVR in later stages after HTx which may delay the progression of allograft vasculopathy

P2266 Time-dependent pattern of vasular remodelling after heart transplantation: insights with intravascular ultrasound and three-dimensional vessel reconstruction

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The progression of transplant coronary artery disease (TxCAD) remains the limiting factor after heart tranplantation (HTx). The mechanisms of coronary artery remodeling during the progression of TxCAD are not yet fully understood.

Methods: In 50 patients (pts) with angiographically normal coronary arteries (LAD = 38, LCx = 10, RCA = 2), serial intravascular ultrasound studies were performed immediately (19 pts, group I) and beyond the first year after HTx (group II, 31 pts) and 12 months thereafter in each group with a motorized pull-back system. Up to 400 precisely matched sites per patient (200 μm stepping, frame rate 5/s) were analyzed using an interactive three-dimensional analysis software package (TomTec™). Total vessel volume (VV), luminal volume (LV) and intima volume (IV) were compared between the baseline (A) and follow-up (B) study.

Results:

	Group I			Group II		
	A	B	p	A	B	p
VV (mm^3)	466.9	437.2	ns	559.8	526.5	<0.5
LV (mm^3)	426.7	390.2	ns	488.8	435.2	<0.001
IV (mm^3)	40.8	47.2	ns	71.0	91.3	<0.05

Although mean vessel volumes did not change in group I, the pattern of remodeling was very heterogeneous, revealing an enlargement remodeling in 42% and shrinkage in 58% of the vessels. In group II, 70% of the pts showed a homogeneous vessel shrinkage.

Conclusion: By serial volumetric studies, heterogeneous patterns of coronary artery remodeling were observed, depending on the time since HTx. In pts late after HTx, the ability for compensatory enlargement of coronary vessels seems to decrease. The pattern of remodeling may have an important clinical and prognostic impact.

P2267 Clinical significance of TGF-β polymorphism and the development of cardiac transplant vasculopathy

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Coronary vasculopathy (CV), characterised by myointimal proliferation determines long term survival following heart transplantation. Transforming growth factor-β1 (TGF) influences neointimal formation and vascular remodeling by regulating smooth muscle cell growth, matrix production and growth factors. Polymorphism at position +915 of the TGF gene affects TGF production, individuals being high or low producers. We assessed this allelic variation on the development of CV.

Methods. CV was diagnosed by coronary angiography. Following DNA extraction sequence specific primers amplified the polymorphic TGF gene region by PCR. Electrophoresis allowed genotype identification. The results were analysed using a Kaplan-Meier actuarial curve and log rank.

Results: 129 patients and 215 angiograms were independently studied. 89.9% were high producers of TGF- β1. High producers were more likely to have CV at any time point (p = 0.0361). Low producers were protected from CV, with no patients developing disease until at least 4 years post transplant. The results were independent of pretransplant diagnosis, donor age, acute rejection episodes. sex.

Conclusions: TGF polymorphism determines susceptibility to CV and should be taken into account in future CV studies. This finding offers the prospect of preventing CV by the pharmacological inhibition of TGF.

P2268 Left and right ventricular pressure-volume loops to study the effect of cardiac tilting and the enabler circulatory support system on ventricular pump function

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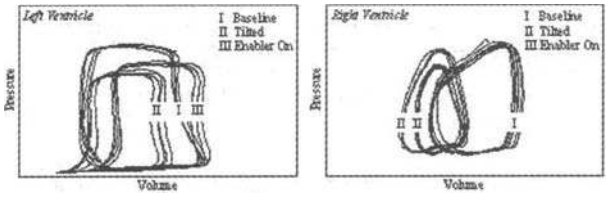
Pressure-volume (PV) loops generated by a conductance catheter are used for the investigation of cardiac pump function in various experiments and treatments. Currently no other technique is available to measure beat-to-beat volume, especially if the anatomy of the heart is changed by surgery or mechanical inhibition. In this study, absolute left and right ventricular PV-loops were simultaneously obtained in the tilted heart to asses the feasibility of the Enabler circulatory support system during beating heart CABG.

Methods: In six sheep, the heart was tilted with an Octopus device to expose the inferior wall. The Enabler was placed with the inlet valve in the right atrium and outlet valve in the pulmonary artery. Absolute PV-loops were obtained with the heart I) in its normal position, II) in the tilted position and III) in the tilted position and the Enabler activated to pump 2.0 l/min.

Results: PV-loops (see fig.) showed a reduction in stroke volume and right ventricular volumes upon cardiac tilting (SV: −31 ± 9%, RVESV: −46 ± 14%, RVEDV: −40 ± 12%). Subsequent Enabler activation improved left ventricular function (SV:+13 ± 8%, LVESV:+17 ± 16%, LVEDV:+14 ± 11%). The net extra output delivered by the Enabler was limited because its activation reduced right ventricular function.



Left and right ventricular PV-loops.

In conclusion, left and right ventricular PV-loops allowed the absolute and precise assessment of cardiac pump function even with the heart in a non-anatomical, tilted position. They showed cardiac tilting has severe hemodynamic consequences and that the Enabler is able to partly correct this.

P2269 Prognostic stratification of heart failure patients with a VO_2max on the grey zone highlighted by 24-hour Holter monitoring

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Background: The Bethesda Consensus 1993 established that a VO_2max < 10 mL/kg is *definite* indication for heart transplantation, between 10 and 14 is a *probable* indication and over 14 is a *no indication* in heart failure patients (pts). However, there is a considerable mortality in patients on the "grey zone", eventually due to ventricular arrhythmias.

Aim: To study the additional prognostic value of 24-hour Holter monitoring in heart failure pts submitted to CPET, specially on those with a VO_2max between 10 and 14 mL/kg/min.

Methods: We performed a retrospective analysis of 53 consecutive pts submitted to their first CPET since 1992 until 1998, whose Holter-ECG was performed with less than one-year interval. Age ranged between 16 and 72 years (53 ± 13 y.o.). Most pts were in NYHA II/III functional class (86%, half in each class) and the others were in class I. Mean ejection fraction was 27 ± 8%. There was an ischemic etiology in 21 pts (40%). No cardiac transplant was performed and 2 pts were submitted to revascularization procedures. Pts were grouped according to their VO_2/kg/min: Group I- >14; Group II > 10 and ≤14; and Group III- ≤10. Ventricular tachycardia (VT) on Holter monitoring occurred in 12 pts (22.6%). Total mortality was 13.2% (7 pts) with a mean follow-up (F-U) of 22 ± 16 months.

Results: Six of the pts who had VT at Holter (6/12–50%) died during F-U. This death rate was significantly higher than the one on the remaining 41 pts (1/41– 2.5%, Fisher's test- p < 0.001). The results by group were the following (table):

	Group I (n = 35)	*Group II* (n = 16)	Group III (n = 2)	
Deaths	1/35 (2.8%)	5/16 (31.2%)	1/2 (50%)	p < 0.01
VT	7/35 (20.0%)	5/16 (31.2%)	0/2 (0%)	NS
Deaths with VT on Holter	1/7 (14.2%)	5/5 (100%)	0/1 (0%)	p < 0.01

Conclusions: 24 h-Holter monitoring, in cardiac failure pts submitted to CPET, conferred an additional prognostic value in the VO_2max 10–14 group, as it identified all patients that subsequently died. Those patients should be considered for ICD or Heart Transplant since they had an ominous outcome in this study.

P2270 Poor outcome following heart transplantation in the presence of diastolic dysfunction: a Doppler echocardiographic and histopathological study

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Aim: To correlate structural and functional myocardial abnormalities suggesting diastolic dysfunction with subsequent clinical progress after heart transplantation.

Methods and results: In 168 heart transplant recipients (age 46 ± 10 years) who survived for at least 24 months following surgery we performed 2D and Doppler echocardiographic studies to assess left ventricular diastolic function (mitral deceleration time [MDT] and isovolumic relaxation time [IVRT]). We examined the relationship between these findings and histopathological staining of endomyocardial biopsies (H & E and antibodies for TGF-B) and clinical course. Recipients were divided into two groups based on the presence (MDT > 140 msecs; group A) or absence (MDT < 140 msecs; group B) of diastolic dysfunction. All assessments were made in the absence of rejection. There was no significant difference in donor age, recipient age, HLA mismatch or ejection fraction between the two groups. MDT and IVRT in group A (69 patients) vs group B (78 patients) were 123 ± 11 vs 168 ± 15, p = <0.001 and 56 ± 9 vs 78 ± 10, p = 0.003 respectively. Recipients in group A had higher fibrosis scores and more TGF-B staining compared to those in group B (p = 0.004 and 0.001 respectively). MDT correlated inversely with fibrosis score and TGF-B staining score (r = −0.45, p = 0.01 and r = −0.36, p = 0.01 respectively). NYHA status was 2.1 ± 0.4 in group A and 1.4 ± 0.2 in group B (p = 0.003). Post-operative survival was 1681 + 141 days in group A and 2693 ± 210 days in group B (p = 0.003).

Conclusion: Echocardiographic evidence of left ventricular diastolic dysfunction is common in cardiac allografts and is associated with increased myocardial fibrosis. Recipients with these features are a subgroup with a poor clinical outcome.

P2271 Predictor of development of severe renal dysfunction during 9 years following heart transplantation

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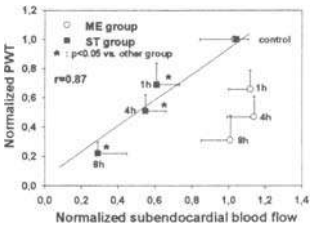
Severe renal dysfunction after heart transplantation (Htx), with high risk for dialysis or kidney transplantation, is considered to develop in approximately 20% of the patients during the first 3 years post-Htx.

Methods: In 151 Htx patients, 40 pre- and post-Htx variables in one subgroup of patients who developed severe renal dysfunction (GFR ≤20) were compared to corresponding variables in patients who did not (GFR > 20) during 9 years following Htx.

Results and conclusions: Despite a similar pre-Htx GFR (65 ± 18 vs 67 ± 16), the patients in subgroup GFR ≤20 developed severe renal dysfunction within 9 years following Htx. The recipient age (p = 0.0002) was higher and the GFR value at the first year post-Htx (p = 0.0001) was lower for patients in group GFR ≤ 20 than in group GFR > 20. Multivariate analysis showed that the recipient age together with GFR at one year post-Htx predicted the develop-ment of post-Htx severe renal dysfunction according to the Poisson model.



This results in a nomogram which predicts if and when a patient has a 50% probability of developing severe renal dysfunction within 9 years post-Htx.

P2272 Association between relocation of calcium binding S100A1 protein and severity of graft rejection in heart transplant recipients

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Background: Immune-mediated cardiomyocyte injury occurs typically during rejection in transplanted hearts and can contribute to development of cardiac dysfunction. This process can be particularly explained by alteration in the intracellular Ca^{2+} handling. Recently, much attention has been paid to the heart specific Ca^{2+}-binding S100A1 protein, which seems to be directly involved in a variety of Ca^{2+} mediated functions of the myocytes. Thus, the aim of the present study was to investigate the ultrastructural localization of S100A1 in myocardial tissue samples of heart transplant recipients (HTR) with mild or moderate rejection.

Material and Methods: 18 HTR (15 males and 3 females, mean age 51 ± 12 years) were divided into 4 groups with respect to severity of allograft rejection according to International Society for Heart Transplantation. Five HTR had no rejection (grade 0); 5 HTR had grade 1A; 5 HTR – grade 2, and 3 HTR – grade 3A. Immunolocalization of S100A1 in myocardial biopsies was performed by confocal laser scanning microscopy. Changes in cytosolic S100A1-concntration in cardiomyocytes were studied by semiquantitative measurements of the fluorescence-intensity in different regions of tissue samples obtained by endomyocardial biopsy.

Results: There were no differences between the groups regarding gender, age, time after transplantation, medical therapy and immunosuppresion including cyclosporine level. A specific relocation of S100A1 into vesicle-like structures near the cell- membrane and in the extracellular space was observed with increasing grade of graft rejection. This relocation resulted in a significant decrease of the cytoplasmic S100A1 content in cardiomyocytes by 10% in grade 1 rejection, 34% in grade 2 and 71% in grade 3 as compared to grade O.

Conclusion: S100A1 Ca^{2+}-binding protein is directly involved in the alterations of cardiomyocytes during allograft rejection. Given its role in the structural organisation and function of the cardiomyocytes, this Ca^{2+}-binding protein could be an important link in the immune-induced injury of the heart.

P2273 Hypercoagulable state in cardiac allograft recipients

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Rapid progressive graft vasculopathy (GVD) is a major cause of morbidity and mortality in cardiac transplant recipients (HTX). Subclinical activation of the coagulatory system has been demonstrated to be associated with progression of conventional coronary artery disease. Aim of this study was to investigate markers of the coagulatory system in HTX and compare them to consecutive control patients (C) from the centers outpatients clinic as data on this aspect are rare. In 81 consecutive HTX from 2 centers we determined Thrombin/Antithrombin-complex (TAT), Prothrombinfragment 1 + 2 (PF1 + 2) and Plasmin Antiplasmin (PAP) and Fibrinogen (F).

Results:

	HTX (mean ± SD)	C (mean ± SD)	p value
TAT (µg/l)	17 ± 35	3.3 ± 5.6	0.001
PF1 + 2 (nmol/l)	1.7 ± 0.98	1.17 ± 0.52	<0.001
PAP (ng/l)	800 ± 350	435 ± 231	<0.001
F (mg/dl)	354 ± 104	238 ± 57	<0.001

Conclusion: These results demonstrate that a hypercoagulable state characterized by increased thrombin generation and degradation exists in cardiac transplant recipients. It is relevant to possibly explain the increased risk of thrombotic comlications and progression of graft atherosclerosis in this group of patients

P2274 Clinical significance of tricuspid valve function after heart transplantation

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Aim: Tricuspid regurgitation (TR) is common following orthotopic heart transplantation (HT) but its natural history and clinical relevance are uncertain. We aimed to document clinical progress of patients after HT in relation to severity of TR.

Methods and results: We studied 208 recipients surviving for at least 6 months following HT by transthoracic echocardiography (870 examinations). TR was graded clinically and by ratio of regurgitant jet area (RJA) to right atrial area. Recipients were divided into those with no TR (group 1), subclinical TR (TR absent clinically and RJA < 25%, group 2) and clinical TR (TR clinically apparent or RJA ≥ 25%, group 3). Age, ischaemic time, pre-operative PVR or TPG, incidence of rejection episodes, ejection fraction and cyclosporin level were not significantly different between the groups. At 12 months after HT mean right atrial and pulmonary artery pressures were higher in group 3 than groups 1 or 2 (p = 0.005 and 0.03 respectively). The annual transition rate from group 1 to 2 was 13% (CI 9%–17%) and from group 2 to 3 it was 48% (CI 36%–71%). At a mean follow-up period of 72 months mean NYHA class in groups 1, 2 and 3 was 1.2, 1.7 and 3.2 respectively (p = 0.04 group 1 vs 2, p = <0.01 group 2 vs 3). The annual development of renal impairment (serum creatinine ≥ 200 micromol/l) in the three groups was 3% (CI 1%–5%), 7% (CI 3%–11%) and 61% (CI 45%–76%) respectively (p = 0.02 group 1 vs 2, p < 0.01 group 2 vs 3). Post-operative survival in days was 2017 + 198 for group 1, 1763 + 215 for group 2 and 1284 + 165 for group 3 (p = 0.03 group 1 vs 2, p < 0.01 group 2 vs 3).

Conclusion: Functional status of the tricuspid valve has significant implications for the long-term progress of HT recipients. Higher degrees of TR are associated with adverse outcome. Subclinical TR frequently progresses and assessment of tricuspid valve function should be an important part of the long-term follow-up after HT.

P2275 Plasma brain natriuretic peptide levels reflect the pattern of left ventricular filling after orthotopic heart transplantation: correlation with Doppler echocardiographic and haemodynamic findings

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Aim: Levels of brain natriuretic peptide (BNP) are increased after orthotopic heart transplantation (HT) and this may be a reflection of abnormal diastolic filling. We studied the relationship between diastolic filling and plasma BNP in HT recipients.

Methods: Left ventricular diastolic function was evaluated at a mean of 35 months post-transplantation in 40 cardiac transplant recipients (mean age 51 years, 30% female) with normal systolic function and no significant valvular disease. All measurements were made in the absence of allograft rejection. Diastolic function was assessed by Doppler echocardiographic parameters (E:A velocity ratio, mitral deceleration time [MDT] and isovolumic ventricular relaxation time [IVRT]). Pulmonary capillary wedge pressure (PCWP) was also measured. Restrictive filling was defined as an MDT < 140 msecs. Plasma BNP levels were measured in the supine position in all patients.

Results: Doppler parameters could be measured in 35 (88%) patients. E:A ratio correlated significantly with PCWP (r = 0.316, p = 0.033). MDT and IVRT correlated inversely with PCWP (r = −0.366, p = 0.028 and r = −0.396, p = 0.019 respectively). An MDT of <140 msecs predicted an elevated PCWP (>18 mmHg) with a sensitivity of 77% and specificity of 84%. Plasma BNP level for patients with restrictive filling was 10.2 ± 2.3 pg/ml compared to 6.4 ± 1.8 pg/ml for those patients without restrictive filling; p = 0.003. There was a significant positive correlation between BNP level and E:A ratio (r = 0.61, p = 0.01). MDT and IVRT correlated inversely with BNP level (r = −0.67, p = 0.02 and r = −0.51, p = 0.03 respectively. Elevations in PCWP were related to high BNP levels (r = 0.487, p = 0.003).

Conclusion: Restrictive ventricular filling is an accurate predictor of an elevated left ventricular filling pressure in HT recipients. Even in the presence of preserved systolic function plasma BNP levels are elevated after HT and correlate with the presence of restrictive physiology in the allograft.

P2276 Enhanced basal nitric oxide production in heart transplant recipients: relation to arterial blood pressure

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Total nitrite and nitrate (NO_2^- + NO_3^-) levels in plasma, considered as an index of endogenous formation of nitric oxide (NO), is reduced in patients with essential hypertension. Most heart transplant recipients (HTx pts) develop hypertension characterised by increased peripheral vascular tone and endothelial dysfunction, but it is unknown if this is due to reduced NO availability.

Methods: 63 clinically stable HTx pts (58 males, age 56 ± 1 years, mean ± SEM) 6 (range 1–13) years after HTx, treated with prednisolone, ciclosporine and azathioprine, were studied with 24 hour blood pressure (BP) monitoring. 46 received antihypertensive treatment, all were in NYHA class I, without any sign of allograft rejection or ongoing infections. Plasma NO_2^- + NO_3^- were measured by enzyme immunoassay based on Griess reaction. Blood samples were compared to 20 age- and sex- matched healthy controls.

Results: Mean (± SEM) 24 h systolic and diastolic BP for HTx pts were 130 ± 3 and 84 ± 8 mmHg, respectively. Central heamodynamics were normal (left ventricular ejection fraction 76 ± 12%, mean pulmonary artery pressure 16 ± 0.5 mmHg). Systemic vascular resistance was elevated (1714 ± 88 dynes sec cm^{-5}). Plasma concentration of NO_2^- + NO_3^- were significantly higher in HTx pts compared to the controls (56 ± 7 Vs 32 ± 3 mmol L^{-1}, $p < 0.01$), and correlated significantly with both systolic and diastolic BP ($r = 0.35$, $p < 0.01$ and $r = 0.39$, $p < 0.01$) in these patients.

Conclusion: Stable long-term HTx pts have significantly higher NO_2^- + NO_3^- levels than healthy controls. The elevated level of NO end products correlated with both systolic and diastolic BP in these patients. This finding may reflect a counter-regulatory vasodilatory mechanism to increased vascular resistance in HTx pts.

SYNCOPE AND DIAGNOSTIC TOOLS

P2277 Non-invasive and invasive studies for arrhythmia risk prediction in patients with myocardial infarction, complete bundle-branch block and syncope

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The prognosis of patients (pts) with bundle branch block (BBB) and myocardial infarction (MI) is poor, mainly in those suffering from syncope. The purpose of this study was to investigate the value of some techniques to evaluate the cause of syncope and the prognosis of these pts.

Methods: we prospectively obtained the results of clinical history, 24 hour Holter monitoring (HM), measurement of LVEF, signal-averaged ECG (SAECG) and programmed ventricular stimulation (PVS) in 124 pts with syncope, MI and BBB. 77 of them had a right (R)BBB and 47 a left (L) BBB.

Results: ventricular tachycardia (VT) was identified as the main cause of syncope: VT was induced in 68.5% of them. According to the results of PVS, pts were divided into 4 groups (gr): 1) gr IA with RBBB and VT (n = 50); 2) gr IB with RBBB but without VT (n = 27); 3) gr IIA with LBBB and VT (n = 35); 4) gr IIB with LBBB but without VT (n = 12). Sensitivity (se) and specificity (sp) of grade IV ventricular arrhythmias on HM for the detection of VT were respectively 42.5 and 47% in RBBB, 62 and 36% in LBBB; se and sp of a LVEF < 40% were 67.5% and 65% in RBBB, 85 and 9% in LBBB; se and sp of the combination of 2 of the 3 SAECG criteria, QRS duration (dur) > 155 ms, LAS dur > 30 ms and RMS 40 < 17 μV were 50 and 57% in RBBB; se and sp of the combination of 2 of the 3 criteria QRS dur > 165 ms, LAS dur > 40 ms and RMS 40 < 17 μV were 73 and 55.5% in LBBB. Cardiac mortality was 22%, 0%, 31% and 17% in grs IA, IB, IIA, IIB. The risk of cardiac mortality was not predicted by HM nor SA ECG, but was predicted by the presence of inducible VT (92% vs 10%**) and a lower LVEF (28 ± 9% vs 38 ± 15%**).

Conclusion: because of the high incidence of inducible sustained VT, the low value of HM, SA ECG, decreased LVEF for the prediction of VT and the poor prognosis of pts with VT and low LVEF, systematic PVS is indicated in pts with MI, syncope and BBB, whatever the noninvasive studies results.

P2278 Forearm blood flow during head-up tilt test and neurocardiogenic syncope: two different patterns of abnormal response

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Controversial findings have been reported regarding the reduction in forearm blood flow (FBF) during the first mins of head-up tilt test in patients (pts) with neurocardiogenic syncope (NCS). The purpose of this study was to evaluate changes in FBF during the first 15 mins of 60° head-up tilt in a) control subjects and b) pts with NCS and positive tilt test response.

Methods: We studied 24 pts with typical history of NCS and subsequent positive tilt test result, 10 male/14 female, mean aged 41 ± 15 years. Pts with subsequently negative tilt test result were not included in the study. Twenty-one apparently healthy subjects, 10 male/11 female, mean aged 37 ± 16 years, were used as controls. FBF measurements, by forearm venous occlusion plethysmography, were conducted at rest (supine position) as well as during the 5th, 10th and 15th min of tilt. FBF was expressed in % limb volume change/sec. ANOVA for repeated measures with Scheffe's test were used for statistical analysis.

Results: Supine resting baseline levels of FBF were similar in NCS patients and control subjects (mean ± 1 SD: 0.035 ± 0.01 vs 0.028 ± 0.01, p: NS). During the 5th, 10th and 15th min of tilt, FBF decreased in controls ($p < 0.0002$, <0.0001 and 0.001 respectively). A mean, stable reduction in FBF values by 40% was observed in controls during the first 15 mins of tilt. In 11/24 pts with NCS, FBF values remained unchanged (<10% change from baseline values) during the 5th, 10th and 15th min of tilt ("*impaired response*"). Conversely, in the remaining 13 NCS pts, FBF values decreased during the 5th and 10th min of tilt ($p < 0.002$ and <0.0001 respectively), but returned to baseline levels during the 15th min ("*unstable response*").

Conclusion: Two different abnormal patterns may be recognized in FBF changes during a consequently positive head-up tilt test. The recognition of different pathophysiologic mechanisms in NCS may have important therapeutic implications.

P2279 Provocation of neurocardiogenic syncope with central serotonergic activation by clomipramine, during head-up tilt test

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The aim of the study was to investigate whether the central serotonergic activation (CSA) using intravenously a serotonin re-uptake inhibitor clomipramine (clom), increase the sensitivity and the specificity of head-up tilt test. The central serotonergic system during this test was also evaluated by measuring the plasma levels of prolactin (PRL) and cortisol (CORT).

Methods: Sixty-nine subjects free of any medical treatment were studied. Forty seven patients had a positive history of recurrent neurocardiogenic syncope (NCS) (mean age 43 ± 17 years, 23 male); 22 normal subjects without history of syncope served as controls (mean age 44 ± 16 years, 12 male). All subjects were tested with two consecutive 60° head-up tilt tests with 24 hours interval. The basic tilt test (BTT) included 30 min of passive tilting and if it was negative, isoproterenol was given at the end of the test. The clom test (CTT) was performed with 5 mg clom infusion at the onset of the tilt test. Blood samples for CORT and PRL measures were taken at baseline 5, 10, and 20 min.

Results: Twenty-three subjects out of 47 of the patient group (PG) (49%) had a positive basic test and none of the controls (CG). The CTT was positive in 38 subjects (80%) of the PG and in 1 of the CG. Plasma levels of PRL and CORT increased significantly in the PG compared to CG. CORT increased in the PG from (mean ± SE) 96 ± 9 ng/ml at baseline to 133 ± 11 ng/ml, and 158 ± 11 ng/ml at 10 and 20 min, versus 84 ± 11 ng/ml to 87 ± 12 ng/ml and 107 ± 10 ng/ml respectively in the CG, $p < 0.0006$). PROL increased in the PG, from 6.6 ± 0.4 ng/ml at baseline to 19.3 ± 2 ng/ml and 19.6 ± 2 ng/ml at 10 and 20 min, versus 5.9 ± 0.6 ng/ml to 6.7 ± 0.7 ng/ml and 7.8 ± 0.9 ng/ml respectively in the CG, $p < 0.00001$.

Conclusion: CTT increase the diagnostic yield for evaluation of neurocardiogenic syncope. The CSA during the test is increased in patients with NCS.

P2280 Biochemical changes involved in the mechanism of neurocardiogenic syncope. observations during tilt table testing

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Background: Neurocardiogenic syncope (NCS) elicits one of the most powerful transient vasodilatory responses observed in human beings. The underlying biochemical mechanism for such a response has not been adequately explored. We hypothesized that various peripheral vasoactive amines and central hormonal changes may be implicated.

Methods: We studied 40 patients (pts) (age 38 ± 3 years, M/F 20/20) with probable vasovagal syncope (4 ± 1 attacks per pt) with repeat measurements of Thromboxane B_2 (TxB_2), 6 Keto-Prostagladine F1a (6 Keto PGF1a) and vasopressin (VAS) before and during a standardized tilt table testing protocol. Twenty pts (50%) developed NCS due to hypotension with (19) or without (1) bradycardia.

Results:

	Rest	15 min	peak
TxB_2 (pg/ml)	211 ± 12 (219 ± 10)	*309 ± 56 (219 ± 19)	*299 ± 32* (259 ± 29)
PGF1a (pg/ml)	258 ± 11 (290 ± 8)	262 ± 16 (306 ± 56)	287 ± 10 (304 ± 12)
vasopressin (pg/ml)	6.5 ± 1 (7.4 ± 2)	4.2 ± 3 (3.4 ± 1.5)	**105 ± 13 (6.3 ± 1.4)

*$p < 0.08$ (intragroup comparison), **$p < 0.001$ (intergroup comparison).

Within parenthsis are the measurements observed in pts with a negative tilt study. The peak values refer to the measurements obtained during either induction of NCS (positive study) or the completion of a negative study.

Conclusion: During tilting, there is a small increase in TxB^2 without any significant change in PGF1a among syncopal pts with or without a positive vagotonic reaction. On the contrary, a dramatic increase in vasopressin accompanies the vagotonic reaction of a positive tilt table testing subject.

P2281 Clinical characteristics and haemodinamic response in patients with asystole during head-up tilt test

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It is not clear if the type of positive response induced by the head-up tilt-table (TT) test reproduces accurately what happens during spontaneous events. If this is the case, patients (pts) presenting asystole during TT should have a different clinical pattern than those with vasodepressor or mixed responses. This study aims to assess this hypothesis by analyzing prospectively entered data from a large cohort of pts who underwent TT test.

Methods: A computerized database was used to identify 77 pts with a TT positive result. Among those, 16 had asystole > 3 sec (4–42 sec) – group A, and 61 had a vasodepressor or mixed response (group B).

Results: There was not differences between groups concerning the duration of the disease and the number of total or per year episodes of syncope. The clinical characteristics of syncope (sudden presentation, presence of triggering stimulus, incidence of seizures, incontinence or traumatism) were also similar. The number of presyncope episodes was significantly lower in group A (2.5 ± 5 vs 15.5 ± 25 in group B; $p < 0.01$). All the asystolic responses during TT appeared in the basal phase, i.e. withouth isoprenaline induction, and had a higher proportion of young patients (≥16 years) than the other kind of positive responses (38% vs 14%; $p < 0.05$). This fact could explain the higher cardiac rate, both at rest and after tilt, observed in group A (75 ± 14 bpm and 90 ± 21 bpm, respectively) with respect to group B (66 ± 12 bpm and 78 ± 17 bpm, respectively; $p < 0.05$ for both comparisons).

Conclusions: An asystolic response following tilt head-up is more frequently seen in children and can not be predicted by an apparently worse clinical profile. These patients have a higher heart rate, both at rest and after tilt; this fact could explain their higher susceptibility to simple tilt without sympathetic stimulus.

P2282 Effectiveness of fosinopril in patients with neurocardiogenic syncope not responding to β-blockade treatment

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Beta-blockade (BB) is currently considered as a treatment of choice for patients (pts) suffering from neurocardiogenic syncope (NCS). However, a subset of the above pts remain symptomatic despite the BB treatment. The aim of the present study was to investigate the effectiveness of the angiotensin converting enzyme inhibitor (ACE-I) fosinopril in pts non responding to BB, given that ACE I can inhibit catecholamine release from sympathetic nerve endings.

Methods: Our study population consisted of 36 pts suffering from NCS who were found to have positive head up tilt test (TT) response with esmolol infusion (which as is it has been previously shown can accurately predict the outcome of the a head up tilt response to BB). The pts included were randomly assigned either to fosinopril 10 mg/die (9 men and 9 women aged 39 ± 5 years-group A), or to placebo (10 men and 8 women aged 41 ± 4 years-group B). TT was performed at a tilt angle of 80° for a maximum of 30 min. In pts with negative baseline TT response, isoproterenol infusion at incremental doses (up to 5 μg/min) was performed. There were not any differences between the 2 groups regarding the blood pressure, heart rate and demographic data. All pts 30 days later were re-evaluated with TT applying the same test procedure. Statistical analysis was performed with x^2 method corrected by Yates formula. P values < 0.05 were considered as statistically significant.

Results: TT resulted positive (inducing symptomatic hypotension associated or not with bradycardia) in 8 pts of group A (44%) and in in 14 pts of group B (78%)-$x^2 = 5.72$, $p < 0.05$. The drug was well tolerated in all but 2 pts who exhibited dry cough and mild hypotension respectively. Such adverse effects, however, were not severe enough to exclude the above pts from the study.

In conclusion, the ACE I fosinopril could be used as a valid alternative treatment in pts suffering from NCS non responding to BB treatment.

P2283 Role of tilt table test negativation in the evaluation of therapeutic efficacy of neurocardiogenic syncope

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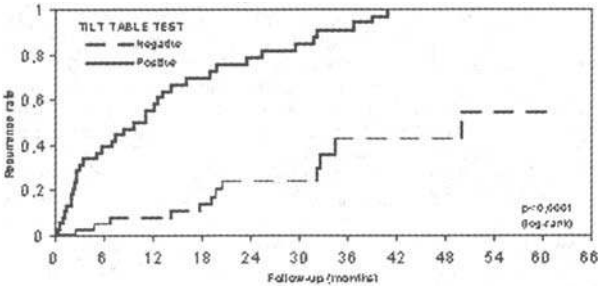
Tilt table test (TT) is a useful method to identify patients (pts) with neurocardiogenic syncope, but its role in the evaluation of therapeutic efficacy is still controversial. The aim of this study was to determine the correlation between TT negativation after therapy administration and recurrence rate and to identify other predictive variables of recurrence during follow-up.

Methods: We studied 82 pts (mean age 27 ± 19 years) with recurrent neurocardiogenic syncope (7 ± 12 episodes – median 4) and positive TT. Once empiric therapy with betablocker or fludrocortisone was initiated, all pts underwent another TT (treatment evaluation test), respecting drugs half-lives. Recurrence rate was analyzed by Kaplan-Meier method and compared by log-rank test, in pts with negative and positive treatment evaluation test. The role of gender, age, number of syncope episodes, duration of symptoms, and drug administered, were also evaluated.

Results: TT negativation after therapy was observed in 43 (52%) pts and was related to significant lower recurrence rate during follow-up ($p < 0.0001$). Significant lower recurrence rate was also observed in pts treated with betablocker and in female ($p = 0.03$ and 0.02, respectively). No other clinical variable was related to significant difference in recurrence rate.



Role of Tilt Table Test Negativation.

Conclusions: TT negativation may be considered an adequate method to determine therapeutic efficacy of neurocardiogenic syncope. Pts treated with betablocker and female presented lower recurrence rate.

P2284 Sertraline treatment for neurocardiogenic syncope

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Several methods were suggested in the treatment of neurocardiogenic syncope (NCS). Recent clinical observations have suggested a beneficial effect of sertraline, a serotonin reuptake inhibitor, in prevention of NCS. The present study was undertaken to investigate the effect of sertraline on the primary treatment of NCS.

Methods: Patients (pts) with unexplained syncope were evaluated with head-up tilt table test (HUTT). Twenty-nine subjects (14 female, mean age: 42 ± 27) who had reproducible NCS induced with HUTT were given sertraline 50 mg/day perorally and followed up for 6 months. HUTTs were performed montly, at least one positive test was considered as "HUTT positive". The patient remained in a supine position for 30 minutes and was then tilted to an angle of 80 degrees for maximum 45 minutes.

Results: Follow-up data showed that NCS during daily life disappeared ("symptomatically negative") in 26 (90%) of 29 and HUTT couldn't induce syncope ("HUTT negative") at all in 27 (93%) of 29 pts treated with sertraline (Table 1).

Table 1. Post-treatment distribution of the patients according to their symptoms and HUTT results.

	HUTT negative	HUTT positive
Symptomatically negative	25 pts	1 pt
Symptomatically positive	2 pts	1 pt

Conclusion: This study suggests that sertraline may efficiently prevent NCS, presumably through inhibition of central reflex axis.

P2285 Syncope work-up: diagnostic yield of routine neurologic evaluation in adult patients hospitalized for syncope: time for change?

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Despite the pivotal role of history and physical examination in the diagnosis of syncope, syncope work-up continues to be a diagnostic dilemma. Expensive diagnostic testing is a common clinical practice.

Clinical records of all patients hospitalized for syncope at two community hospitals in 1994–1995 were reviewed. Patients were included if they had carotid duplex scanning and/or CT scanning of brain, and/or EEG as a part of syncope work-up. A total of 406 patients were admitted with an initial diagnosis of syncope. 29 (7.1%) patients with TIA or clinical stroke were excluded from the study. 377 patients, mean age 66.6, 43% males, were included in final analysis. Orthostatics were done in 80 (24%) of which 41 (51%) had orthostatic changes explaining syncope. Number of diagnostic tests performed and percent abnormal are shown in the table.

	Carotid Duplex	CT Brain	EEG
Test n (%)	140 (37%)	195 (52%)	163 (43%)
Abnormal n (%)	8 (5.7%)*	8 (4.1%)**	11 (6.7%)**

* 70% stenosis of at least one carotid artery. **Old Infarcts. ***Nonspecific

Out of 498 CT scans, duplex carotid, and EEG studies, only 27 (5.4%) were abnormal. None of these abnormalities explained the final diagnosis of syncope. Average length of stay was 5.09 ± 3.6 days. Despite this extensive work-up no definitive cause was found in 154 (38%) of patients. Evaluation of orthostatic change in blood pressure and heart rate at bedside had the highest diagnostic yield, but was only performed in a small group of patients (24%).

Our data strengthen the argument for good clinical evaluation as the most cost effective and rewarding diagnostic modality for patients presenting with syncope to the emergency centers.

P2286 Long-term follow-up and outcome of patients presenting with recurrent syncope of unknown aetiology and normal heart

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Background: The purpose of this study was to assess the long term clinical course and prognosis of patients (pts) presenting with recurrent syncope (sync) of unknown etiology (SUE), namely of pts in whom the initial cardiovascular (CV) and neurological (Neuro) evaluation failed to reveal a respective disorder.

Methods: One hundred and twenty one pts (44 ± 18 years, 62 M) with 4 ± 3 SUE attacks per pt were prospectively studied over a mean follow-up period of 24 ± 7 months. All pts were initially assessed at baseline with a complete CV and Neuro examination including electrocardiography, echocardiography and a standard tilt table test protocol (TTT). The latter was at first performed without isoproterenol and only if negative, it was continued with the addition of intravenous isoproterenol. The pts were divided into Gr 1 (n = 49) and Gr 2 (n = 72) with a positive and a negative TTT response respectively. A positive TTT response, namely the reproduction of sync, was further classified into mixed (38), vasodepressor (9) or cardioinhibitory (2). B-blocker therapy was only prescribed to pts with a positive TTT, while all pts were asked to be seen at regular intervals or whenever symptoms recurred. Attention was paid to the development of new revealing cardiac or neurological manifestation during follow-up (FU).

Results. All but one pts remain alive. The Gr 1 pt who died suddenly at 18 months was found to have coronary artery disease after the mitral evaluation. Recurrent sync was observed in 6 of the 49 Gr 1 pts (14.3%) and in 11 of the 72 Gr 2 pts (15.2%). TTT stage at which sync occurred and the type of the associated vagotonic reaction observed, were not predictors of symptom recurrence among Gr 1 pts. Of the 40 Gr 1 pts asked to take long-term B-blocker therapy, only 15 pts were receiving the drug at 6 month FU. During FU, new cardiac or neurological disorder was established in 6 Gr 1 and 10 Gr 2 pts respectively.

Conclusions. Pts presenting with recurrent SUE have a favorable long-term prognosis irregardless of the TTT results. Sync recurrence is expected in a minority of these pts and cannot be predicted by the results of the baseline TTT. Although B-blockers therapy has been recommended to avoid recurrence, drug compliance is low in the setting. A persistent survey to reveal an unsuspected cardiac or neurological cause of sync is advised even if the initial evaluation is negative.

P2287 The outcome of electrophysiologic studies in non-invasively unexplained syncope can be predicted by a predefined score system

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Electrophysiologic studies (EPS) have been used to uncover the underlying arrhythmic mechanism in patients (pts) with non-invasively unexplained syncope (S). In 643 consecutive patients with S, an EPS was performed. The diagnostic yield of the EPS was 35% (223/643 pts had a positive EPS).

Aim of this study was to establish a score system which predicts best a positive electrophysiologic finding. By the use of a logistic regression model, history of injury during S ($p < 0.001$), ejection fraction $\leq 40\%$ ($p = 0.03$), and PR interval ≥ 200 ms ($p = 0.001$) were independent predictors of an abnormal EPS study. These 3 variables were entered into a score system. The max. score consisted of 3 points (injury = 1 point, EF $\leq 40\%$ = 1 point, PR interval $\geq$ 200 ms = 1 point)

Results:

Score	Sensitivity	Specificity	PPV	NPV
1	54%	75%	54%	75%
2	24%	97%	79%	70%
3	9%	99%	100%	67%

PPV/NPV = positive/negative predictive value

Conclusion 1. A predefined score using clinical and easily measurable variables is helpful in predicting a positive EPS result in pts with non-invasively unexplained syncope. 2. A score of ≥ 2 predicts a positive EPS response in more than 79% of pts with non-invasively unexplained syncope.

P2288 Risk stratification and management of patients with syncope of unknown aetiology: the role of a baseline electrocardiographic evaluation prior to electrophysiology testing

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Background: The electrophysiology testing (EPT) plays an important role in the risk stratification of patients (pts) with syncope of unknown etiology (SUE). However, the EPT value is limited by a non well defined diagnostic accuracy when applied indiscriminately to pts with SUE.

Methods: In this study, we examined the role of the surface 12 lead electrocardiogram (ECG) and of a 24 hour ECG recording (Holter) in the selection process of SUE pts most likely to benefit from EPT. One hundred pts (52 ± 11 years, M: 58) with SUE were divided into 3 groups according to the 12 lead ECG picture and the presence of either wide or narrow QRS complex tachycardia runs (TR) on Holter. Sixty four Gr-A pts had an abnormal ECG (conduction defects, bundle branch block, bradycardia, Q or delta wave), 16 Gr-B pts had a normal ECG with TR on Holter while the other 20 Gr-C pts had a normal ECG without TR on Holter. All pts underwent a comprehensive baseline EPT including intracardiac interval measurements, sinus and atrioventricular node function assessment as well as programmed atrial and ventricular stimulation.

Results: 51/64 (80%) Gr-A pts and 11/16 (68%) Gr-B pts had at least one abnormal EPT finding (p = NS). On the contrary, none of the 20 Gr-C pts had any abnormal finding on EPT. The most common abnormal EPT finding was the induction of sustained monomorphic ventricular tachycardia either on the basis of ischemic or dilated cardiomyopathy among 19 Gr-A pts (30%) or idiopathic among 7 Gr-B pts (43%) (p: NS). Sinus node dysfunction, serious conduction defects and rapidly conducting bypass tracts, were only observed in Gr-A pts.

Conclusions: The presence of either an abnormal ECG or TR on Holter at the non-invasive evaluation of the SUE pt, should be further studied with EPT in order to exclude important arrhythmic causes of syncope. If such an abbreviated noninvasive evaluation is non revealing, the EPT could be postponed.

P2289 Diagnostic yield of insertable loop recorder in patients with recurrent isolated syncope: International Study on Syncope of Uncertain Etiology (ISSUE)

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The International (Italy and Spain) Study on Syncope of Uncertain Origin (ISSUE) aims to evaluate the diagnostic yield of a manually activated insertable loop recorder (ILR) (Reveal, Medtronic Inc.) in different groups of patients (pts) with recurrent syncopes of uncertain etiology. Isolated syncope is defined as a syncope in pts with normal ECG and no other comorbidity in whom the mechanism remains unexplained after complete conventional investigations.

Since November 1997, ILR was implanted in 45 pts (23 females, 22 males, mean age 63 ± 17 years) with isolated syncope. The number of syncopes in the last 2 years was 8 ± 15 (median = 4) and the duration of symptoms was 5 ± 6 years (median = 3).

Conventional investigations which included Holter and telemetry in 98% pts, echocardiogram in 78% pts, tilt table testing in 100% pts, electrophysiological study in 78%, pts and carotid sinus massage in 100% pts, were all negative.

Results: After a mean follow-up period of 6.9 ± 4.1 months: 11 (24%) pts had at least one syncopal event, 3 (7%) pts had pre-syncope and 1 pt had angina.

Out of the 11 pts with syncope, a sinus arrest with an asystole was documented in 6 pts, normal sinus rhythm was recorded in 2 pts, and 3 pts were not able to activate the device. Out of the 3 pts with presyncope, a supraventricular tachycardia was recorded in 2 pts, and normal sinus rhythm in 1 pts. In the patient who had angina, ST-T changes were documented that were followed by an episode of ventricular fibrillation.

Conclusions: Syncopal recurrence in pts with isolated syncope during medium-term period follow-up is low. The most frequent finding in those pts was sinus arrest with asystole. Larger follow-up period is necessary.

P2290 In patients with unexplained syncope, implantable loop recorders give a greater diagnostic yeild than electrophysiological testing

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Patients with unexplained syncope can be difficult to evaluate. Between December 1997 and November 1998 29 patients were fitted with implantable subcutaneous loop recorders (ILRs) {Reveal™, Medtronic, Minneapolis, Mn}. The patients were aged 15–77 years (mean age 46 yrs), 20 were female. The time from first syncope to implant was 2–27 years, median 3 yrs. All patients presented with witnessed recurrent syncope (2–18 events, median 5 events). Before implantation all patients were investigated for arrhythmias with ambulatory ECG monitoring or a patient-activated ECG recorder, electrophysiology study, and tilt-table testing/carotid sinus massage. No abnormality was identified in any of the patients. Other cardiac investigations were echocardiography (29), cardiac catheterisation (6), cardiac MRI (2). 17 patients had no structural heart disease identified and 1 patient was known to have corrected Tetralogy of Fallot; 5 patients had trivial aortic valve disease or coronary disease and 3 patients had impaired LV function (EF 39%, 44% and 50% on LV angiography). Neurological investigations were negative (CT scan 3, EEG 6).

Results: All post implant syncopal episodes were documented by ILRs. To date 15 patients (52%) have activated their ILR during a syncopal episode to determine cardiac rhythm and rate during the episode. Activation of the ILR has occurred between 0.25 and 4 (median 1) months after implant (ILR life is approximately 16 months). The ILR recording has facilitated appropriate patient management in all these patients. Syncope has been correlated with cardiac arrhythmia in 8 patients (28%).

Conclusion: In this patient group, the diagnostic yield of an ILR is greater than that of electrophysiological study. In addition, documentation of normal sinus rhythm during syncope also aids patient management. ILRs should be used in place of electrophysiological study in the investigation of syncope of unknown cause in patients with no or trivial structural heart disease.

VENTRICULAR ARRHYTHMIAS AND SUDDEN DEATH

P2291 Predicting effect of d,l-sotalol on ventricular tachycardia inducibility from the response of RR variability to drug

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D, l-sotalol is an effective antiarrhythmic drug in the prevention of ventricular tachycardia (VT), but less effective than defibrillator for the prevention of sudden death. The purpose of the study was to report a rapid means for the identification of non-responders to d, l-sotalol in patients (pts) with spotaneous and inducible VT.

Methods: programmed ventricular stimulation and RR variability were studied in the control state (CS) and 10 days after treatment with 160 to 320 mg of d, l-sotalol in 36 pts, with VT.

Results: in 14 patients (group I) d, l-sotalol suppressed the VT inducibility. In 22 pts (group II) sustained VT remained inducible during d, l-sotalol treatment. The VT rate was slowed in 8 pts and unchanged or accelerated in 14 pts. At baseline, HRV was similar in both groups. During treatment with d, l-sotalol, the parameters reflecting the parasympathetic activity pNN50, rMSSD and HF increased in both groups: HF increased from 75 ± 68 to 146 ± 134 in group I ($p < 0.05$) and from 60 ± 49 to 125 ± 79 in group II ($p < 0.05$). Other parameters were unchanged in group I. In group II, the parameters associated with sympathetic activity (CV, LF/HF) decreased significantly: CV decreased from 13 ± 4 to 9 ± 2 ($p < 0.001$) and LF/HF from 4.7 ± 3 to 3 ± 2.02 ($p < 0.05$).

Conclusion: the betablocking effect of d, l-sotalol produced a significant improvement over control values in indices of parasympathetic tone in all the treated patients. But, only in non-responders to sotalol, the drug decreased the HRV parameters associated with sympathetic activity. Therefore, the effects of d, l-sotalol on heart rate variability could help to detect the non-responders to the drug and to avoid an electrophysiologic study.

P2292 Time delay stability of baroreflex feedback system and autonomic nervous system dysfunction

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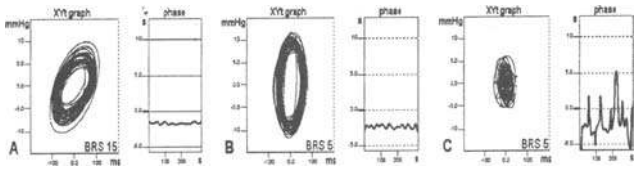
Dysfunction of the baroreflex feedback system (BFS) play important role in pathophysiology of sudden cardiac death (SCD). The aim of the study was the development of new methods enabling the analysis of BFS function in time. The BFS stability is analyzed especially in the graphic form: a) XYt graph (X axis for R-R intervals variability [ms], Y axis for SBP variability [in mm Hg] and t axis for time [s]); b) immediate phase between systolic blood pressure (SBP) and heart rate (HR).

Methods: 25 healthy volunteers, 15 patients with essential hypertension (EH), 23 patients with defibrillator (ICD) for documented ventricular tachycardia/fibrilation. Methodology: continual recording of blood pressure (Finapres), ECG, frequency and depth of breathing (original system ANNA1) for 5 minutes at rest and during the managed breathing frequency 6 × min.$^{-1}$ (deep breathing) and 20 × min.$^{-1}$ (shallow breathing).

Results: The best results were achieved at deep breathing (6 × mill.$^{-1}$). Typical findings of individual groups are shown in the Figures



A) Healthy individuals: a very stable value of the phase shift (approx. −1.7 s) and a symmetrical XYt graph represent very good characteristics of the BFS; B) patients with EH: higher phase shift (approx. −2.5 s), but still good BFS characteristics, which may have a connection with the so called re-setting of BFS.; C) patients with ICD, as far as their BRS can ever be evaluated (it was not possible in 13 patients: 6 exhibited an extremely low heart rate variability and 7 suffered numerous dysrythmias): total chaos in BFS (system unstable). The findings shown in Figure C did not occur in groups A and B. Patients in B and C exhibit the same baroreflex sensitivity (BRS) value of 5 ms × mm. Hg.$^{-1}$ However, although the BRS values of groups B and C are similar, their characteristics and prognosis vary widely.

Conclusion: The detection of the phase shift and XYt graph create a new technique of individual evaluation of autonomic nervous system dysfunction, especially in patients exhibiting the same values of decreased BRS.

P2293 Age and sudden cardiovascular death following myocardial infarction

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Sudden cardiac death (SCD) accounts for approximately 50% of all cardiovascular deaths after acute myocardial infarction (AMI). The aim of the present study was to assess the incidence and relative incidence of SCD following AMI in different groups of age.

Methods: We analyzed data from 6676 consecutive patients with AMI screened for the Trandolapril Cardiac Evaluation (TRACE) study. The screening period was 2 years and the follow-up 2–4 years. A central mortality committee classified the deaths of the randomized patients with respect to mode and cause of death. Deaths of non-randomized patients were classified applying similar criteria to information from the death certificate and the patient file. SCD was defined as cardiovascular death within one hour of onset of symptoms.

Results: Of the 5983 patients alive at discharge 1659 died during follow-up. Of these deaths 535 were classified as SCD and 726 as non-sudden cardiovascular. The patients were divided into 4 age groups (<56 y, 56–65 y, 66–75 y, >75 y). Cardiovascular death comprised 75–77% of all deaths in the four age groups. The 3-year mortality due to SCD was found to increase significantly with increasing age group; 4%, 7%, 11% and 16% respectively. However the incidence of SCD relative to death of all cause and to cardio- vascular death decreased significantly with increasing age group (44%, 40%, 33% and 27%) and (58%, 52%, 43% and 35%) respectively. No upper age-limit could be detected for SCD.

Conclusion: Increasing age is associated with increased risk of SCD following AMI, but decreased risk of SCD relative to all-cause and cardiovascular mortality, even if cardiovascular death comprises the same proportion of deaths in all age groups. Studies aiming at reducing SCD following AMI should consider this distribution of SCD in different groups of age in order to achieve the best relation between sensitivity and specificity.

P2294 Pause-dependent torsades de pointes in acquired long QT interval: long-term clinical outcome

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Long term prognostic of pause-dependent torsades de pointes (PD TDP) due to acquired long QT syndrome, a disorder that may lead to sudden death (SD), have not been fully investigated.

Methods. 93 pts (age 74.7 ± 9.5, 73 females) were included based on the association of 4 criteria: (1) ECG documented PD TDP; (2) prolonged QT interval and corrected QT using Bazett's formula (QTc); (3) long-short initiation sequence; (4) baseline bradycardia or drug or metabolite disturbance known to induce PDTP. After correction of all precipitating factors, absolute dispersions of QT and QTc were measured, as QTmax-QTmin, and QTc max-QTc min, respectively, before discharge. Long term clinical outcome was evaluated based on the occurrence of the following adverse events (AE): syncope (S), TDP recurrence (TDPR) and (SD). Pts were categorized according to presence or absence of AE (AE+, AE−).

Results. No difference was found between AE+ and AE− regarding age (72 ± 12 vs 75 ± 8), gender (78% vs 79% female), kaliemia (3.6 ± 0.9 vs 3.6 ± 0.6), heart rate (52 ± 12 vs 56 ± 15). During a mean follow-up of 27 ± 26 months (range 1–123 months) 49 events occurred in 27 pts: 18 S, 15 TDPR and 16 SD. Univariate analysis and multivariate analysis were performed on 6 variables using Cox model with two combined end points defined as following:

n = 93	AE		SD and/or TDPR	
	Uni.	Multi	Uni.	Multi
History of MI	0.11	–	0.18	–
Echo LVEF (%)	0.10	–	0.065	–
Mean QT (ms)	0.016	0.128	0.014	0.09
Mean QTc (ms)	0.26	–	0.12	–
QT max–QT min (ms)	0.018	0.12	0.037	0.1
QTc max–QTc min (ms)	0.0075	0.04	0.017	0.04

Conclusions: High rates of arrhythmic events are found in a population of PD TDP due to acquired long QT syndrome despite correction of initial precipating factors. QTc dispersion appears to be the only independent predictor of arrhythmic events at a long term follow-up.

P2295 Drug-induced torsade de pointes: the problem of cross-sensitivity

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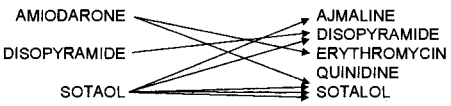
Torsade de pointes (TDP) is a form of potentially life-threatening ventricular tachyarrhythmia. It may occur in setting of a congenital long QT syndrome, however, most often it develops secondary to treatment with drugs prolonging repolarization, i.e. drugs which lengthen the cardiac action potential. Between 1989 and 1997, we have collected data from 91 patients (pts.) who developed drug-induced TDP. We could identify eight pts (9%) (8 females, mean age 58 ± 10 yrs.), who developed at least 2 episodes of TDP while being treated with different drugs. Time interval between the TDP episodes ranged from 7 days to 5 years. The QTc was measured 420 ± 59 ms$^{1/2}$ prior to drug treatment and increased to 540 ± 70 ms$^{1/2}$ at the time of TDP. There was no evidence for a congenital long QT syndrome in any of the pts. The type of cross-sensitivity (drugs on which pts. developed their TDP) is shown on the graph:



Conclusions: Thus, a potential cross-reactivity of proarrhythmic potential should be considered if another repolarization prolonging drug is to be administered to a patient who has already experienced drug-induced TDP. Therefor repolarization prolonging drugs should be completely avoided in these pts.

P2296 The central role of QT dispersion and left ventricular function as predictive factors of ventricular fibrillation in pause-dependent torsades de pointes associated with acquired long QT interval

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Predictive factors of ventricular fibrillation (VF) in pause-dependent torsades de pointes (PDTP) due to acquired long QT syndrome remain unknown.

Methods. 91 pts were included based on the association of 4 criteria: (1) ECG documented PTDP; (2) prolonged QT interval and corrected QT using Bazett's formula (QTc); (3) long-short initiation sequence; (4) baseline bradycardia or drug or metabolite disturbance known to induce PDTP. Pts were divided into 2 groups: PDTP with documented VF responsible of cardiac arrest treated by cardioversion (**GI**) and PDTP without cardiac arrest (**GII**) before admission or during the hospital staying with continuous monitoring. Absolute and relative dispersions of QT and QTc were measured as QTmax-QTmin, standard deviation (SD) of QT/QTmean, QTc max-QTc min, SD of QTc/QTc mean, respectively in the 12 lead standard ECG at admission.

Results. No difference was found between **GI** and **GII** regarding age (74.8 ± 8 vs 73.7 ± 9), gender (71.1 vs 77.3 female), kaliemia (3.6 ± 8 vs 3.5 ± 7), baseline heart rate (56.6 ± 15 vs 54.7 ± 15).

Univariate analysis	GI (n = 38)	GII (n = 53)	p
History of MI	12/38 (32%)	7/53 (13.2%)	p = 0.035
Echo LVEF (%)	43.9 ± 14	65 ± 9	p < 0.0001*
QT mean (ms)	591 ± 73	514 ± 78	p < 0.0001
QTc mean (ms)	563 ± 76	508 ± 9	p = 0.002
QT max-QT min (ms)	166 ± 56	84 ± 49	p < 0.0001
SD QT/QT mean (%)	9.9 ± 3.5	6.3 ± 3.2	p < 0.0001
QTc max-QTc min (ms)	158. ± 57	81 ± 44	p < 0.0001
SD QTc/QTc mean (%)	9.9 ± 3.6	6.2 ± 3.0	p < 0.0001*

*Stepwise regression analysis showed that LVEF and relative dispersion of QTc were the only independent factors predictive of VF.

Conclusions In pts with acquired conditions susceptible of inducing torsades de pointe, LV function and QTc relative dispersion should be carefully measured due to their peculiar value as risk factors of VF.

P2297 Gender-defined pattern of ventricular repolarisation: a possible explanation of predisposing to drug-induced torsades de pointes in women?

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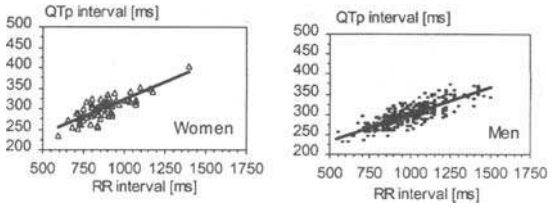
Gender-specific difference in ventricular repolarization duration and relation to cardiac cycle length may explain a higher frequency of drug-induced torsades de pointes in women. The characteristics of QT interval components have been suggested to be as important as the QT interval itself.

Methods: QT_{peak} (QT_p) and T_{peak}-T_{end} (T_pT_e) intervals and T_pT_e/QT_p ratio were evaluated in 1100 healthy volunteers (910 men, age 32 ± 11; 190 women, age 35 ± 15) by QT Guard software (Marquette Medical Systems). To assess gender-dependent relation between QT interval components and cardiac cycle length, the slopes of linear regressions of QT_p and T_pT_e intervals plotted against the corresponding RR interveal were compared.

Results: A significant gender-specific difference was observed in the duration of the early and late phases of repolarization. The QT_p interval was significantly longer in women than in men (300 ± 27 vs 291 ± 27 ms, p < 0.0003), whereas men had a significantly prolonged T_pT_e interval (93 ± 6 vs 89 ± 6 ms, p < 0.0001). Respectively, the T_pT_e/QT_p ratio was lower in women than in men (0.30 ± 0.03 vs 0.32 ± 0.03, p < 0.0001). In all subjects, QT_p/RR slopes were significantly steeper in women compared to men (0.1504 vs 0.1292; 0.1430 vs 0.1281; p < 0.05). Women had more labile relation between ventricular repolarisation and cycle length, i.e. increase in steepness of QT_p/RR and decrease in T_pT_e/RR with age, while the same relation in men remained stable.



Conclusion: A significant difference in QT interval components indicates gender-specific shapes of the ascending and descending T wave. Prolonged early phase of repolarization and a progressive increase in the QT_p interval at slower heart rate may facilitate drug-induced arrhythmias in women.

P2298 Verapamil suppresses early afterdepolarizations and torsade de pointes in an isolated rabbit heart model of LQT1 and LQT3

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Background: Torsade de pointes (TDP) is a potentially life-threatening arrhythmia typically seen in acquired QT-prolongation and the long QT-syndrome (LQTS). Early afterdepolarisations (EAD) and triggered activity are discussed as the underlying mechanism of TDP. As there is evidence that calcium channel blockers can suppress EAD we studied the effects of verapamil on a recently developed model for LQT1 (KCNQ1) and a new model for LQT3 (SCN5A).

Methods: In this model, the potassium channel blocker sotalol (S, 10 μM), and erythromycin (E, 150 μM) simulate LQT1, whereas veratradine (V, 0.5 μM) by inhibition of sodium channel inactivation mimics LQT3. The induction of TDP was studied in the presence of bradycardia and hypokalemia [n = 18].

Results: S, E, and V lead to a significant increase in QT-interval. During sinus rhythm no arryhthmias occurred irrespective of drug dose and potassium concentration. During bradycardia (AV block) and hypokalemia (1.5 μM) TDP and EAD reproducibly occurred. Monophasic action potentials demonstrated EAD in endocardial and only rarely in epicardial recordings. Although verapamil had no effect on QT-prolongation none of the S and E treated hearts demonstrated TPD in the presence of verapamil. EAD were also nearly completely suppressed. In V treated hearts verapamil also diminished the occurrence of TDP (only 2 out of 6 hearts showed TDP and EAD after administration of V).

Conclusion: Verapamil suppresses TDP and EAD in an experimental model for LQT3 and LQT1 without changing QT intervals. Thus, verapamil preserves the antiarrhythmic effect of action potential prolongation of class III agents so that it might be a valuable additional therapeutic option in patients with abnormal QT-prolongation at risk for TDP.

P2299 Does sports activity enhance the risk of sudden death in young people?

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Methods: We prospectively studied the incidence and the cause of sudden death (SD) in both competitive athletes and nonathletes (≤35 years) in the Veneto Region of Italy from January 1979 to June 1998 according to a specific clinico-pathologic protocol of investigation. During the study period the young population of the Veneto Region averaged 2,009,600 persons with a rate of participation in competitive athletics of 9.6%.

Results: There were 300 sudden deaths (0.85 per 100,000 persons per year): 55 among competitive athletes (1.6 per 100.000 per years) and 245 among nonathletes (0.77 per 100,000 per year). The estimated relative risk of SD among athletes as compared with nonathletes was 2.1 (95% confidence interval, 1.5 to 2.8; p < 0.0001). The Table shows the main causes of SD in young athletes vs nonathletes:

Cause	Total (N = 300)	Athletes (N = 55)	Nonathletes (N = 245)
Obstructive coronary artery disease	54 (18%)	10 (18%)	44 (18%)
Right ventricular cardiomyopathy	35 (12%)	13 (24%)*	22 (9.0%)
Myocarditis	32 (11%)	5 (9.0%)	27 (11%)
Mitral valve prolapse	27 (9.0%)	6 (11%)	21 (8.6%)
Disease of conduction system	24 (8.0%)	4 (7.2%)	20 (8.2%)
Hypertrophic cardiomyopathy	18 (6.0%)	1 (1.8%)	17 (6.9%)
Anomalous coronary artery origin	7 (2.3%)	6 (11%)**	1 (0.4%)
Other	103 (34%)	10 (18%)	93 (38%)

*$p = 0.005$; **$p < 0.001$ for the comparison with nonathletes*

Conclusions: The incidence of SD was increased 2.1 times in young competitive athletes as compared with nonathletes. Arrhythmogenic right ventricular cardiomyopathy and anomalous coronary artery origin were the only cardiovascular conditions significantly associated with SD during sports.

P2300 Idiopathic ventricular arrythmias or concealed cardiomyopathy?

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We compared clinical and electrophysiological features of idiopathic ventricular arrythmias (IVA) with myocardial histology in IVA of different QRS morphologies to define whether these arrhythmias represent the expression of specific myocardial diseases.

Methods: study involves 24 pts with monomorphic idiopathic ventricular tachycardia (VT) and ventricular extrasystoles (VE), in which echocardiography and heart catheterization failed to detect structural abnormalities of the heart. All patients underwent direct surgery during cardiopulmonary bypass for refractory IVA. Catheter electrophysiologic study with mapping and intraoperative epi- and endocardial mappings and intraoperative myocardial biopsy were performed in all cases. Biopsy specimens were obtained by direct excision of subendocardial and intramural layers of myocardium in arrhythmogenic sites and in distant areas of ventricles.

Results: 16 pts had VT or VE of left bundle branch block morphology (LBBB) and right axis deviation (RAD) and 8 pts had paroxysmal VT of right bundle branch block (RBBB) and left axis deviation (LAD). VTs with RBBB and LAD were inducible with programmed stimulation and sensitive to verapamil, His-deflection on VT was identifiable in 6 patients during 15–20 ms in QRS complex and arrhythmogenic sites were localised in the left ventricle in posteroapical part of interventricular septum (IVS). In patients with LBBB morphology and RAD different responses to electrical stimulation were observed and arrythmogenic sites were localised on IVS in right ventricular outflow. Biopsies of patients with LBBB and RAD showed histological features compatible with arrhythmogenic right ventricular displasia (ARVD) – interstitial adipose infiltration with fibrosis and myocyte hypertrophy, which were confined to the outflow part of IVS. In patients with VT of RBBB and LAD changes consistent with dilated cardiomyopathy were involving both ventricles.

In conclusion, we suggest that concealed arrythmogenic cardiomyopathy is an aetiologic basis for refractory IVA. Concealed localized myopathic process of ARVD is the most common cause for IVA with LBBB and RAD and latent diffuse myopathic process (possibly initial stage of dilated cardiomyopathy) – for IVA with RBBB and LAD.

P2301 A 10 year follow-up study of elite athletes with frequent and complex ventricular arrhythmias

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Few long term follow-up studies are conducted in subjects with frequent and complex ventricular arrhythmias with apparently "normal" hearts, these studies usually show a benign prognosis. Up to date no studies of this kind have been conducted in athletes. Nevertheless in some cases sudden death can be the only dramatic sign of an underlying silent cardiomyopathy and frequently occurs during exercise. Therefore, early identification of myocardial diseases in athletes with ventricular arrhythmias is the main goal of a pre-participation cardiovascular screening.

Methods: From 1988 to 1998 we studied a group of 250 athletes referred to our Institute for ventricular arrhythmias. From this group we selected a subgroup of 82 elite athletes with frequent and complex ventricular arrhythmias (Group A – mean age 25.2 yr.) The inclusion criterium was a 24-hour Holter monitoring showing the presence of >2000 ventricular ectopic beats and >15 ventricular couplets. These athletes were compared to a control group of 70 athletes (mean age 23.8 yr.), with < 10 VEB's in the 24 Hours (Group B). All athletes underwent a cardiovascular screening including physical examination, routine blood test, chest X-rays, resting and stress-test ecg, color-Doppler echocardiogram, 24-hour Holter monitoring and time-domain signal-averaged ECG. Furthermore, 28 athletes (Group A) underwent a cardiac magnetic resonance imaging, 21 a cardionuclear scintigraphy, 9 transesophageal echocardiography, 5 a myocardial biopsy and 19 an endocavitary electrophysiologic study.

Results: Twenty-eight athletes of Group A had an underlying heart disease (34.1%) versus 1/70 (1.4%) of the control athletes (Group B – $p < 0.0001$). In particular, 4 had right ventricular arrhythmogenic dysplasia, 5 myocarditis, 9 abnormal dilatation of the left ventricle, 8 mitral valve prolapse, 1 atrial septum defect and 1 bicuspid aortic valve. Our ten years follow-up period shows until now a favourable outcome and no cases of sudden death.

Conclusion: This study shows the usefulness of an extensive cardiovascular pre-participation screening in identifying subclinical heart diseases in athletes with frequent and complex ventricular arrhythmias and the necessity of a prolonged follow-up period to monitor the arrhythmia and eventual evolution of the underlying cardiopathy. However up to date these arrhythmic athletes have a similar prognosis to those without ventricular arrhythmias

P2302 Clinical profile of congenital coronary artery anomalies with origin from the wrong aortic sinus leading to sudden death in young competitive athletes

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Congenital coronary artery anomalies with origin from the wrong aortic sinus are not uncommonly associated with sudden death (SD) in young athletes, with these catastrophic events probably provoked by myocardial ischemia. Such coronary anomalies are rarely identified during life, often because of insufficient clinical suspicion. However, they are amenable to surgical treatment, emphasizing the importance of timely clinical identification.

Because there is a paucity of data available characterizing the clinical profile of these coronary malformations, we reviewed 2 large registries of SDs in young competitive athletes, recorded consecutively in the US and Italy. We assembled 27 SDs in young athletes, identified solely at autopsy as due to either left main coronary artery from the right aortic sinus (n = 23) or right coronary artery from the left sinus (n = 4). All athletes died during (n = 25) or immediately after (n = 2) intense exertion on the athletic field. Of the 27 athletes, 15 (55%) had no clinical manifestations or testing during life. In the remaining 12 (45%) certain clinical data were available. Ages were 11–32 years (mean 16 ± 7). Premonitory symptoms had occurred in 10, including syncope in 4 (exertional in 3, recurrent in 2; occurring 3–24 months prior to SD) and chest pain in 5 (exertional in 3, all single episodes; occurring ≤ 24 months prior to SD). All cardiovascular testing was within normal limits, including basal 12-lead ECG (in 9/9), stress ECG with maximal exercise (in 6/6) and left ventricular wall motion and cardiac dimensions by echocardiography (in 2/2).

In conclusion: 1) standard testing with ECG under resting or exercise conditions is unlikely to provide clinical evidence of myocardial ischemia and would not be reliable screening tests in large athletic populations; 2) premonitory cardiac symptoms not uncommonly occurred shortly before SD, suggesting that a history of exertional syncope or chest pain requires exclusion of this anomaly; 3) a high index of clinical suspicion is crucial for the in vivo identification of these anomalies in physically active individuals.

P2303 Does the acceleration of ventricular fibrillation imply an increase in the complexity of arrhythmia?

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With the purpose of determining whether the acceleration of ventricle fibrillation (VF) implies an increase in the complexity of the arrhythmia, 12 Langendorff-perfused rabbit hearts were used to analyze the epicardial activation maps obtained during VF using a multiple electrode (121 unipolar electrodes, interelectrode distance = 1 mm) under control conditions, following myocardial stretching (intraventricular balloon), after administering verapamil (Vp, 0.2–0.8 μmol), and upon adding myocardial stretch to Vp perfusion.

Thirty seconds after VF induction by overdriving, and maintaining myocardial perfusion, activation maps were obtained at 100-ms intervals over a 2-s period, classifying the results from lesser to greater complexity (I = one wavelet without block lines, II = two simultaneous wavelets with block lines, III = three or more wavelets with multiple block lines).

Both stretching and Vp accelerate the fibrillatory process (median VV interval: control = 68 ± 6 ms, stretch = 49 ± 14 ms, $p < 0.001$; Vp = 51 ± 5 ms, $p < 0.001$ vs control). Stretch-induced acceleration causes a significant variation in the types of maps, with type III increments and type I and II decrements (control: I = 19%, II = 49%, III = 32%; stretch: I = 8%, II = 33%. III = 59%, $p < 0.001$), whereas Vp-induced acceleration is accompanied by type III decrements and type I and II increments (Vp: I = 24%, II = 58%, III = 18%, $p < 0.001$). On applying stretch during Vp perfusion, the fibrillatory process is not accelerated to a greater degree than with Vp alone (stretch + Vp: median of the VV intervals = 47 ± 6 ms); however, type I and II decrements and type III increments are recorded, but with percentages similar to control.

Conclusions: VF acceleration does not always imply an increase in the complexity of arrhythmia. Myocardial stretching and Vp accelerate the fibrillatory process; however, while stretching increases the complexity of arrhythmia, Vp reduces it. The effects upon arrhythmia complexity are in turn countered when stretching is applied under the action of Vp.

P2304 The cardioselective ATP-sensitive potassium channel antagonist HMR 1883 attentuates T wave changes and prevents ventricular fibrillation induced by myocardial ischaemia

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The activation of ATP-sensitive potassium channels during myocardial ischemia leads to potassium efflux, reductions in action potential duration, dispersion of repolarization and ventricular fibrillation. Drugs that inactivate these channels should attenuate these ischemic changes and thereby prevent ventriclar fibrillation. However, non-selective ATP-sensitve potassium channel antagonists have been reported to reduce coronary blood flow and to depress cardiac function. Furthermore, these agents can also alter pancreatic channels promoting insulin release and hypoglycemia. A cardioselective ATP-sensitive potassium channel antagonist, HMR 1883, 1-[[5-[2-(5-chloro-o-ansamido)ethyl]-2-methoxyphenyl]sulfonyl]-3-methylthiourea, may offer cardioprotection without the untoward actions of existing drugs. To test this hypothesis, ventricular fibrillation was induced in 13 dogs with healed myocardial infarctions by a 2 minute coronary occlusion during the last minute of exercise. On subsequent days, the exercise plus ischemia test was repeated after either HMR 1883 (3.0 mg/kg i.v.) or glibenclamide (1.0 mg/kg i.v., n = 7). Ischemia elicited several significant (ANOVA $p < 0.01$) changes including: reductions in refractory period (control 121 ± 2, occlusion 115 ± 2 ms), ST-segment depression (−3.3 ± 0.7 mm), dispersion of repolarization as measured by the descending portion of the T wave (Tpeak-Tend, control 34 ± 3, occlusion 40 ± 6 ms) and T wave oscillations (n = 9). HMR 1883 pretreatment prevented the reduction in refractory period (HMR 122 ± 2, occlusion 121 ± 3 ms), the increase in repolarization (Tpeak-Tend, HMR 35 ± 2, occlusion 29 ± 3 ms), attentuated the ST-depression (−1.8 ± 0.4 mm) and suppressed T wave oscillations (n = 6). This drug also prevented VF in 11 of 13 animals ($p < 0.001$). Interestingly, HMR 1883 did not alter the ischemic T wave changes in the 2 animals that were not protected. In a similar manner, glibenclamide also reduced these ischemic changes and protected 6 of 7 animals ($p < 0.01$). However, in contrast to HMR 1883, this drug also reduced blood glucose, coronary blood flow and left ventricular dp/dt maximum. These data suggest that the cardioselective ATP-sensitive potassium channel antagonist HMR 1883 can reduce ischemic changes in refractory period and repolarization, thereby protecting against ventricular fibrillation without major hemodynamic actions or altering blood glucose.

P2305 Nuclear morphometry of the myocardial cells as a diagnostic tool in cases of sudden death due to acute myocardial infarction

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Sudden cardiac death (SCD) due to acute myocardial infarction (AMI) is one of the leading causes of death. However, in a significant percentage of individuals who die suddenly, no indication of AMI is found during post-mortem examination, especially when the time interval between symptoms appearance and death is short. In the present study, we have examined whether nuclear morphometry (NM) could differentiate individuals dying of AMI within 1 our from symptoms onset, from those dying of other non-cardiac causes.

Methods: Our study population consisted of 20 individuals (group A), who died suddenly, within 1 hour (mean time 35 ± 13 min.), of a clinically recognized (by means of the symptoms and the presence of ST segment elevation) AMI, before death. In addition, in the post mortem examination, acute coronary thrombosis was identified in all cases as the cause of death. In all individuals, in not fewer than 10 paraffin embedded and sectioned tissue blocks of full thickness left ventricular wall (sampled from areas supplied by the occluded coronary artery), 100 nuclei were studied. In the above nuclei, we have evaluated certain morphometric parameters, such as, minimum, maximum, mean and standard deviation perimeter and area. The aforementioned nuclear parameters were compared with those of a control population (group B), in which 20 individuals whose sudden death was caused by traffic accidents, were included. All individuals of group B were found to have coronary arteries free of significant stenosis and their left ventricular samples were obtained in a spiral stepwise manner from the apex to the base. All measurements were performed at a ×600 magnification, using a microscope connected to an IBM compatible PC and to a high-resolution monitor. The program used was the commercially available Image Pro II processing system. Statistical analysis was done using Student's t-test, Mann-Whitney nonparametric method and multivariate analysis by means of the discriminant analysis method, both in a linear and a stepwise approach. Statistical significance of the mean nuclear perimeter (MNP) cut-off point was calculated by means of x^2.

Results: Except for the minimum area, we have found a statistically significant difference of all parameters between the two groups, with the values of group A exceeding the corresponding values of group B. With stepwise discriminant analysis method, the MNP was selected as the best predictor of cardiac death. MNP achieved a correct reclassification percentage (based on Fisher's linear discriminant function) of 92.5% (85% and 100% for groups A and B respectively). Moreover, by applying the cutoff of 172 μm between the 2 groups for the MNP, we could identify the individuals who died suddenly of AMI with a specificity of 100% and sensitivity 85%, ($p < 0.001$).

In conclusion, (MNP) could be applied in cases of sudden death when AMI is suspected but cannot be proved with the available methods. In the above cases, when MNP of the myocardial cells exceeds 172 μm, AMI should be considered as the most probable cause of death.

P2306 Is there an electrogram pattern predictive of successful application during transthoracic RF epicardial catheter ablation to treat ventricular tachycardia?

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Transthoracic epicardial RF catheter ablation is being utilized to treat post-MI and Chagasic VT. However, entrainment maneuvers can not be performed to define whether a site is part of the circuit since the epicardial stimulation threshold is too high in most patients. The aim of this study was to define whether there are epicardial electrograms patterns predictive of ablation success.

Methods: A regular ablation catheter was introduced into the pericardial space by transthoracic puncture during 21 procedures in 19 consecutive patients. The electrograms obtained from 239 sites were analyzed and defined as mid-diastolic potentials, continuous activity and early signal. A 60° C pulse was delivered for 10 seconds at each site. Electrogram duration and precocity were determined for each application.

Results: VT was interrupted at 47 of 239 sites (19%). At 57 sites, electrograms were defined as mid-diastolic signals (24%). VT interruption occurred in 5 sites (9%) whereas 52 applications did not interrupt VT. Duration and precocity did not differ between successful and not successful applications. Electrograms were defined as continuous electrical activity at 27 sites (11%) and interruption occurred in 8 of them (30%). An early electrogram was found in 155 sites (65%). RF interrupted VT in 34 sites (22%) but electrogram duration (181 ± 72 ms versus 177 ± 68 ms) and precocity (107 ± 47 ms versus 94 ± 44 ms) did not differ among these sites.

Conclusion: Electrogram pattern is not helpful in defining a site for a successful epicardial RF application. Although safe, epicardial catheter ablation based on "burning-mapping" is not ideal because this approach is only effective in 20% of the sites.

P2307 Long ablation cycles result in increased depth of multi-electrode ablation lesions using pulsed radiofrequency energy

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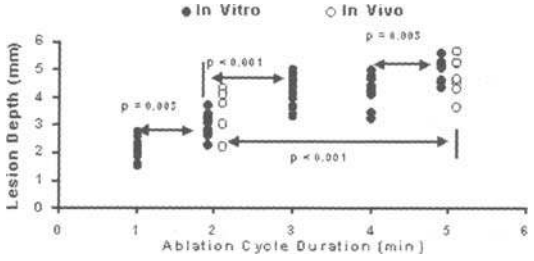
Ablation cycles of 60–120 seconds are typically used during RF ablation with a single distal tip electrode. It has been assumed that similar ablation durations would suffice for multiple electrode RF ablation. However, multiple electrode RF ablation creates a larger heat pool in the tissue than distal tip ablation, and may require longer ablation cycles to achieve the maximum steady-state tissue damage.

Methods: A RF controller (Bard) that rapidly distributes sequential pulses of RF energy in 5 ms "packets" to up to 4 electrodes under temperature (T) control was used to create linear lesions in vitro and in vivo. A quad-polar ablation catheter (Bard)with four 4 mm electrodes, 3 mm spacing, and T monitoring and control of each electrode was used for the ablation of approximately 4 cm^3 peices of bovine myocardium in bovine blood at a target T of 60°C with 50 W of power. The electrode T, energy delivered to electrodes (E), lesion length (LL), and depth (LD) were measured during ablations at five ablation cycle durations (AC) of 1, 2, 3, 4 and 5 minutes. A two and 5-minute ablation were performed in the left ventricle of 10 goats. Paired comparisons of the in vivo lesions were performed.

Results: All lesions were continuous. In vitro, all electrodes maintained 60°C for the full AC. LD increased with AC (chart) and was directly proportional to E during the ablation ($R = 0.89$, $p < 0.01$). LL was approximately 28 mm in all cases. In vivo, 2 min vs. 5 min AC LD was 3.5 ± 0.7 mm vs. 4.8 ± 0.7 mm ($p < 0.01$), with similar LL (20 ± 8 vs. 24 ± 8 mm) and T (46 ± 5 vs. 47 ± 4°C). The E increased from 9.6 ± 2.6 to 18.9 ± 7.2 kJ ($p < 0.03$).



Lesion Depth vs. Ablation Cycle Duration.

Conclusion: Lesion depth of ablations from multiple electrodes using rapid sequential pulsed RF energy increases with increasing ablation duration up to 5 min.

P2308 Therapy of slow ventricular tachycardias: a substantial and increasing problem in patients with implantable cardioverter-defibrillator

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The therapy of slow ventricular tachycardias (SLVT) ≤ 160 beats per minute (bpm) in patients (pts) with implantable cardioverter-defibrillator (ICD) is an increasing problem in the follow-up (FU) of these pts. The aim of this study was to evaluate the frequency, development and therapy of these SLVT.

Results: In 294 pts with ICDs of the third generation, 56 pts (8 pts DCM, 48 pts CAD, LVEF 37 ± 14%, echocardiographic LVED 67 ± 8 mm) were with SLVT (138 ± 17 (110–175) bpm). At the time of implantation SLVT was known in 48 pts (48/294 16%) and 8 pts (3%) developed unknown SLVT after 19 ± 7 (6–41) months. In 23 of the 48 pts SLVT were detected during FU (mean 7 ± 7; 1–29 months), 15 pts received antiarrhythmic agents (AA): 9 amiodarone, 2 d, 1-sotalol, 2 mexiletine, 1 flecainide. VT-frequency decreased about 18 ± 7 bpm in 13 of these 23 pts (56%), possibly due to a newly started AA-therapy in 7 pts (3 amiodarone, 2 d, 1-sotalol, 1 mexilitine, 1 flecainide). Unknown SLVTs that were not detected by the ICD occurred in 8 pts, 4 of these pts were on AA-therapy since the implantation, 4 had no AA. Detected SLVT (cycle length 400–600 msec, duration 75 ± 20 sec, onset and stability programmed) were effectively terminated by antitachycardia pacing in 87% of episodes (90% pts), and in 13% by shock. Inadaquate therapy was started in 4 pts due to sinus tachycardia. Neither the slowing of VT-cycle length nor the appearance of new SLVT correlated with worsening of the LV-function.

Conclusion: The incidence of inadequate therapy, in pts with SLVT (12%) equales to the whole ICD collective (11%) with Vts > 160 bpm, if detection-duration is sufficiently long with simultanous programming of onset and stability. In 56% of the pts, the frequency of known SLVT decreases during FU, this is accompanied by a new AA-therapy in 54%, but occurs spontaneously in 46% without a change of LV-function. These features of SLVTS should be taken into account during the initial programming of ICDs.

P2309 Open-chest radiofrequency ablation with the "showerhead" catheter: experimental experience with a new, limited surgical approach to the treatment of ventricular tachycardia

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Conventional closed-chest radiofrequency current ablation (RFCA) of ventricular tachycardia (VT) has met limited success due to insufficient mapping and lesion size (LS). VT surgery is associated with high morbidity and mortality due to ventriculotomy and cardiopulmonary bypass (CPB). We developed a mapping and ablation tool (AT) with a steerable shaft (5.2 mm diameter (D)) and an electrode (E) head (14.3 mm D, Figure) carrying 16 mapping/ablation E's (3 mm D each) for open-chest RFCA of VT. Saline irrigation was provided via 5 channels between the E's. A customized software allowed on-line color-coded visualization of the endocardial activation sequence. In 6 pigs (German landrace) we investigated the feasibility of the AT for left ventricular (LV) mapping and RFCA using transmitral LV access after left atrial incision without CPB. Mapping was performed under echocardiographic (echo) guidance and with arterial/left atrial pressure recording. The origin of 2 focal LV discharge sites (posterior and anterior wall) achieved by epicardial pacing was mapped and L's created by consecutive RFCAs. LS was macroscopically assessed after tetrazolium blue staining.

Results: There were no signs of hemodynamic compromise in any animal and only mild mitral regurgitation in echo. Mean L size was: length 6.7 ± 1.8, width 5.1 ± 2.5, depth 2.6 ± 0.9 mm and volume 48.2 ± 37.3 mm^3. All lesions were within 5 mm radius of the pacing E.

Conclusion: LV mapping with this new "shower-head" AT is feasible and large LS may be achieved. Further studies are needed to evaluate this approach in RFCA of macroreentrant VT.

P2310 QT parameters do not predict recurrences of ventricular arrhythmias after defibrillator implantation in patients with coronary artery disease and life-threatening ventricular arrhythmias

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QT dispersion (Qtd, the difference between the maximum and the minimum QT duration of the surface ECG) is believed to reflect regional differences in repolarisation, and has been proposed as a risk factor for the development of ventricular arrhythmias (VA) after acute myocardial infarction (AMI). We evaluated the prognostic value of QT parameters for recurrences of VA after defibrillator (ICD) implantation in patients with coronary artery disease (CAD) and VA.

Methods: At the moment of ICD implantation, we studied QT parameters QTmax, QTcmax and QTd) derived from a simultaneous 12 lead ECG (50 mm/sec) in 57 patients (55 men, age 66 ± 9 years) with CAD (mean vessel disease score 2.3 ± 0.7 and a mean ejection fraction 34 ± 13%) and life-threatening VA. Patients were followed during 582 ± 301 days for recurrences of VA treated by ICD antitachycardia pacing and/or shock.

Results: During follow-up 28 patients (49%, group I) had recurrences of VA requiring ICD treatment and 29 patients (51%, group II) had no recurrences. Mean values ± SD for the QT parameters are given in the table for the whole group and groups I and II. No significant differences were noted between groups I and II.

	Total group	Group I	Group II	P-value
QTmax (ms)	439 ± 50	437 ± 65	441 ± 39	NS
QTcmax (ms)	475 ± 46	472 ± 51	477 ± 43	NS
QTd (ms)	45 ± 19	45 ± 23	45 ± 15	NS

Conclusions: QT parameters (including QTmax, QTcmax and QTd) do not predict recurrences of VA in patients with CAD and ICD implants.

P2311 A new approach to elucidate the mechanism of wide QRS complex tachycardia through the analysis of the first postpacing interval following entrainment by right ventricular apex stimulation

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Background: Definitive criteria – based on the recording of a His or bundle-branch electrogram- have been established for the diagnosis of bundle-branch reentry (BBR) ventricular tachycardia (BBR-VT). However, the use of these criteria is limited because catheter instability, concealment by the perihisian ventricular activation, or severe His-Purkinje disease, may make difficult and time consuming the recording of the His or right bundle branch electrogram during tachycardia. Since the first postpacing interval after entrainment (FPI) has been correlated with the distance from the pacing site to the reentrant circuit, we postulated that BBR-VT entrainment by pacing from the right ventricular apex (RVa) – the normal area of insertion of the right bundle branch- should result in an FPI close to the tachycardia cycle length (TCL) and that this may differentiate BBR-VT from other mechanisms of wide QRS complex tachycardia with VA dissociation, such as myocardial reentrant ventricular tachycardia (MR-VT) or AV nodal reentrant tachycardia (AVNR-T).

Methods: Transient entrainment by pacing from the RVa was attempted in 9 consecutive patients with 13 BBR-VT, 24 consecutive patients with 26 MR-VT and 34 consecutive patients with 34AVNR-T. Pacing cycle length was 10–30 ms shorter than the TCL. Measurements were done at 200 mm/sec with electronic callipers.

Results:

	BBR-VT	MR-VT	AVNR-TV
TCL (ms)	286 ± 36	289 ± 50	341 ± 58*
FPI – TCL (ms)	5 ± 15**	88 ± 44**	149 ± 34**
FPI – TCL range (ms)	−21/+26	+36/+178	+100/+228

Anova, *p < 0.02, **p < 0.0001

Conclusions: An FPI less than 30 ms longer than the TCL, following entrainment by RVa stimulation, makes unlikely MR-VT or AVNR-T and suggests a BBR mechanism. This finding should lead to further investigation to establish or rule out the BBR-VT diagnosis using standard criteria. On the other hand, an FPI more than 30 ms longer than the TCL suggests tachycardia mechanisms other than BBR.

P2312 Relation between genetic CTG expansion and development of sustained ventricular arrhythmias in myotonic dystrophy

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Background: Sustained ventricular arrhythmias (SVA) have been documented and linked to the high incidence of sudden death seen in patients with myotonic dystrophy (MD). A significant relationship has been demonstrated between an abnormally high number of repetitions of the cytosine-thymine-guanine (CTG) sequence in locus 19q13.3 and a high density of ventricular ectopy. This finding suggests that the size of the expansion is a predictor for the development of SVA in MD. However, no studies have been reported addressing the size of the expansion in patients with both MD and SVA.

Methods: 5 patients (39 ± 7 years, 4 male) with MD, non-significant structural heart disease, and SVA, underwent quantification of the CTG expansion. All patients had at least one sustained monomorphic ventricular tachycardia, both clinically documented and induced by programmed stimulation. All underwent blood DNA amplification by PCR and CTG expansion analysis by Southern electrophoresis. The results were compared with those obtained from a control group of 25 consecutive patients (40 ± 11 years, 13 male) with MD and non-clinically documented or suspected SVA. There were no significant clinical differences between the two groups.

Results:

	n	CTG repeats
SVA	5	1,120 ± 698
No SVA	25	559 ± 324
p		<0.01

Conclusions: The size of CTG expansion in locus 19q13.3 is a predictor for the development of SVA in patients with MD.

P2313 Prediction of pre-discharge cognitive deficits in cardiac arrest survivors using serum protein s-100 and neuron specific enolase

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Background: Over 30% of out-of-hospital cardiac arrest (OHCA) survivors suffer significant memory deficit, mediated by hypoxic brain injury during cardiac arrest. Brain enzyme assays can predict survival after stroke but have not been evaluated as predictors of functional deficits in OHCA survivors. This study evaluates serum protein S-100 and neuron specific enolase (NSE) as markers of brain injury after OHCA.

Methods: Of 66 consecutive early OHCA survivors, 34 survived to discharge. 32 were assessed with the Rivermead Behavioural Memory Test (RBMT), a test of episodic long term memory (maximum score 24 points). Serum was obtained from OHCA survivors on admission, at 24 and 72 hours. We compared NSE and S-100 levels at each time in those with severe memory impairment (Group A, RBMT < 16) and without (Group B, RBMT≥16). We calculated correlation coefficients for enzyme levels versus RBMT scores.

Results: S-100 level at 24 hours was the best predictor of memory impairment at discharge, mean (95%CI) Group A: 0.24 (0.15–0.33). Group B: 0.08 (0.05–0.11), p = 0.004. Admission and 72 hour S-100, and all NSE estimates, were poorer predictors. Correlation values are shown in table.

S100 and NSE levels vs RBMT scores

Correlations vs RBMT	r	r^2	p value
S100 24 hours (μg/l)	−0.52	0.27	0.009
NSE 24 hours (ng/ml)	−0.36	0.13	0.05

Conclusions: Estimation of serum levels NSE and S-100 24 hours after resuscitation predict memory function after OHCA. A 24 hour S100 value >0.15 μg/l was highly predictive of memory impairment, and may be a useful index for planning rehabilitation.

P2314 Public cardiopulmonary resuscitation training program and its effect in a country area of Japan: Iwate CPR propagating Committee

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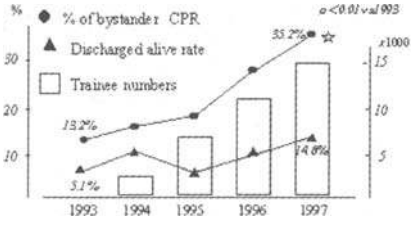
Incidence of cardiac arrest due to ischemic heart disease in Japan was less than that in USA or Europe. In Iwate prefecture, a country area of Japan, 300 km north-east from Tokyo, 1.4 million population, 300 nontraumatic out-of-hospital cardiac arrests are occurring every year. EMS system responded for the victims within seven minutes, but survivor from nontraumatic out-of-hospital cardiac arrest was 5 percents. Iwate CPR Committee has founded on from 1993, including Iwate Medical Association, Iwate Red Cross, Iwate Fire Department, Iwate Commercial Association etc. First Action: CPR instructor were cultivated with the same skill and teaching method. Second Action: Pamphlets and videotapes were made for giving lessons in CPR technique and importance of early bystander CPR. Third Action: On-TV campaign for gathering people to the training program was performed. By 1997, 2,000 CPR instructors were nurtured, 150,000 persons (10 percents of Iwate prefectual population) were trained on the CPR program during these four years. In a year, about 80 victims of out-of-hospital cardiac arrest had been transported to our Iwate Emergency Medical Center, and only 11 (13.2%)of them underwent bystander CPR in 1993. In 1997, the ratio of bystander CPR improved significantly up to 35.2% (p < 0.01, vs.1993).



Effect of CPR Spreading.

This ratio was more than twice average in Japan. The ratio of patients who were discharged alive from hospital increased from 5.1% to 14.6%, but it was not statistically significant. This CPR propagating program should be continued.

P2315 Evaluation of serum protein S-100 and neuron specific enolase as predictors of death after resuscitated cardiac arrest

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Background: Prediction of outcome after resuscitated out-of-hospital cardiac arrest (OHCA) is difficult. This study evaluates the prognostic value of protein S100 and neuron specific enolase (NSE) after OHCA.

Methods: Serum was obtained from 66 early OHCA survivors on admission (adm) and at 24 and 72 hours. NSE and S100 were measured using radioimmunoassay. We compared median (range) enzyme levels at each time point in the survivors (n = 34) and in those who died in hospital (n = 32). Receiver operating characteristic plots were derived and optimal cut-off values obtained for predicting in-hospital death.

Results: summarised in table.

NSE and S-100 levels

	Survived	Died	p value
S100 adm (μg/l)	0.67 [0.01–6.70]	2.02 [0.06–12.30]	p<0.001
S100 24 hrs (μg/l)	0.19 [0.00–0.58]	1.11 [0.05–9.20]	p<0.001
S100 72 hrs (μg/l)	0.11 [0.00–0.44]	0.81 [0.02–3.00]	p<0.001
NSE adm (ng/ml)	16.6 [6.7–40.7]	24.1 [7.4–56.1]	p<0.001
NSE 24 hrs (ng/ml)	17.5 [9.2–70.9]	49.9 [12.9–170.0]	p<0.001
NSE 72 hrs (ng/ml)	13.8 [6.5–59.9]	53.8 [11.5–116.5]	p = 0.03

Conclusions: Estimation of serum NSE and S100 24 hours after resuscitation helps predict outcome after OHCA. Although no cut off values for either enzyme at any time point gave good combined sensitivity and specificity, 24 hour cut-off values of 0.6 μg/l (S100) and 35 ng/ml (NSE) had 100% and 95% specificity respectively for in-hospital death and are likely to be clinically useful indices for planning management and counselling patients' relatives.

P2316 Cardiac arrest and cerebral blood flow autoregulation

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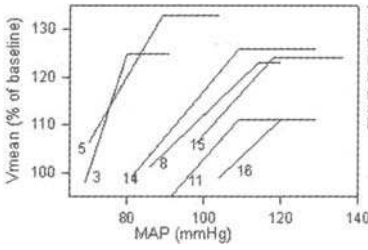
Introduction: Normally cerebral blood flow(CBF) is kept constant within wide limits of mean arterial pressure(MAP; 60–150 mmHg) due to autoregulation. We determined the lower limit of cerebral autoregulation within 12 hours after cardiac resuscitation.

Methods: Six healthy males (median age 30 yrs., range 21–61) and 18 patients (3 females, age 69 yrs. (42–81)) were included. Changes in CBF as determined by transcranial Doppler mean flow velocity (Vmean) in the middle cerebral artery was measured during a stepwise rise in MAP induced by infusion of norepinephrine. MAP was plotted against the Vmean and a lower limit of autoregulation was identified by double regression analysis based on least square measurements. $PaCO_2$ was kept at 36 mmHg (22–60) during the study.

Results: MAP was increased from 80 (72–90) to 112 mmHg (110–124) in the volunteers and from 78 (46–118) to 106 mmHg (60–149) in the patients. The lower limit of cerebral autoregulation was 76 mmHg (41–79) in the volunteers, and 109 mmHg (80–120) in seven (figure) of twelve patients with preserved autoregulation ($p < 0.01$), in whom a lower limit of autoregulation could be identified. The remaining 6 patients had impaired autoregulation i.e. a linear correlation between Vmean and MAP. There was no difference in baseline MAP, Vmean, $PaCO_2$ or duration of cardiac arrest between the two groups of patients or between the two subgroups of patients with preserved autoregulation.



The lower limit of cerebral autoregulation calculated by transcranial Doppler ultrasonography mean flow velocity (Vmean) in the middle cerebral artery in the seven patients with right-shifted autoregulation curve. Numbers indicate patients.

Conclusion: In the acute phase after cardiac arrest cerebral autoregulation is impaired or right-shifted in a majority of patients. Our finding indicates that MAP should be kept at a higher level than commonly accepted in patients resuscitated from cardiac arrest in order to secure cerebral perfusion.

P2317 Immediate coronay intervention and mild hypothermia in comatose survivors of out-of-hospital ventricular fibrillation improve patient outcome

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A good recovery rate of patients with out-of-hospital cardiac arrest is still low. There is evidence that coronary reperfusion therapy for acute myocardial infarction (MI) reduce the mortality and hypothermia therapy for traumatic brain injury improve the neurologic outcome. Consequently, we performed immediate coronary angiography plus intervention and mild hypothermia when indicated in comatose survivors of out-of-hospital ventricular fibrillation (Vf).

Methods: This study was performed in sixteen consecutive patients who had cardiac cause of Vf and met the indication criteria of mild hypothermia. Immediate coronary angiography was performed in patients who had return of spontaneous circulation (ROSC) by standard advanced cardiac life support and coronary intervention was attempted in patients who had acute coronary-artery occlusion. Subsequently in patients systolic blood pressure above 90 mmHg and Glasgow coma score (GCS) of 3 to 5, hypothermia was induced by 34°C coil cooling and continued for at least two days Furthermore fluid-nutrition-anticoagulation manegement by complete parenteral nutrition and continous hemodialysis-filtration. Outcome was assessed both in terms of survival rate and good recoveny rate.

Results: The cardiac cause of Vf was acute coronary syndrome in 14 patients hypertrophic myopathy in 1 and other cause in 1. The mean time from Vf to start of CPR was 9.2 ± 7.6 min; the mean time until ROSC, 39.6 ± 22.6 min; the successful reperfusion rate, 88.9% the mean GCS before hypothermia, 3.6 ± 0.6; the mean core temperature and duration at cooling stage, 34.3 ± 0.5°C and 83 ± 39 hr. Of these 16 patients, 81.2% (n = 13) survived at hospital discharge and 68.6% (n = 11) exhibited a good recovery rate.

Conclusions: The strategy of immediate coronary angiography plus intervention and mild hypothermia for cardiopulmonary cerebral resuscitation resulted in a 69% good recovery rate in comatose suvivors with out-of-hospital Vf. To confirm this result, larger, randomized, prospective, controlled studies using this strategy should be conducted.

P2318 Is electrophysiologically guided amiodarone therapy still indicated in patients with sustained ventricular tachyarrhythmias?

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We analyzed the outcome of 98 consecutive patients (pts) with sustained ventricular tachyarrhythmias (VT) treated with electrophysiologically guided (EP) amiodarone (amio).

Methods: 88 men, 10 women, mean age: 59 ± 11 year, mean ejection fraction: 36 ± 11% with VT were treated with EP guided amio. The underlying cardiopathy was ischemic in 87 pts, dilated in 9 pts and hypertrophic in 2 pts. According to the results of the EP study after a mean amio charging dose of 13.1 ± 1.3 g, pts were classified as "responders" (group 1 = 48 pts) or "non responders" (group 2 = 50 pts): Group 1 pts continued amio whereas group 2 pts were treated as follows: defibrillator (ICD) = 40 pts; surgery = 3 pts; RF ablation = 2 pts; 4 pts in Group 2 were excluded for follow-up because the scheduled ICD implantation could not be performed.

Results: During a mean follow-up of more than 5 years, total mortality and sudden cardiac death were significantly lower in Group 2 pts compared with group 1 pts (p: < 0.03 and 0.009, respectively). Furthermore, 6 pts in group 1 switched to an ICD.

In conclusion, EP guided amio "responders" have an impaired suvival compared with "non responders" treated with an ICD; therefore even EP guided amio therapy is obsolete for these pts.

P2319 Randomized comparison of 150 J biphasic and 200-360 J monophasic waveform automatic external defibrillators in out-of-hospital cardiac arrest victims

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Background: Since the 1960s, external defibrillators have traditionally relied on high-energy monophasic shocks. In 1996, a biphasic waveform automatic external defibrillator (AED) was introduced that delivers 150 J shocks. This study compared 200–360 J monophasic waveform AEDs to a 150 J impedance-compensating biphasic waveform AED.

Methods: The AEDs were randomly selected in response to 338 out-of-hospital cardiac arrests in four emergency medical service (EMS) systems. Of these arrests, 113 had a cardiac etiology with ventricular fibrillation as the first monitored rhythm and was shocked by an AED. Time from emergency call to first shock was 8.9 ± 3.0 minutes; collapse to first shock was 12.3 ± 4.2 minutes. The primary endpoint was successful defibrillation with 3 shocks or fewer. Secondary endpoints included first shock defibrillation efficacy, return of spontaneous circulation (ROSC), and survival to hospital admission and discharge.

Results: Study results are provided in the table below. *Survival to hospital discharge not yet known for four admitted patients.

	200–3060 J	150 J	P-value
Defibrillation, ≤3 shoks	40/60 (67%)	53/54 (98%)	<0.0001
Defibrillation, 1st shock only	35/60 (58%)	51/54 (94%)	<0.0001
ROSC	33/60 (55%)	41/54 (76%)	0.02
Survival, admission	31/60 (52%)	33/54 (61%)	0.3
Survival, discharge	16/58 (28%)	14/52 (27%)	0.9

Conclusions: The 150 J impedance-compensating biphasic waveform defibrillated at higher rates than 200–360 J monophasic shocks, resulting in significantly more patients achieving ROSC. EMS system outcomes of survival to hospital admission and discharge were not statistically different.

P2320 Re-entrant activity during ventricular fibrillation: an experimental study of the modifications in circuit size produced by antiarrhythmic drugs

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With the purpose of analyzing the characteristics of reentrant activity during ventricular fibrillation (VF) and its modifications following the administration of antiarrhythmic drugs, 32 Langendorff-perfused rabbit hearts were used to record fibrillatory activity induced by overdriving with an epicardial multiple electrode (121 unipolar electrodes, interelectrode distance = 1 mm) positioned on the free wall of the left ventricle. While coronary perfusion was maintained under both control conditions and following Flecainide (Fl, 1 μmol, n = 10), D-sotalol (Sot, 20 μmol, n = 10) or Verapamil (Vp, 0.2–0.8 μmol, n = 12), activation maps were obtained at 100-ms intervals over a 2-s period. In those maps reflecting closed loop reentry, the number of consecutive loops were quantified, along with the dimensions of the central line of the rotation (LG) and the area (AR) encompassed by it plus two electrodes surrounding the central zone – to record reentrant activity.

Closed loop reentry is observed in between 4.5% and 9% of the maps analyzed in each group. The number of consecutive loops does not differ significantly during Fl (control = 1.4 ± 0.6, Fl = 1.3 ± 0.5 loops) and Sot perfusion (control = 1.2 ± 0.3, Sot = 1.0 ± 0.1), though it increases with Vp (control = 1.3 ± 0.4, Vp = 2.1 ± 1.1, $p < 0.02$). The length of the central zone and the area encompassed by it plus two electrodes increases significantly during perfusion of Fl (control LG = 5 ± 1, Fl LG = 7 ± 1 mm, $p < 0.001$; control AR = 45 ± 6, Fl AR = 64 ± 6 mm^2, $p < 0.001$) and Sot (control LG = 5 ± 1, Sot LG = 7 ± 1 mm, $p < 0.001$; control AR = 43 ± 6, Sot AR = 57 ± 7 mm^2, $p < 0.001$), and decreases under the influence of Vp (control LG = 5 ± 1, Vp LG = 4 ± 1 mm, $p < 0.02$; control AR = 49 ± 4, Vp AR = 37 ± 5 mm^2, $p < 0.001$).

Conclusions: Reentrant activity can be recorded by epicardial mapping during VF. The dimensions of the LG and AR increase under the influence of F1 and Sot, and decrease with Vp.

P2321 Wedensky cardiac modulation: dose-related separation of patients with ventricular tachycardia from healthy controls

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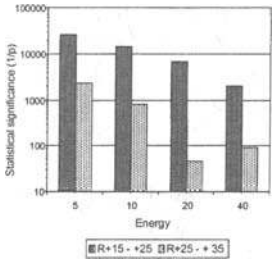
Wedensky phenomenon is the effect of a subthreshold stimulation without capture that reduces the stimulation threshold and changes the action potential of a subsequent suprathreshold stimulation with capture.

Patients with EP documented ventricular tachycardia (n = 47, mean age 63 ± 13 years, 83% male) and healthy controls (n = 30, 44 ± 16 years, 60% male) were subjected to a subthreshold external stimulation between precordial and left subscapular patches. Stimuli of 5, 10, 20, and 40 mA were delivered for 2 ms after a 20 ms delay following a real-time R wave detection. 60 to 200 subthreshold stimulated QRS complexes were averaged and compared with the same number of non-stimulated complexes. Vector magnitude wavelet decompositions (53 scales of central frequencies 40–250 Hz) were obtained for both stimulated and non-stimulated complexes and their difference characterised the Wedensky phenomenon numerically. The surface area of the 3D envelope of the wavelet residuum was measured in a window 20 ± 5 ms after the R peak (a window centred around the stimulation moment) and the subsequent 10 ms windows (30 ± 5 ms after the R peak). The areas of the residuum spectral 3D envelope in these windows were statistically compared in the VT patients and healthy controls.



All differences were highly significant (up to $p < 0.00005$ – figure) the manifestation being more pronounced in the control group. The separation of the groups was more significant in the window around the stimulation moment. The significance decreased with increasing subthreshold stimulation energy. Thus, (a) Wedensky phenomenon in the late QRS part is brief, (b) VT pts are less sensitive to the phenomenon, especially at very low subthreshold energies.

P2322 Validation of a semiautomatic external defibrillator for narrow and wide QRS tachycardia

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Background: Semiautomatic external defibrillators (SAED) are widely used to treat life-threatening ventricular arrhythmias. However, neither sensitivity nor specificity of their advice to give a shock are well established.

Methods: Therefore, we studied sensitivity and specificity of the advices of the SAED ForeRunner™ (Heartstream, Inc. Seattle, USA) to shock spontaneously occurring and induced narrow and wide QRS tachycardias during routine electrophysiological studies. Moreover, right ventricular stimulation at cycle lengths of 380, 370, 360, ... up to 300 ms was performed. In every patient each paced cycle length was analysed.

Results: In 50 consecutive patients (26 males, 24 females) we analysed 274 tachycardias with the SAED (58 spontaneous or induced tachycardias, 216 right ventricular stimulations). In all 29 narrow QRS tachycardias (median heart rate 185/min, range 140–250/min) no electric countershock was advised, specificity of 100%. In 22 of 29 (76%) spontaneous or induced wide QRS tachycardias (median heart rate 180/min, range 130–270/min) no electric countershock was advised. In 158 of 216 (73%) right ventricular stimulations no electric countershock was advised. Admitting the SAED should shock a wide QRS tachycardia at a certain heart rate, we found the following sensitivities at different rates in all wide QRS tachycardias:

Heart rates (≥/min):	160	170	180	190	200	210	220	230	240	250	260
Sensitivities (%):	29	34	41	47	50	43	50	60	67	50	100
Tachycardias (n):	217	165	111	60	34	7	6	5	3	2	1

Conclusions: The specificity of the SAED ForeRunner™ to recognize narrow QRS tachycardias is excellent. However, the sensitivity of the SAED to detect a potentially harmful wide QRS tachycardia seems to be limited.

PACING AND ICD-RELATED PROBLEMS

P2323 Safety and performance of a new dual-chamber implantable cardioverter-defibrillator: results from a European multicentre study

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The purpose of this prospective multicenter (36 European centers) study was to evaluate the safety and performance of a new dual-chamber ICD (Medtronic Model 7271 GEM DR). Between 11/97 and 5/98 a total of 216 patients (pts) were implanted. Indications (non-exclusive) for ICD implant were survival of sudden cardiac death (56%), recurrent poorly tolerated sustained VT (75%) or MADIT (3%). The typical pt was a 61 years old male (79%) suffering from coronary artery disease (64%) and/or dilated cardiomyopathy (22%), with an ejection fraction of 39%. During a follow up (FU) period of 2.9 ± 1.4 months 70 pts experienced 1108 ventricular tachyarrhythmia episo-des and 48 pts experienced 486 supraventricular tachycardia (SVT) episodes, of which EGM was stored by the device. All VT/VF (of which 99.6% were treated successfully) and the majority (71%) of the SVT episodes (untreated) were appropriately detected. During the FU period 110 pts experienced 187 adverse events (AE). Inappropriate VT/VF detection occurred in only 26 pts (12%). AEs resulting in death (6), requiring surgical intervention (37) or hospitalization (52) were classified as severe and occurred in 66 pts (31%). Four pts died of heart failure and two pts died of electromechanical dissociation. None of the deaths were considered to be device relat-ed. Severe Device Related AEs, including 10 lead dislodge-ments and 10 inappropriate VT/VF detections, occurred in 29 pts (13%).

Conclusion: The new Dual-Chamber ICD proved to be safe and effective with a low rate of adverse events. The new PR-Logic algorithm seems to be very useful for the correct discrimination of supraventricular from ventricular arrhythmias.

P2324 Rate characteristics and circadian variation of atrial tachyarrhythmia recurrences: first lessons from patients with a dual-chamber defibrillator with atrial tiered therapies

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A new dual-chamber implantable cardioverter-defibrillator (ICD) provides additional atrial therapies. Moreover, the activation of the atrial therapies can be freely programmed to any time of the day. there is no systematic data, yet, about the incidence and duration of paroxysmal atrial tachyarrhythmias (AT) in patients with an ICD. Since activation of atrial therapies does not only influence the rhythm, but also quality of life, the aim of this prospective study was, to assess the clinical characteristics as atrial rate, duration and circadian variation of AT episodes in ICD-patients to guide appropriate programming of atrial therapies.

Patients and Methods: 225 episodes from 19/34 patients with a dual-chamber ICD Medtronic Jewel AF 7250 were included in the analysis. Duration of the episodes and circadian distribution of the AT episodes (E) were assessed using the device data log. Furthermore, the atrial rate measured as the median PP-interval of each episode was determined.

Results: The mean atrial cycle length was >220 ms in 78% of the E. In all these E the device classified the activation pattern as regular. The duration of the AT episode was <1 min in 64 E, 1–5 min 107 E, 5 min–24 h in 52 E and >24 h in 4 E. The mean duration was 11 min. The circadian variation of AT episodes exhibited a significant peak between noon and 6 p.m. (0–6 a.m 11 E, 6 a.m–noon 25 E, noon-6 p.m. 63 E and 6 p.m.–12 p.m. 23 E) ($p < 0.05$).

Conclusions: 1. 78% of the AT reveal a regular atrial activity with a median cycle length > 220 ms. Thus, atrial antitachycardia pacing therapies should be extensively programmed in all patients. **2.** 98.3% of the episodes terminate spontaneously within 24 hrs. Empiric atrial shock programming should therefore be avoided, because the vast majority is non-sustained and terminates spontaneously **3.** Shock therapy should be programmed in patients with persistent AT during the sleep hours to reduce pain perception.

P2325 Re-used pacemakers – an alternative in elderly patients

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Aim: The aim of this study was to investigate the safety and the cost-benefit ratio of re-used pacemakers (PM) in elderly patients in a retrospective case-controlled study in an area with poor health care services.

Methods: 131 patients (gr. I) with an age > 70 years (mean age 79 ± 5 years) who received a re-used PM were matched for date of implantation and mode (AAI, VVI, DDD) to 140 patients (mean age 79 ± 9 years) (gr. II) who received new PM. Criteria for re-use were PM implanted <1 year and no sign of damage at examination and interrogation. The majority of PM was provided by the Bank of PM "Stimubank" Nancy, France. All patients were observed for a mean of 35 ± 21 month for complications defined as infections and signs of PM malfunction and PM replacement earlier than anticipated due to battery depletion. A cost-benefit analysis was performed for survival and time to PM replacement.

Results: The number of complications did not differ significantly between the group implanted with re-used PM (infections 4, malfunctions 5) and the group implanted with new PM (infections 3, malfunctions 6). There was no early replacement due to battery depletion in either of the two groups.

76 of 131 patients (57%) died after an average implantation time of 3.3 years and before needing PM replacement. 78 patients of group II (55%) died after an average implantation time of 3.2 years. The cost-benefit analysis revealed a substantial economical advantage for the group implanted with re-used PM.

Conclusion: The re-use of PM can be performed without increased risk to the patients provided that a proper routine for technical control and sterilization is followed. Reuse of PM makes it possible to implant advanced pacing systems with a very good cost-benefit ratio in patients in whom life expectancy is lower than that of the PM.

P2326 Cardiac resynchronization for heart failure: do patients with prior indications for pacing benefit?

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The InSync™ study is a prospective, multicenter, non-randomized trial evaluating Cardiac Resynchronization (CR) therapy in patients (pts.) with advanced heart failure (NYHA Class III/IV), dilated cardiomyopathy (EF < = 35%, LVEDD = > 60 mm) and ventricular conduction delays (QRS = > 150 ms). Pts. with prior pacing systems were also included in this evaluation. Clinical effects of cardiac resynchronization were compared between these pts. and pts. without a prior pacing system.

Methods: 53 pts. implanted with the InSync system, including a transvenous left ventricular lead via the coronary sinus, were included in this analysis. From this group, 17 had a previous pacing system and 36 had no prior pacing system. We have excluded 7 pts. who did not have a previous pacing system yet were indicated for pacing at the time of InSync implantation. Measured parameters included QRS duration, NYHA classification, 6 min hall walk, and Quality of Life (Minnesota Living with HF)

Analysis: 1) *within* each group, statistically significant changes in clinical endpoints at one and three months were observed compared to baseline. 2) *Between* group comparisons, with p-values, are shown in the table below.

Clinical Endpoint	Δ Pts with prev. pacing system	Δ Pts without prev. pacing system	p-value
QRS duration (msec)	47.4 ± 30 (N = 16)	18.9 ± 32.2 (N = 33)	0.005
NYHA classification	0.9 ± 0.7 (N = 17)	1.1 ± 0.9 (N = 36)	0.305
6 minute hallwalk (m)	46.3 ± 67.4 (N = 11)	66.8 ± 95.2 (N = 28)	0.519
Quality of Life score	14.9 ± 23.1 (N = 16)	18.1 ± 26.1 (N = 35)	0.672

Conclusions: These data from the InSync trial demonstrate increased patient benefit from CR at 3 months in both groups, those with prior pacing systems in place, and those not previously indicated for pacing. The data also suggest a trend toward greater improvement in pts. receiving a system for the first time. Longer term studies will be required to evaluate the benefit of CR in both patient groups.

P2327 Long-term outcome of patients with multiple (≥3) non-infected transvenous leads

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Lead extraction is associated with a relatively high number of complications. However, the presence of multiple (≥3) leads have been related to thromboembolic manifestations. We studied 48 consecutive patients (pts) with ≥3 non-infected leads. No additional care was provided except for aspirin 80 mg bid and annually performed echo Doppler studies. Clinical follow-up included signs of right heart failure, subclavian and/or axillary vein thrombosis, hospital admissions and cumulative mortality. Echo Doppler studies assessed the presence of right atrial or right ventricular spontaneous contrast and tricuspid regurgitation. Pts were compared with age-matched controls with dual chamber stimulation. In the study group 24 pts had two ventricular leads, 14 had two atrial leads and 10 had two atrial and two ventricular leads. Median follow-up was 7.4 ± 2.2 years.

	Multiple leads (n = 48)	Controls (n = 48)	p-value n
RHF	15%	13%	–
Vthr	13%	10%	–
HA	1.1 ± 0.27	1.3 ± 0.30	–
SPEC	4%	4%	–
TR	23%	4%	p < 0.05
MORT	13%	15%	–

RHF = right heart failure; Vthr = vein thrombosis; HA = hospital admissions/year; SPEC = spontaneous echo contrast; TR = tricuspid regurgitation; MORT = mortality.

Conclusion: patients with multiple ≥3 leads experience no clinical adverse outcome during long term follow-up despite a significant higher incidence of echocardiographic assessed tricuspid regurgitation.

P2328 Impact of chronic ddd pacing on sympathovagal balance in patients with hypertrophic obstructive cardiomyopathy

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Autonomic dysfunction has been reported in patients with hypertrophic obstructive cardiomyopathy (HOCM). Although DDD pacing has been proved useful for the relief of symptoms, it has not been investigated whether it has any impact on autonomic nervous system activity in HOCM patients. The aim of this study was to examine if DDD pacing changes sympathovagal balance, as assessed by heart rate variability (HRV), in such patients.

Methods: We studied 11 pts (7 men, age 52 ± 8 years) with HOCM refractory to drugs. In all pts a DDD pacemaker was implanted and the AV delay was programmed to ensure a full ventricular activation sequence. Time domain indexes of HRV (mean NN, SDANN, SDNN, SD, rMSSD, pNN50) were determined from 24-hour Holter recordings 1 week before and 1 year after pacemaker implantation. The pacemaker was turned off during the second recordings. The same indexes were determined in 10 healthy controls at the same time points.

Results: The controls showed no significant differences in any of the measured parameters between the 2 time points. The HOCM pts showed an increase in SD (from 27 ± 13 to 41 ± 13 ms, $p < 0.001$), rMSSD (from 18 ± 5 to 32 ± 8 ms, $p < 0.001$) and pNN50 (from 1.03 ± 1.06 to 8.52 ± 4.84%, $p < 0.0001$). As a result, the values of these 3 parameters in the HOCM pts, which were lower than in the controls before pacing, were restored to normal levels by the end of the study.

Conclusions: Our findings indicate that long term pacing in HOCM pts restores the sympathovagal balance in the heart by increasing vagal activity. Thus, DDD pacing may have a beneficial impact on the prognosis of such patients.

P2329 Atrial pacing reduces mode switching episodes in patients with paroxysmal atrial fibrillation

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Atrial pacing (AP) has been reported to be effective in reducing atrial fibrillation (AF) recurrences. However, the efficacy of AP has been demonstrated only by the reduction of patients' symptoms, a parameter that represents a potential bias. Recently it has been demonstrated that the pace-makers' mode-switching (MS) algorithms are reliable in detecting paroxysmal episodes of atrial tachyarrhythmias. The aim of our study was to prospectively analyze the effect of AP on MS episodes in patients with AF undergoing pace-maker (PM) implant because of coexisting sick sinus syndrome or atrioventricular block.

Methods. Twenty-three patients underwent PM implantation. Before hospital discharge, the PM were programmed in the DDD mode with bipolar atrial and ventricular sensing and pacing. The lower and the upper atrial rate were, respectively, programmed to 50 bpm and 220 minus patient age bpm. All the patients received the same antiarrhythmic medications used before PM implantation. At a follow-up of 4 months (follow-up period I), PM were reprogrammed in DDDR mode, with a lower rate of 75 bpm, and followed-up for the next 4 months (follow-up period II).

Results. During the 4 months of follow-up period I 19/23 (82.6%) patients had at least one symptomatic AF episode, and 21/23 (91.3%) patients had at least one MS episode. The overall mean number of AF episodes/patient was 3.1 ± 3.8 and was reduced to 0.7 ± 1 ($p = 0.005$) in the follow-up period II. In the follow-up period II a lower number of MS episodes/patient were observed than follow-up period II (5.9 ± 7.8 vs 49.9 ± 87, $p = 0.05$). This was associated with an higher percentage of AP time (85.4 ± 15.9 vs 39.6 ± 22.5, $p < 0.001$). An inverse correlation was found between the logarithm number of MS episodes and the percentage of AP time ($r = -0.53$). A direct correlation was found between the AF episodes and the MS episodes ($r = 0.7$).

Conclusions. The results of this study show that AP reduces MS episodes in patients with paroxysmal AF. Its efficacy is correlated with the percentage time of AP. These data seems to confirm, in an objective way, the efficacy of AP in reducing AF recurrences.

P2330 The importance of electrode placement in the right atrium for sensing of early onset of atrial intrinsic activity

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Background: Multisite atrial pacing algorithms are new pacing concepts for the prevention of onset of atrial arrhythmias. A central roll in these prevention concepts plays the early sensing of the onset of atrial activity. The aim of this study was to investigate the importance of the placement of the atrial electrodes for sensing of early onset of atrial intrinsic activity.

Methods: In 11 female merino sheep (4.6 ± 1.3 years; 66.3 ± 6.1 kg) EP-catheters were placed fluoroscopically at the high right atrium (HRA) and at the coronary sinus ostium (Cs-Os). A modified single-VDD-lead was placed with the atrial ring electrodes floating in the high and mid right atrium. The P-wave onset to floating electrodes, to the HRA, and to the Cs-Os position were measured during intrinsic rhythm (1000 Hz sampling rate; unfiltered signal).

Results: In 10 of 11 experiments, the earliest sensing of onset of atrial intrinsic activity was observed over the atrial floating ring electrodes. The onset of the atrial signal sensing was recorded 18.4 ± 16.6 ms earlier using floating electrodes compared to wall contact electrodes in the HRA position ($p < 0.05$), and 40.0 + 16.9 ms earlier compared to the Cs-Os position ($p < 0.05$). The difference of onset sensing between HRA and Cs-Os position was also significant ($p < 0.05$). The onset of atrial intrinsic activity was sensed 19.9 ± 8.1 ms earlier using floating ring electrodes compared to the onset of the P-wave in the surface ECG ($p < 0.05$).

Conclusion: The intra-individual comparison of the onset sensing of atrial intrinsic activity is significantly dependent on the location of atrial wall contact electrodes. Sensing of the onset of atrial intrinsic activity can be done significantly earlier using floating ring electrodes in the mid right atrium compared to wall contact electrodes. Therefore, atrial sensing using floating ring electrodes may be helpful in early detection of atrial arrhythmias.

P2331 Does implantation of single-lead VDD-pacemakers reduce the costs of pacing therapy in patients with isolated AV block?

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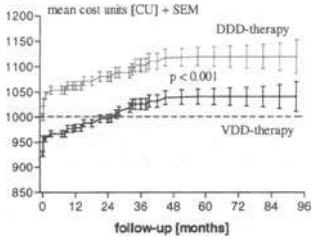
Implantation of single-lead VDD-pacemakers is an established alternative to DDD-pacing in patients with AV-block and normal sinus node function. This study compares long-term cost-efficacy of both systems.

360 patients with isolated AV-block received single-lead VDD-pacemaker (VDD, n = 180) and DDD-systems (DDD, n = 180) in alternating order and were followed over a period of 42 ± 15 months. Costs of implantation included: Costs of devices, leads and operation material, of surgeon, nurse and medical technician and of hospitalisation. Follow-up costs included routine pacemaker controls as well as costs of pacemaker-related complications. Costs were converted into virtual cost units (CU): mean costs of uncomplicated DDD-pacemaker implantation defined 1000 CU. Endpoints of the study were death, any operative revision and complete loss of AV-synchrony.

Costs of devices were not different (721 ± 65 CU in VDD vs. 722 ± 76 CU in DDD). However, due to lower cost of leads and shorter implantation times (44.3 ± 5.1 min in VDD vs. 74.4 ± 13.5 min in DDD, p < 0.001) overall costs of an uncomplicated pacemaker implantation were significantly lower in the VDD-group (fig). Furthermore, a tendency to less re-operations in the VDD-group (3.3 vs. 6.1%, p = 0.15) led to reduced follow-up costs per year (14 ± 22 CU in VDD vs. 22 ± 30 CU in DDD, p = 0.002). Study endpoint was reached in 12.8% of patients with VDD and 14.4% with DDD (n.s.).



Assuming a mean battery lifetime of 6 years, about 10% cost reduction compared to DDD-devices can be achieved by VDD-pacemaker implantation without reducing the efficacy of pacemaker therapy in patients with isolated AV-block.

P2332 Clinical response to pacemaker therapy: carotid sinus hypersensitivity versus vasovagal syncope

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Vasodepression and cardioinbibition are two components of the efferent pathways underlying neurocardiogenic syndromes (NCS), including carotid sinus hypersensitivity (CSH) and vasovagal syncope (VVS). It has been suggested that the relative contribution of the two efferent components is likely different in CSH and VVS; therefore, conjectured that response to pacemaker (PM) therapy is expected to be different. In this retrospective study, clinical responses (improved, asymptomatic) were assessed by a prospective survey in 230 pts with CSH (age 69 ± 12 yrs, F/M = 44/186) and 24 pts with VVS (age 57 ± 23 yrs, F/M = 10/14) following PM implantation between 1984-1996. f/u was completed in 166/230 pts (72%, mean f/u 2.5 ± 2.9 yrs) with CSH and in 24/24 pts (100%, mean f/u 2.0 ± 1.6 yrs) with VVS. Survival free from recurrent symptoms was assessed by the Kaplan-Meier method:

Clinical Response	NCS	F/U (probability)			
		1 yr	2 yr	3 yr	P
Asymptomatic	CSH	0.82	0.76	0.71	0.001
	VVS	0.65	0.42	0.31	
Improve or	CSH	0.96	0.96	0.94	0.01
Asymptomatic	VVS	0.90	0.82	0.68	

CSH pts are older (p = 0.02), male predominant (p = 0.01), and with longer pauses (p = 0.01). Multivariate analysis showed older age (p = 0.05) in VVS pts and presence of prodromes (p = 0.05) in CSH pts were predictors for recurrent symptoms. Mode of pacing was not an independent predictor for recurrent symptoms in either group (p > 0.05).

Conclusion: 1) Long-term response to conventional PM therapy is significantly more favorable in pts with CSH when compared to pts with VVS; 2) Significant differences in clinical characteristics are present between these two NCS; 3) Careful evaluation of mode of pacing in pts with VVS is warranted.

P2333 Does the ventricular activation sequence affect myocardial contractility during exercise?

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Background: Right ventricular (RV) pacing result in delay between right and left ventricular contraction, hence unfavorable haemodynamics effects. Peak endocardial acceleration (PEA) measured by an implantable acceleration sensor at the tip of the pacing lead reflects myocardial contractility. Thus, it can be used to assess ventricular performance with native ventricular activation and RV pacing during submaximal and maximal treadmill exercises.

Methods: PEA sensing DDDR pacemakers (Best-Living, Sorin Biomedics) were implanted in 15 patients (age 71 ± 8 year) with sick sinus syndrome, with the ventricular leads implanted into the RV apex in all patients. The sensor was tailored to a rate of 90 to 100 bpm using a 2-minute walking test. The patients were subjected to submaximal treadmill exercise test at 2 mph 0% gradient and maximal exercise test using the CAEP protocol. During exercise, the pacemakers were randomly programmed to DDDR with: 1) RV pacing using an atrioventricular delay (AVD) optimized non-invasively by echo-Doppler to obtain highest cardiac output and longest diastolic filling time (paced AVD); 2) normal ventricular activation by programmed an AVD long enough to allowed intrinsic AV conduction (native AVD). PEA values were recorded beat by beat by pacemaker telemetry both at rest and during exercise. The maximum changes in PEA (ΔPEA) during exercise with the 2 ventricular activation sequences were compared using t-tests.

Results: The mean paced AVD and native AVD were 142 ± 42 ms and 208 ± 20 ms respectively.

	2 mph, 0%	CAEP		
	ΔPEA (G)	ΔPEA (G)	Exercise duration (s)	Exercise workload (METS)
Paced AVD	0.53 ± 0.04	1.1 ± 0.15	496 ± 35 s	4.0 ± 0.27
Native AVD	1.0 ± 0.17	1.1 ± 0.17	479 ± 51	3.8 ± 0.33
P value	<0.01	NS	NS	NS

Conclusion: The ventricular contractility was significantly better with native AVD than paced AVD during submaximal exercise tests. During maximal treadmill exercise, PEA was a less sensitive indicator for ventricular performance.

P2334 A prospective, randomized comparison of QRS duration and QT interval between right ventricular apical and high septal lead placement in patients with dual-chamber pacemakers implanted for high-degree block

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Background: Pacing from the right ventricular apex produces a wide and bizarre QRS complex, reflecting abnormal activation of the myocardium. Right ventricular high septal pacing produces more normal depolarisation and repolarisation patterns and should, therefore, produce a narrower QRS complex and shorter QT interval. Current data suggests that QRS prolongation can predict deterioration in systolic function with time.

Methods: We studied 24 patients receiving first implant dual chamber pacemakers for high degree AV block]. Patients were randomised to active fixation lead on the septum (n = 11) or a passive fixation lead in the apex (n = 13). ECGs were recorded pre implant, at 24 hours, and at 1 and 4 months post implant. All traces were recorded at 50 mm/sec and measurements were taken manually from the start of the bipolar pacing spike. Mean QRS duration and QT interval were calculated from the mean of 3 consecutive complexes per lead (36 complexes per ECG)

Results: The septal group QRS duration was significantly shorter at 24 hours and 4 months, and QT shorter at 4 months. Data are shown as mean ± standard deviation

	QRS (millisec)		QT (millisec)	
	Apical	Septal	Apical	Septal
Pre	107.5 ± 27.1	96.9 ± 28.5	493.8 ± 69.6	464.9 ± 127.0
24 hrs	160.8 ± 15.7	145.4 ± 15.4*	440.9 ± 26.6	422.3 ± 28.8
1 m	160.7 ± 14.8	150.0 ± 9.2	433.6 ± 22.0	395.7 ± 46.5
4 m	161.7 ± 7.4	145.9 ± 11.7*	426.7 ± 27.7	385.3 ± 14.9*

*p < 0.01

Conclusion: Septal pacing results in narrower QRS complexes and shorter QT intervals than apical pacing in the medium to long-term. These data suggest the potential for preserved cardiac function with septal lead placement over time; this observation will require further investigation.

P2335 Should single-lead VDD pacemakers be implanted in young patients?

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Implantation of single-lead VDD-pacemakers is established in patients with AV-block and normal sinus node function. However, there is concern whether these devices should be implanted in physically active young patients in whom development of sinus node disease and atrial undersensing are of particular interest.

232 consecutive patients with isolated AV-block and VDD-pacemakers were investigated. This population was subdivided into 2 groups according to age at time of implantation: age $\leq$ 60 years (group A, n = 62) and age > 60 years (group B, n = 170). Follow-up visits included pacemaker telemetry, Holter monitoring and exercise testing 2 and 12 weeks after implantation followed by 6-months intervals. Minimal intraoperative ($MPOT_{IOP}$) and telemetered atrial potentials 2 weeks after implantation ($MPOT_{TEL}$), incidence of atrial undersensing (US), sinus node dysfunction (SND) and atrial arrhythmias (AA) as well as the maintenance of AV-synchronous pacing mode (AVS) were investigated.

	Age $\leq$ 60 years (A)	Age > 60 years (B)	p-value
$MPOT_{IOP}$ [mV]	1.61 ± 0.47	1.21 ± 0.57	<0.001
$MPOT_{Tel}$ [mV]	1.20 ± 0.55	0.65 ± 0.51	<0.001
US [%]	6.5	22.9	0.004
SND [%]	0.0	2.9	0.17
AA [%]	1.6	10.6	0.03
AVS [%]	1.6	93.5	0.048
Follow-up [months]	36 ± 11	33 ± 17	n.s.

Due to higher intraoperative atrial potential amplitudes and a less marked postoperative decrease of potential, $MPOT_{Tel}$ was higher in group A. In correspondence, incidence of US was markedly lower compared to group B. Showing a low overall incidence, SND was only observed in group B. Furthermore, incidence of AA was lower in group A. After a mean follow-up of 36 months, 98.4% of group A patients remained in the VDD-pacing mode.

Our data show a very low incidence of sinus node dysfunction and atrial arrhythmias in young patients with AV-block. Atrial sensing is improved compared to older patients. Thus, youth of patient should not be a reason to avoid VDD-pacemaker implantation.

P2336 Left ventricle coronary vein accessibility for implantation of a defibrillating ICD and/or pacing lead system

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Background: Pacing and ICD lead systems that incorporate an electrode inserted transvenously into coronary veins residing on the left ventricle have been proposed.

Methods: A study was conducted in twenty-four patients (Pts) receiving an ICD system to evaluate the ease of placing a lead into two different preselected coronary target veins on the left ventricle. The prototype lead emulated a left venous access (LVA) defibrillation and/or pacing lead and consisted of a modified 0.018″ guidewire. The LVA lead was inserted from the left subclavian vein into the coronary sinus via a guide catheter. Pts were randomized to attempt LVA lead insertion into either the anterior interventricular (AIV) or posterior vein (PV). Positioning was guided by a venogram. A crossover to the other vein location was allowed only if the initially randomized vein was not accessible.

Results: The LVA lead was successfully positioned in either the AIV or PV in all Pts (100%). The LVA lead was successfully inserted into the AIV in 12/13 Pts attempted (92%). In one patient the AIV was very narrow and therefore the LVA lead could not be passed. Mean time for insertion into the AIV was 16.0 ± 13.6 min (median = 10 min, range = 3–38 min). The LVA lead was successfully inserted into the PV in 12/14 Pts attempted (86%). In two Pts, the PV was too tortuous for placement of the LVA lead. Mean time insertion into the PV was 16.3 ± 14.6 min (median = 11 min, range = 1–50 min).

Conclusion: This is the first major study of the accessibility of coronary veins located on the left ventricle as potential sites for pacing or ICD lead system implantation. Results showed these sites can be accessed with a high degree of success. Pacing or ICD systems, particularly for patients with congestive heart failure, utilizing a lead placed deep into a coronary vein residing on the left ventricle are feasible.

P2337 Validation of the basis of paced activation sequence mapping

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Paced activation sequence mapping (PASM) has been used for the ablation of atrial tachycardias. PASM attempts to locate the tachycardia origin by reproducing during pacing the activation sequence obtained during tachycardia. Our objective was to test the strength of the basic principles of this technique by studying the paced intra-atrial conduction, the reproducibility of time measurements and the resolution.

Methods and results: In 20 patients undergoing an electrophysiologic study, a decapolar catheter was stably set at the lateral right atrium describing a figure-of-9 in 45° LAO view. Three consecutive 10 mm-spaced electrode pairs were selected. Bipolar pacing was consecutively performed from each of them and bipolar electrograms were recorded from the others. Pacing protocol consisted of a train of 7 impulses at 2 drive cycle lengths (300 and 350 ms) and 2 pacing outputs (twice and tenfold the threshold amplitude at 2 ms pulse width). Local activation time was considered as the point when the largest rapid deflection crosses the baseline. We analyzed 240 pacing sequences. Cycle length and activation direction did not influence conduction time. The change in pacing output from twice to tenfold the threshold value shortened the conduction time by 1.9 ms [95% confidence interval (CI) 1.5–2.2 ms, p < 001]. Two observers measured twice a random sample of 48 recording (20%). The 95% limits of intraobserver and interobserver agreement were ± 2.6 ms and ± 2.9 ms respectively. The resolution was estimated by measuring the successive time changes in the relative activation of 2 appropriately placed references produced when pacing site is switched to each contiguous 3 mm-spaced electrode pair of a 20-pole catheter set into the coronary sinus. The median shift was 7.5 (range 2.5–20) ms per 3 mm.

Conclusions: The low intra and interobserver variability and high temporal-spatial resolution support PASM as an alternative to conventional activation mapping to localize focal tachycardias. The small impact of a tenfold increase in pacing output suggests that formal threshold measurements may not be necessary.

P2338 Evaluation of the left ventricular contractile function in irregular heart beat created by different pacing mode

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Backgrond: The assessment of the left ventricular (LV) contractile function during atrial fibrilation is problematic due to beat to beat variability. Purpose: We evaluated LV systolic function during varying RR intervals produced by different pacing conditions using a canine atrial fibrillation (AF) model.

Methods: Epicardial echocardiography, LV pressure recording and aortic flow measurement were performed simultaneously in 8 healthy mongrel dogs during triggered AF and right ventricular (RV) pacing. AF was induced by programmed random rapid right atrial pacing. Heart rate was slowed during AF by vagus nerve stimulation (VNS). The AV junction was subsequently ablated by radiofrequency energy and random slow rate RV pacing was performed. The LV stroke volume (SV) was calculated using LV outflow Doppler velocity profile. The maximum value of the first derivative of LV pressure curve (+dP/dt) and aortic peak flow rate (AOF) by transonic flow meter were also recorded. The ratio of the preceding RR interval to the pre-preceding RR interval (RR1/RR2) was evaluated during all conditions.

Results: 1) All the variables showed significant positive correlation with RR1/RR2 in each pacing mode. 2) The value at RR1/RR2 = 1 in the linear regression line showed similar change by different pacing mode for all variables (table).

	Base(sinus)	Rapid AF	AF+vNS	Ablation+Rvpace
SV (ml)	18.2	10.7	15,2	14.9
AOF (l/min)	1.02	0.48	0.76	0.64
+dP/dt (mmHg)	2727	2406	2838	2421

The value at RR1/RR2 = 1 in the linear regression line for each indeces in different pacing modes.

Conclusions: 1) Indices of LV contractile function during periods of variable RR intervals closely correlated to the ratio of the preceding RR interval to the pre-preceding RR interval. 2) The value at RR1/RR2 = 1 can allow us to estimate LV contractile function during atrial fibrillation.

P2339 Detection of atrial arrhythmias in DDD pacemaker by automatic interpretation of data analysis – a new tool for follow-up

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Arrhythmias and pacemaker (PM) dysfunction are difficult to document even during follow-up. In the new generation of PMs, a variety of diagnostic tools are available, which makes rhythm control possible. Analysis is time consuming and requires experience.

Methods: With a recently introduced software (AIDA), Holter data of the PM are automatically analysed and results are shown in a comprehensive way. In the AIDA multicenter trial, 836 patients (pts) were included in 12 countries. Chorus II PM, equipped with an automatic fall back mode switching algorithm, was implanted in 232 pts. PM Holter data were compared with surface Holter electrocardiogram after 1 day (D1) and with clinical symptomatology after 28 days (D28). Bipolar atrial lead was mandatory to adjust high sensitivity (0.4 mV).

Results: Study group consisted of 151 males (65%) and 81 females (35%) with a mean age of 69 ± 12 years. After D1, 35 pts (15%) developed at least one episode of supraventricular tachycardia (SVT) (26 pts atrial fibrillation, 9 pts atrial tachycardia). Sensitivity and specificity was 97.2% and 96.4% for AIDA compared to Holter. Lead fixation type (tined 43%, screw-in 57%) did not effect SVT incidence. Pts with SVT were older (73 ± 10 vs. 68 ± 12 years, $p < 0.01$). After D28, 100 pts (47%) developed SVT, of whom 51% were asymptomatic. Thirty six pts (36%) were asymptomatic and with no history of SVT. Arrhythmias (AA) detected at D1 are shown in the table.

Arrhythmias detected at D1:

	Sensitivity	Specificity
Atrial sensing failure	80%	98%
Atrial sensing failure during AA	95%	100%
Endless loop tachycardia	100%	100%
Ventricular ectopic beats	93%	99%
Atrioventricular crosstalk	83%	99%

In conclusion, the new AIDA software in the Chorus II PM seems to be a useful tool in detecting SVT, delivering reliable results as compared to surface Holter, the "golden standard" so far.

P2340 Paradoxical undersensing of high atrial rates with increasing sensitivity in dual-chamber pacemakers

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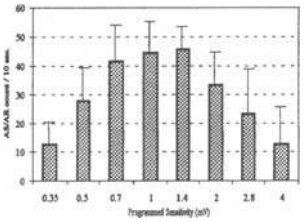
Dual chamber pacemaker therapy in patients with supraventricular arrhythmias depends critically on an accurate detection of the atrial rate.

Background: We developed a sheep model of atrial fibrillation (AF) based on rapid atrial pacing. We used bipolar atrial leads in all animals to assure appropriate atrial sensing. In a subgroup, Thera D(R) (Medtronic®) pacemakers, programmed to deliver a burst of 42 Hz on detection of sinus rhythm (SR), were implanted. In 5 sheep that developed chronic AF, we noticed during the arrhythmia a significantly higher frequency of inappropriate bursts at higher sensitivity levels, indicating that the pacemaker misjudged the atrial tachycardia.

Methods: We assessed the atrial detection by counting the atrial sensed events (AS/AR) reported by Thera D(R) and Marathon (Intermedics®) DDD(R) pacemakers in sheep with AF and using a waveform generator.

Results: We demonstrated that paradoxically during AF the pacemaker recognized fewer atrial events at a higher sensitivity (cf. graph. for Thera D(R)). Using the waveform generator we saw that at rates above 6 Hz (cycle length < 166 ms) there was a critical sensitivity above which the pacemaker failed to report appropriately the atrial activity. This cut-off value was a function of the amplitude and waveform of the signal used. It was possible to mislead the Thera's mode switch feature.



Conclusion: This paradoxical undersensing can not be explained by a programmable software defined setting, but is hardware dependent and based on saturation of the atrial amplifier. Knowledge of this behavior is important for cardiologists using dual chamber pacemakers in patients with paroxysmal AF. There is an optimal sensitivity level dependent on the amplitude of the atrial sensed signal. It may therefore not be appropriate to program the sensitivity as high as possible.

P2341 The SYDIT (Syncope: Diagnosis and Treatment) study: preliminary data

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Background: Cardiac pacing has proven a valuable therapeutic option in the treatment of recurrent cardioinhibitory vasovagal syncope. However, an empirical tilt-guided pharmacological therapy has been considered the first step in a correct approach to recurrent vasovagal syncope so far.

Methods: Aim of the present open randomized clinical trial is to compare the effectiveness and safety of pharmacological therapy (Atenolol or Etilephrine) versus cardiac pacing (DDD with rate drop response function, RDR) in the long-term treatment of recurrent vasovagal syncope. Patients are included in the investigation if they fulfill the following criteria: 1) no cardiac disease, 2) age > 35 yrs, 3) at least 3 syncopal spells in the preceding 2 yrs, 4) positive head -up tilt testing with an heart rate drop of more than 30% and a lower heart rate less than 50 bpm. Eligible patients are randomized to pharmacological therapy (initially Atenolol 100 mg die, with a switch to Etilephrine 50 mg die in case of syncope recurrence despite treatment) or cardiac DDD with RDR pacing (pacemaker Medtronic Thera DR). Pacemaker programming is made according to the heart rate behavior during head-up tilt testing. Patients are followed for syncope recurrence (main end-point).

Results: To date 24 patients have been included and randomized (15 females and 9 males, mean age 59.1 yrs); 11 patients have received a pacemaker while 13 patients are on drug treatment. During the follow-up (mean duration 5.8 months) 3 patients on pharmacological treatment have experienced a syncopal episode, while no such event has been noted in any pacemaker patient.

P2342 Spontaneous sarcoplasmic reticulum Ca^{2+} release occurs at lower luminal Ca^{2+} content in heart failure

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Ventricular arrhythmias are common in heart failure (HF). One postulated mechanism for the generation of ventricular arrhythmias is spontaneous sarcoplasmic reticulum (SR) Ca^{2+} release which may generate early after depolarisations via activation of the Na^+-Ca^{2+} exchanger. There is evidence, however, that SR Ca^{2+} uptake and therefore SR Ca^{2+} content is reduced in HF, which would be expected to reduce the likelihood of spontaneous SR Ca^{2+} release. We measured frequency and amplitude of spontaneous SR Ca^{2+} release in permeabilised ventricular myocytes from a rabbit model of HF.

Methods: Single ventricular myocytes were isolated from the hearts of New Zealand White rabbits with HF induced by coronary artery ligation and from sham operated rabbits. Myocytes were permeabilised using β-escin, allowing perfusion of the cytosol with a mock intracellular solution containing 100–250 nM $CaCl_2$. SR Ca^{2+} release was measured by inclusion of Fura-2. The frequency of spontaneous release was measured at 100–250 nM cytosolic [Ca^{2+}]. Amplitude of spontaneous Ca^{2+} release reflected SR Ca^{2+} content.

Results: The table shows that SR Ca^{2+} content was lower in HF cells. Spontaneous Ca^{2+} release is less frequent at low cytosolic [Ca^{2+}], but above 150 nM Ca^{2+}, this difference disappears.

Cytosolic [Ca]	100 nm	150 nm	200 nm	250 nm
HF amp. (nM)	27.2 ± 7.2	37.5 ± 4.3	48.7 ± 4.1	65.6 ± 6.3
Sham amp. (nM)	49.4 ± 7.4	68.4 ± 9.2	73.4 ± 10.4	106.7 ± 14.1
p =	>0.05	<0.05	<0.05	<0.01
HF freq. (Hz)	0.01 ± 0.01	0.03 ± 0.01	0.08 ± 0.01	0.14 ± 0.02
Sham freq. (Hz)	0.03 ± 0.01	0.05 ± 0.01	0.09 ± 0.01	0.14 ± 0.02
p =	>0.05	<0.05	>0.05	>0.05

Conclusion: In situations of increased cytosolic Ca^{2+} levels, spontaneous SR Ca^{2+} release remains a potential arrhythmogenic mechanism despite a reduction in SR Ca^{2+} content.

P2343 Ventricular arrhythmias in rabbits with overload induced heart failure are related to calcium aftertransients

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Background: Ventricular arrhythmias are common in patients with heart failure. Calcium handling is abnormal in failing myocardium. We studied the relation between arrhythmias *in vivo* and calcium handling *in vitro* in a combined volume and pressure overload model of heart failure in the rabbit.

Methods: In control rabbits and rabbits with heart failure (HF rabbits) 24 hour Holter recordings were made. Myocytes were isolated from the same hearts and loaded with Indo-1 to measure intracellular calcium in isolated myocytes. Rapid cooling was performed to estimate sarcoplasmic reticular calcium content (SRCC). Burstpacing during exposure to norepinephrine (50 nMol/L) was used to elicit aftertransients (elevations in calcium following a stimulated calcium transient).

Results: Arrhythmias were not observed in control rabbits (n = 5). In 4 of 6 HF rabbits ventricular couplets and/or short runs of ventricular tachycardia (VT) were detected. In 9 of 13 cells isolated from HF rabbits hearts with couplets or VT, calcium aftertransients could be induced, but only in one out of 18 cells from hearts from control rabbits or HF rabbits without couplets or VT ($p < 0.05$). Both diastolic and systolic calcium were elevated in HF rabbits compared with control rabbits (26 HF rabbit cells vs 17 control rabbit cells: diastolic calcium 125.5 ± 12.0 vs 75.5 ± 5.9 and systolic calcium 285.3 ± 29.7 vs 187.7 ± 16.5, $p < 0.05$). SRCC tends to be higher in myocytes from HF rabbits (23 HF rabbit cells 375.1 ± 46.9 vs 17 control rabbit cells 270.2 ± 17.6 nMol/L).

Conclusion: In rabbits with overload induced heart failure, ventricular arrhythmias are related to calcium aftertransients. The occurrence of aftertransients may be related to altered calcium release from the sarcoplasmic reticulum.

P2344 Transvenous techniques for pacing and ICD leads removal: a long-term single centre experience

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Transvenous removal of pacing and ICD leads has today an high success rate and a low incidence of serious complications. This has changed the management of infected leads as well as of most abandoned leads. However, the procedures are often complex and the experience of the operators seems to affect both results and complications.

Materials and Methods: From December 1989, 582 leads in 365 pts (261 men, 104 women, mean age 65.2 years, range 17–93) were managed. In total, 551 pacing leads, 354 ventricular and 197 atrial leads, and 31 defibrillating leads, among which 21 ventricular, 3 atrial and 7 SVC leads, required removal; their mean implantation period was 66.2 months (range 0.5–276). We used the Cook Vascular extraction kit and, when necessary, other intravascular tools (Catchers and Lassos, Sulzer Osypka).

Results: Among the 582 leads, the technique was judged to be not applicable in 14 (2.4%) leads. Removal was attempted in 568 leads; 534 leads (503 pacing leads and all the 31 ICD leads) were removed (94%). Globally, 91.8% of the leads submitted to our attention were successfully extracted. The success rate has increased over time. In the first 3 years (63 leads) it was 73%, while in the period 1993–95 (160 leads) it was 88.1%; in the last 3 years (345 leads) 97.7% of the leads were removed. Serious complications occurred in 6 cases (1.01%); we observed 3 cases of cardiac tamponade, 2 pulmonary embolisms, 1 undesired dislodgement of a chronic pacing lead.

Conclusions: Our experience shows that the success rate and the complications are highly affected by the experience of the staff. The transvenous removal techniques are very effective in well trained and experienced Centres; the possibility of life-treathening complications requires the availability of cardiosurgical stand-by.

P2345 Ancillary tools in pacemaker and defibrillator lead extraction using the vascoextor lead removal system

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A new pacing lead removal system (VascoExtor, VascoMed, D) with 3 types of locking stylets (S, L or K) and recently 1 type (Magic) was used over 25 months to extract 40 pacemaker leads in 24 pts and 3 defibrillator (ICD) leads in 3 pts (19 men & 8 women, aged 66 ± 14 yrs). Indication was pacer infection (n = 19), pacer (n = 4) or ICD (n = 3) lead dysfunction or prior to ICD implant (n = 1). Leads were in place for 3.7 ± 3.9 yrs. Infections involved both pocket & lead(s) and were due to S. epidermidis (12), S. aureus (5), S. aureus plus E. coli (1) or fungi (n = 1). Skin erosion was present in 14 pts. Of the 40 pacing leads, 10 were unipolar ventricular, 14 bipolar ventricular, 4 unipolar atrial, 8 bipolar atrial, 2 unipolar VDD, all tined, and 2 bipolar active fixation atrial leads. The ICD leads were 2 two-coil leads (Endotak, CPI) and 1 one-coil lead (EnGuard, Telectronics). Using the S (11 pts) or K (7 pts) or Magic (2 pts) stylets, all pacing leads & 2 ICD leads were removed in 20 pts from a right (n = 15) or left (n = 4) or right & left (n = 1) subclavian approach by traction (6 atrial leads) or sole use of VascoExtor stylets (25 pacing leads/2 ICD leads). However, in 7 pts (26%) ancillary tools were required. In 3 pts fragments of atrial and ventricular leads were captured and removed with a noose catheter or a pigtail catheter or a bioptome. In another pt, locking could not be effected and a noose catheter from a right femoral (RF) approach was used and aided by pigtail & Amplatz catheters plus a bioptome to finally remove 2 leads. In a pt with ICD lead, a combined left subclavian (stylet S) and RF approach (using a noose catheter) was required due to lead separation. In a pt with a dysfunctional unipolar ventricular lead implanted 12 years earlier, to facilitate exchange of locking stylets, a motor drive unit was used, but extraction failed. VascoExtor sheaths were helpful only in 1 pt. Finally, lead removal was successful in 26/27 pts (96%) or 42/43 leads (98%) without complications.

Conclusion: to enhance the success of pacing or defibrillator lead extraction with use of the VascoExtor locking stylet system, an array of ancillary tools are required in 26% of pts.

P2346 Usefulness of intracardiac echocardiography during transvenous leads removal procedures. An early experience

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Although transvenous lead removal is today an effective and safe technique, possible life-treathening complications must be considered, which require careful monitoring and fast diagnosis. In addition, the availability of information about 1) the condition of the intravascular part of the leads to remove, 2) the presence and extension of adhaerences to the venous wall, 3) the dimension of endocarditis vegetations and their relation with the cardiac structures, is very helpful for planning and performing removal procedures. The aim of our study was to evaluate the usefulness of Intracardiac Echocardiography (ICE) during transvenous lead removal procedures.

Materials and Methods: ICE was performed in 6 patients (4 men, mean age 74.6 years) who underwent removal of 10 pacing leads due to infection of the pacing system. 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, ICE Ultra, connected to Clear View Ultra EC 1003 ultrasound console (Boston Scientific Corp., S. José, CA, USA). The ICE catheter was inserted through the femoral (5 pts) and right internal jugular vein (1 pt).

Results: In all the patients, the ICE catheter allowed clear visualization of the leads and their course. The adhaerences to the venous wall were easily detected in all cases. During dilation by sheath, ICE allowed monitoring the dilation, and the relation between the sheath and the anatomical structures. In 1 patient, ICE allowed detection of small vegetation on the lead, which was not identified by TEE. During the removal procedure, the position of the vegetation and its relation with the dilating sheath were easily monitored. No complication related to the use of ICE was observed.

Conclusions: Transvenous lead removal represents another field for possible application of ICE. Our initial experience confirmed the usefulness of this imaging technique in guiding the procedure and monitoring the possible complications.

P2347 Laser-assisted endocardial lead extraction: a venographic study

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Excimer laser assisted endocardial lead extraction is described as a safe and efficacious procedure. Although the laser energy used has a limited adsorption depth (0.06 mm), it is not clear whether or not local tissue damage can unexpectedly occur, and cause unwanted complications.

We retrospectively assessed the effects of laser-assisted lead extraction on related venous structures.

Fourteen patients (pts) (12 male) required complete explantation of pacing systems for infection (7), erosion (6), and intractable discomfort (1). Mean age (+SD) was 64.4 +16.2 years. Mean duration (+SD) of lead implant was 91.9 +23.3 months. Total leads removed were 36 leads (2.6/patient). Laser assisted extraction was required for 28 leads, whereas countertraction using a locking stylet was sufficient for the remaining eight leads. No acute complications occurred. One pt developed superior vena caval obstruction within 4 weeks.

Venography was performed in this cohort of pts. Mean duration to venography (post-procedure) was 18 weeks (14.8). Venography in 6 (43%) of the pts demonstrated abnormalities of the implantation vein. Four pts had complete occlusion of the implant subclavian vein, of which three were asymptomatic. The other two had narrowing of the subclavian vein. The remaining eight venograms were normal.

Conclusion: Despite the reported safety of laser-assisted endocardial lead extraction, venography demonstrates that damage to associated venous structures is common. This may be of no clinical consequence, but further long-term follow-up is necessary.

P2348 Injury of the tricuspid valve resulting from laser sheath extraction of chronically implanted pacemaker and ICD leads

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Introduction: The laser sheath is successful for extracting chronically implanted pacemaker and ICD leads. However, there are no data on the risk of injuring the tricuspid valve with application of the laser during extraction of ventricular leads. Therefore, transesopagheal echocardiography was performed before and after laser sheath extraction.

Methods: In 12 consecutive patients (pts) 9 ventricular pacing leads and 3 ICD leads were extracted with an Excimer laser sheath. Mean age 61.5 years (range 33 to 85 years). A 12 F laser sheath was used in 7 leads, a 14 F in 2 leads, a 16 F in 2 ICD leads and a 12 F and 16 F in one ICD lead. Indication for extraction was infection in 5 pts and lead malfunction in 7 pts.

Results: Before extraction, 9 pts had mild, 3 pts moderate tricuspid valve regurgitation. After extraction, regurgitation remained unchanged in 9 pts but increased from mild to moderate in 3 pts, including an ICD patient. In all 3 pts a new regurgitation jet through the leaflet was apparent with colorflow. A new tear in a leaflet was visible on 2-D echocardiography in 2 pts. The laser sheath used in these pts was 12 F in 2 pts, 12 F/16 F in 1 pt. (ICD lead).

Conclusion: Laser sheath extraction of ventricular pacemaker and ICD leads resulted in direct injury to the leaflets of the tricuspid valve in 25% of pts, with significant echocardiographic increase in valve regurgitation. Although the clinical consequences need further evaluation, these results caution against indiscriminate extraction of multiple superfluous leads in asymptomatic patients.

P2349 Prevention of pacemaker and defibrillator infections: safety and efficacy of perioperative H_2O_2 use in 990 patients

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Background: Infections of biomaterials are of concern following implantation. Despite the preventive use of antibiotics, there is an infection rate of 2–5% associated with implantation of pacemakers and defibrillators.

Methods: In collaboration with the institute for microbiology we tested the possible benefit of 3% H_2O_2 in treating polyurethane and silicone electrodes and found a significant reduction of the number of bacteria after a single wiping and rinsing and of the polymere structures. Additional in vitro tests also showed that 3% H_2O_2 had no effect on the structural integrity of the silicone and polyurethane material determined by SEM and by mechanical testing. Based on these experimental results, all patients (pts) were prospectively treated with the adjunctive use of 3% H_2O_2 during implantation. A single dose of a standard cephalosporine was given before implantation to all pts.

Results: From 1993 to 1997, 990 pts were operated by the same implanting cardiologist. 721 operations were new implantations, 269 replacements. Among those were 150 defibrillator, 435 DDD, 139 AAI, and 266 VVI pacemaker implantations. The mean age for pacemaker pts was 73.2 ± 12.5, for defibrillators 56 ± 11.6 years. The mean operation time for pacemakers was 42.4 ± 22.7, for defibrillators 51.3 ± 25.6 minutes. Among those 990 pts, one infection of a defibrillator and one infection of a pacemaker occurred in the perioperative setting, both with staphylococcus epidermidis (0.2%). The infection rate for the same center and implanting physician with no significant difference as far as the type of pacemaker, age or other patient related factors were concerned, showed an infection rate of 1.83% for the years prior to the use of H_2O_2 ($p < 0.01$).

Conclusions: The perioperative use of H_2O_2 in 990 pts reveals this method to be highly effective and safe in the prevention of perioperative infections of pacemakers and defibrillators. Its use is simple, fast and highly cost-effective.

P2350 Myocardial perfusion abnormalities in permanent paced patients without coronary artery disease

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The aim of this study was to evaluate the frequency and the topography of myocardial defects (M.D.) assessed by Thallium tomography (SPECT) in patients (pts) with permanent cardiac pacing. 28 pts implanted with dual chamber pacing for AV block (18 pts) and sinus node disease (10 pts) with normal coronary arteries were included in this prospective study and were divided in group 1 (16 pts) with normal myocardial perfusion and group 2 (12 pts) with reversible or not myocardial defect. All pts underwent exercise test, dipyridamole SPECT, echocardiography with analysis of septal movement (S.M.) radionuclide angiography with left ventricular ejection fraction (LVEF) and coronary angiography. Thallium images were divided in 16 segments and the severity of reduction in Thallium uptake was scored using a four point grading system in each patient (1 = normal uptake to 4 = severe reduction).

Results:

	Group 1	Group 2	
Age	66.3 ± 5.5	64.1 ± 11.6	NS
Angina	11	9	NS
Permanent pacing (mths)	54 ± 22.8	48.4 ± 21.8	NS
LVEF (%)	63.7 ± 3.7	53.1 ± 5.6	$p < 0.0005$
Paradoxal S.M.	5	10	$p < 0.01$

In 9 pts. reversible or irreversible defect was present in infero-apical (75%) or septo-apical territory (25%). A good correlation was noticed between the severity of defect and altered LVEF in paced pts.

Conclusion: Moderate M.D. can be induced by permanent cardiac pacing in pts without CAD (42.9%). Apical permanent pacing can deteriorate LVEF in some pts with myocardial perfusion abnormalities.

P2351 A new algorithm to optimize the AV delay based on the QT interval: for which patients?

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Optimal programming of AV delay (AVD) in dual chamber pacemaker is essential to allow a good mechanical synchronization of the atrium and ventricle, and an adequate ventricular filling time. Our previous studies showed an apparent relation between the optimal AVD and the longest QT interval (Qti). The aim of the study was to evaluate accurately the variations of QTi versus the AVD. The study was conducted in 11 patients (pts), 70 ± 18 years old, presented with a 2/1 (4 pts) or a complete AV block (7 pts) and implanted with a Vitatron Diamond I or Diamond II device. Ejection fraction (EF) was normal (>60%: EFN) for 7 pts and low (<45%: EFL) for 4 pts.

Methods: Pacing rate was fixed at 80 bpm to capture the atrium. The pacing mode was set on DDDR mode and the AVD varied from 90 to 300 ms by step of 30 ms. External ECG associated with device event markers was recorded continuously during all the measurements at a paper speed of 200 mm/sec to measure accurately QTi.

Results (*: $p < 0.005$):

(ms)	EFN	EFL	p
Optimal AVD	130 ± 50	168 ± 62	0.16
Longer QTi	334 ± 16	374 ± 19	0.003*
Non adequate AVD	186 ± 45	214 ± 70	0.24
Shorter QTi	331 ± 16	367 ± 20	0.007*
p (AVD)	0.23	0.21	
p (QTi)	0.0014*	0.0011*	

Conclusion: The new results confirmed the existing relation between QTi and optimal AVD. The most significant variation was found for patients with low EF. A new study has been set up to measure automatically QTi for different AVD.

P2352 Three-year follow-up of VDD therapy: results of the ELVIS study

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The aim of the study was to evaluate the role of VDD-pacing in pacemaker-therapy.

Methods: From 19. Jan 94 to 26 July 96 176 patients (p) in 10 German investigational centers recieved the VDD-pacer Unity™ (Intermedics, Angleton TX, USA) for symptomatic AV block. All p were chronotropically competent. 36 months post implant data from 99 p were analyzed.

Results: Of these 99 p 28 died, of which in 22 cases the underlying cause was heart disease. No significant changes concerning sinus node function could be observed over time. AV-sequential stimulation reached 98.1%, mode survival was 92% at 36 month follow-up.

Follow-Up	1 month	12 months	36 months
Patients (n)	102	153	71
Sinus rate (min^{-1})	76.8 ± 14.7	75.2 ± 13.6	80.7 ± 15.4
AV-synchronisation (%)	96.5 ± 6.6	98.0 ± 4.9	98.1 ± 15.4
VVI-stimulation (%)	2.2 ± 5.9	1.1 ± 4.8	0.8 ± 2.6
Mode-survival (%)	100	93.4	92.0
Permanent Afib (%)	0	3.2	8
Paroxysmal Afib (%)	n.i.*	n.i.	9%
Revisions (n)	3	0	0
Atrial signal (mV)	1.1 ± 0.5	1.2 ± 0.5	1.2 ± 0.4
Deaths (n)	0	8	28

*not investigated

The incidence of permanent atrial fibrillation (pAfib) reached 3.2% within the first year and 8% at the end of the 36 months period. Paroxysmal Afib was recorded in 9%. 4 of the p with pAfib had CAD, one had hypertonus. No significant difference regarding sinus rate and p-amplitude at 1 month follow-up could be observed in comparison to those p, in whom no Afib evolved over time. P with sinus rates between 50 and 60 min^{-1} did not develop Afib. Need for revision was very low with a rate of 1.7%.

Conclusions: 1. VDD-pacing is physiologic and efficient. 2. Incidence of pAfib is associated with the underlying heart desease and not with the VDD-mode. 3. Need for revision is low.

P2353 One-year follow-up multicentre study using the Olbi stimulation technique with an implantable single-lead pacing system

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Purpose: In a multicenter study the clinical practicability of single lead dual chamber stimulation was investigated. During the 12 months follow-up the feasibility of the atrial stimulation with biphasic pulses, the chronaxy rheobase relation during floating stimulation and the technical integrity of the lead were proven.

Methods: In 42 pts (mean age: 75 ± 10 years), indication AV-block II–III without sinus node dysfunction, a single lead VDD system (DROMOS SL M7, BIOTRONIK) was implanted, which is able to stimulate the atrium with two overlapping biphasic pulses (OLBI-Stimulation). We determined the atrial and diaphragmatic pacing threshold at 4 different pulse durations in different positions up to 12 months after implantation.

Results: For the chronaxy rheobase relation only the examinations with successful atrial stimulation at 0.25 ms, 0.5 ms, 0.75 ms and 1.0 ms pulse duration were used. For discharge the pulse duration threshold relation is shown in the following table:

Pulse duration (ms):	0.25	0.50	0.75	1.00
Atrial threshold (V):	2.94 ± 0.99	2.23 ± 0.67	1.99 ± 0.61	1.85 ± 0.47

The atrial stimulation was successful in 27 of 42 patients at discharge, in 22 of 33 patients at 6–8 weeks follow-up, in 15 of 30 patients at 6 months follow-up, and 13 of 22 patients 12 months post implantation. The atrial pacing threshold at 0.25 ms pulse duration increased from 2.7 V at discharge to 3.1 V at 6 months to 3.3 V at 12 months follow-up. The P-wave amplitude decreased from 1.7 mV at discharge to 1.5 mV at 6 months follow-up and to 1.4 mV at 12 months follow-up.

The development of the ventricular sensing and pacing threshold is shown in the following table:

	Discharge	6–8 weeks	6 months	12 months
R wave (mV):	9.7 ± 3.9	12.3 ± 4.8	13.1 ± 5.0	12.6 ± 6.5
Pacing threshold (V):	1.5 ± 0.7	1.6 ± 0.7	1.5 ± 1.3	1.3 ± 0.4

Conclusion: With the use of OLBI stimulation the successful stimulation of the atrium is possible. The lead shows a high reliability concerning the atrial and ventricular sensing threshold, and the ventricular pacing threshold. It could be demonstrated that there exists a well defined chronaxy rheobase relation for atrial pacing using the OLBI stimulation. For the clinical application further technical developments are necessary.

P2354 Clinical validation of new pacing-sensing configurations for automatic atrial capture verification in pacemakers

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Introduction: Automatic Capture Verification (ACV) may guarantee maximal patient safety; it may also increase device longevity and save time during follow-ups. A major obstacle for ACV by evoked response detection is pacing induced afterpotential (AP). It is more problematic in atrial than in ventricular ACV, because atrial evoked response (AER) is smaller and occurs earlier after pacing. The aim of this study is to perform atrial ACV by analyzing AER signals using a conventional monophasic waveform to pace atrium between A-tip and Can. To reduce AP, small coupling capacitors (CC), and independent pairs of electrodes between A-ring and V-tip (AV) or between A-ring and an electrically isolated indifferent electrode (AI) were used for AER sensing.

Method: Patients (pts), indicated for DDD pacemaker, were included in the acute study. After lead implantation and routine measurements, a custom made external pacing system (Guidant/CPI, St. Paul, MN) with multi-channel data acquisition capability was connected to the leads. An automatic protocol with step-up and stepdown pacing (0.1 to 7.1 V at 0.5 ms, steps of 0.1 V) was performed. Different CC (2 μF and 15 μF) were used. AI and AV signals were independently analyzed both real-time and off-line to detect AER. Every pacing beat was also visually inspected and compared with surface ECG to verify capture. With the intracardiac signals properly filtered, the detection was based on the signal within a window of 12–60 ms after the pacing spike.

Result: Data from 17 acute pts, age 66.0 ± 13.0 yr., were analyzed. Bipolar atrial lead measurements, using a standard PSA, were (mean ± SD) impedance 736 ± 240Ω, P-wave amplitude 4.7 ± 2.5 mV, slew-rate 1.7 ± 1.3 $V.s^{-1}$ and pacing threshold at 0.5 ms 0.9 ± 0.4 V. The results with CC = 2□F showed that out of 3225 collected atrial pacing beats, correct capture verification was 99.91% for sensing in the AI and 99.44% in the AV channel. Although smaller CC is preferable for shorter and smaller AP, the results showed that larger CC worked well too (99.91% and 99.41%, respectively).

Conclusion: The new independent pacing-sensing configurations can greatly reduce and shorten after-potentials. Therefore, they provide AER signals that can be used for atrial ACV.

P2355 Correlation between sensor signal and sinus rhythm in patients implanted with a rate responsive pacemaker driven by contractility: long-term evaluation

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Background: From December 95 to October 97, 100 patients (pts) were implanted with the dual chamber Rate Responsive (RR) system (SORIN Living 1 – BEST) for a multicentric European clinical evaluation. The first study assessed the good correlation between Peak Endocardial Acceleration (PEA) and sinus atrial rate and demonstrated that PEA is a significant parameter for driving RR.

Aim of the study: From January 97 to October 97 a group of 70 pts enrolled in the clinical study (mean age 67 ± 11.8 yrs, 42 male, 28 female) were evaluated at 1 year. Sixty-one pts out of 70 underwent stress test, and in 42 pts 24 h Holter monitoring, including continuous recording of the PEA signal, was performed. PEA signal values at rest and during stress test were analysed and compared with 1 month data.

Results: The PEA and HR data at 1 year vs 1 month are summarised in the following table:

	Basal conditions		Maximum	
(1 g = 9.8 m/sec^2)	PEA (g)	HR (ppm)	PEA (g)	HR (ppm)
1 month	0.41 ± 0.26	73 ± 9	1.63 ± 0.77 ± 123 ± 20	
1 year	0.45 ± 0.29	71 ± 11	1.72 ± 0.83	127 ± 15

The PEA vs HR correlation during stress test at 1 month was R = 0.63 ± 0.16 ($p < 0.005$) while at 1 year was R = 0.71 ± 0.18 ($p < 0.005$). During the 24 h Holter monitoring the PEA signal followed very closely the spontaneous heart rate (data at rest: PEA = 0.41 ± 0.3, HR = 65 ± 10; during activity: PEA = 1.4 ± 0.7, HR = 104 ± 18).

Conclusions: The 1 year follow-up data confirmed a good correlation between PEA and spontaneous heart rate in patients with normal sinus function. The PEA signal demonstrated to be a stable parameter in long term conditions and reliable to be used as physiological sensor in driving RR pacemakers and monitoring heart rate changes. The long term experience also demonstrated the absence of any adverse effect and the reliability of the sensor mounted on the tip of a standard lead.

P2356 Threshold values in biventricular pacing for congestive heart failure

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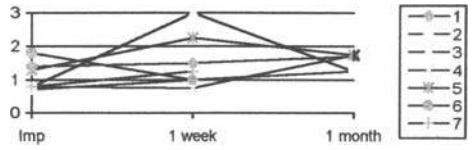
Synchronous biventricular pacing with the electrodes implanted in the right ventricule (RV) and the coronary sinus (CS) has been evolved as a new modality for intractable congestive heart failure. Pacing threshold (T) in CS has been a major limitation for left ventricular (LV) pacing. However with the new CS leads and new lead technology it has been possible to achieve lower T values. We evaluated the T values in biventricular pacing during implantation and follow-up up to 1 month.

Methods and Results: Seven patients (5 M, 2 F; mean age 61.6 ± 8.5, range 52–73), 5 ischaemic and 2 idiopathic dilated cardiomyopathy were included in the study. Mean efor capacity was 3.0 ± 2.7 METS with Naughton protocol and mean EF was 27.9 ± 10.8%. All patients had intraventricular conduction defect and 2 had atrial fibrillation. RV and CS leads (Medtronics 2188 CS lead) and an additional atrial lead for the patients in sinus rhythm were implanted with a mean implantation time of 93.0 ± 12.8 min and a mean scopy time of 28.8 ± 5.1 min. T values for atrium, RV and CS could be measured separately as the QRS axis changed at the point of CS T with the output gradually decreased. T values are given below.

	Baseline			First Week
	Threshold (V)	P or R wave (mV)	Impedance (Ω)	Threshold (V)
Atrium	0.8 ± 0.2	11.6 ± 8.2	507 ± 130	0.6 ± 0.3
RV	0.4 ± 0.1	19.9 ± 6.6	606 ± 110	0.7 ± 0.3
CS	1.1 ± 0.4	19.2 ± 9.5	629 ± 136	1.5 ± 0.9
Biventricular	0.8 ± 0.3	22.1 ± 7.2	836 ± 199	1.5 ± 0.9



Conclusion: Therefore we conclude that pacing from the CS with the new electrodes may solve the T problem for LV pacing.

P2357 Feature of the clinical manifestation of myocardial infarction in females in Kyrgyzstan

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The aim of the investigation was to evaluate feature of the clinical course of myocardial infarction (MI) in females. Case histories of 387 patients with MI who were admitted to the coronary care unit were studied. Risk factors, clinical manifestation, complications and in hospital mortality were evaluated. There were 262 males and 125 females. The mean age of males and females was 55.8 ± 3.0 and 62.9 ± 3.1, respectively ($p > 0.05$). White females had more frequently MI than Kyrgyz females (80.8% vs 7.2%, $p < 0.001$). Majority females (93.6%) had menopausal period. Females as compared to males more frequently had prior history of arterial hypertention (43.2% vs 16.8%, $p < 0.01$), type I and II diabetes (15.2% vs 5.7%, $p < 0.01$), obesity (16.0% vs 6.9%, $p < 0.01$). Females less frequently had previous MI (13.6% vs 24.8%, $p < 0.01$), smoking (8.0% vs 52.0%, $p < 0.001$). There were no significant difference in the size, localization and incidence of necrosis by ECG between the groups. Females had a somewhat higher incidence of heart failure (Killip) during the in hospital period than males but the difference was not statistically significant (35.9% vs 28.6%, $p > 0.05$). Recurrent MI occurred more often in females compared to males (18.4% vs 9.5%, $p < 0.05$). In hospital mortality rate was of 12% in females vs 5.7% in males ($p < 0.05$).

Thus, the incidence of MI is lower in females than in males. MI more frequently develops in white females with more comorbid condition: hypertention, diabetes, obesity. The incidence of recurrent ischemia, in hospital mortality occurs more frequently in females.

P2358 Silent myocardial ischaemia and diabetes mellitus in Mexican patients with coronary heart disease

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Patients with diabetes are at increased risk for coronary heart disease and perhaps also for silent ischemia. We conducted a cross-sectional study to assess the effect of diabetes on the occurrence of silent ischemia.

Methods: A total of 249 patients with coronary heart disease was screened with a 24-hour Holter electrocardiogram. Silent myocardial ischemia was diagnosed according to the American Heart Association criteria. All recordings were blinded analyzed by two independent physicians and one of the authors. Diabetes was diagnosed according to the American Diabetes Association criteria. Continuos variables were analyzed using ANOVA or the Kruskal-Wallis (KW) test. To evaluate the independent effect of diabetes on the occurrence of silent ischemia, a logistic regression analysis was conducted. Odds ratios (OR) were calculated to assess association, with 95% confidence intervals ($CI_{95\%}$).

Results: There were 165 non-diabetics and 84 diabetics. Silent ischemia was more frequent in diabetics (52% vs. 44%), but there was no difference on the mean number of ischemic events. Total ischemic time per 24 hours was similar, but the median duration of ischemia in 24 hours was greater in diabetics (66 minutes vs. 40.5 min.; KW = 4.8, p = 0.03), as was the median ischemic time per episode (41.3 vs. 27.6; KW 5.31, p = 0.02). Duration of diabetes was related to silent ischemia and there was a 3.5% increased risk for each year of diabetes history (OR 1.03, $CI_{95\%}$ 1.0–1.08).

In conclusion, diabetes may increase the risk of silent myocardial ischemia. Diabetic autonomic neuropathy involving the cardiac afferent sympathetic system may be its cause. Silent ischemia seems to be more severe in diabetics, mainly as the evolution of the disease is longer.

Day 4

Tuesday, August 31, 1999

OPTIMIZED CARDIAC PACING

2440 Haemodynamic effects of adjunct DDD-pacing in patients with high-grade atrioventricular block after transcoronary ablation of septum hypertrophy for hypertrophic obstructive cardiomyopathy

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Transcoronary ablation of septum hypertrophy (TASH) is an effective catheter interventional therapy for HOCM. However, beside reduction of septal thickness, elimination of outflow obstruction and improvement of symptoms, the injection of 96% ethanol into a first septal branch leads to intermittent or permanent high-grade AV block in up to 28% of the pts..

To evaluate the relative merits of isolated TASH compared with those of a combined therapy, the symptomatic and hemodynamic benefits of adjunct DDD-pacing were estimated by serial invasive measurements 2 weeks and 7 months after intervention. 32 out of 119 pts. (27%) treated catheter-interventionally were provided with a dual-chamber pacemaker because of high-grade AV block 48 hours after TASH, and 9 additional pts. (8%) had preexisting pacemaker therapy of HOCM. During follow-up pacemaker dependence was observed in 14 pts. (12%) because of a persistent high-grade AV block. With regard to baseline characteristics – like age, gender, septal thickness, gradients, NYHA functional class, exercise tolerance and PA-mean pressure at workload – no significant differences were found between the 78 pts. (65%) with an isolated TASH-procedure and the 41 pts. (35%) with a concomitant DDD-pacemaker therapy.

In the "pacemaker provided group" the decrease in resting gradient (-38 ± 40 versus -45 ± 37 mmHg, n.s), postextrasystolic gradient (-109 ± 60 versus -108 ± 48 mmHg, n.s.), NYHA functional class (-1.4 ± 0.7 versus -1.3 ± 0.6, n.s.) and pulmonary artery mean pressure at workload (-8 ± 9 versus -8 ± 8 mmHg, n.s.) did not exceed the effects documented in the "isolated TASH group". However, pts. with an isolated TASH procedure demonstrated a more pronounced improvement of the exercise tolerance ($+28 \pm 23$ versus $+15 \pm 21$ watts, $p = 0.044$), a more complete preservation of the left ventricular ejection fraction (-1% versus -5%) and were treated by a lower amount of ethanol injected (3.2 ± 1.9 versus 4.1 ± 2.6 ml).

Conclusion: The necessity of adjunct DDD-pacing seems to be a result of a more aggressive ablation procedure and does not improve the symptomatic and hemodynamic benefits of TASH in HOCM.

2441 Effect of atrioventricular delay on left ventricular diastolic function in patients with DDD-pacing for complete atrioventricular block

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Dual Chamber (DDD) pacing with a short atrioventricular (A-V) delay may improve cardiac function in patients (pts) with heart failure and compromised systolic left ventricular (LV) function, as suggested by preliminary observations. However, comprehensive data on how permanent DDD-pacing affects hearts with abnormal LV-diastolic parameters and preserved systolic LV-function are currently incomplete. This study was designed to evaluate how A-V delay affects already impaired Doppler-derived LV-diastolic indexes in pts with normal systolic LV-function.

Methods: Eleven pts [5 males/6 females aged 65.4 ± 14.2 years (range 25–78)] were enrolled. Pts had a DDD pacemaker implanted for complete A-V block, were asymptomatic (NYHA Class I, LV-ejection fraction > 57%) and were examined 1 year after implantation. Pts underwent Doppler assessment of transmitral flow during pacing at A-V delay values of 100, 150 and 200 ms in a randomized fashion. The following Doppler indices were measured: peak E wave velocity (PVE), peak A wave velocity (PVA), E/A ratio, E wave deceleration time (DTE), mitral filling time (MFT) and isovolumic relaxation time (IVRT). Calculations were done at a constant heart rate of 80 bpm in all pts.

Results: Comparisons between measurements at different A-V delay values are depicted in the table. DTE could not be measured at 200 ms because of E and A wave fusion. "p" denotes overall significance for repeated measures ANOVA test.

Variables	Atrioventricular delay values (ms)			p
	100	150	200	
PVE (m/s)	0.50 ± 0.11	0.48 ± 0.13	0.45 ± 0.12	<0.0005
PVA (m/s)	0.82 ± 0.19	0.88 ± 0.14	0.94 ± 0.15	<0.001
E/A ratio	0.63 ± 0.23	0.56 ± 0.14	0.50 ± 0.12	<0.037
MFT (s)	0.39 ± 0.05	0.36 ± 0.04	0.31 ± 0.04	<0.0005
IVRT (s)	0.10 ± 0.02	0.11 ± 0.02	0.10 ± 0.01	<0.352
DTE (s)	0.12 ± 0.02	0.10 ± 0.01	–	–

Paired comparisons between the various A-V delay values investigated showed significant differences in all variables studied except IVRT (the highest significance [$p < 0.0005$] was found comparing A-V delay values of 100 and 200 ms).

Conclusion: During permanent DDD-pacing for complete A-V block, Doppler indices of diastolic LV-function improved significantly at the shortest A-V delay value investigated (optimal measurements at 100 ms).

2442 Optimized atrioventricular pacing on right, left or biventricular sites impressively improves quality of life

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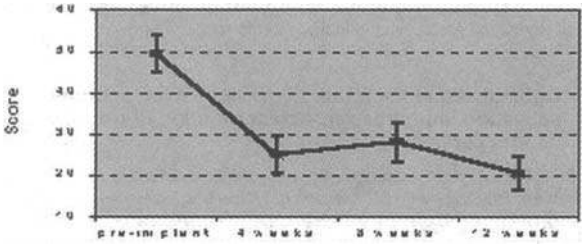
Atrioventricular (AV) pacing has recently been introduced as a promising method to improve clinical outcome in patients (pts.) with end-stage congestive heart failure (CHF).

Methods: In 42 pts. (21 males, 21 females, 60 ± 6 years) with CHF (EF $21 \pm 7\%$), permanent pacemaker systems for right (RV), left ventricular (LV) or biventricular (BIV) stimulation were implanted. Best unichamber (RV or LV) and BIV modes at different AV intervals were evaluated in terms of pulse pressure and first derivative of LV pressure (dP/dt). For long term follow-up, pts. were stimulated at best unichamber or BIV mode for 4 weeks (w) in a randomized fashion. After a wash-out period with no pacing for another 4 w, permanent pacing in the remaining mode was tested. Quality of life was evaluated by the Minnesota Living with Heart Failure Questionnaire (LHFQ), designed for CHF patients. LHFQ contains 21 items addressing physical and emotional dimension.

Results: Improvement in quality of life observed by reduction of LHFQ Score could be demonstrated impressively after 4 weeks ($p < 0.001$). After a wash-out period (8 weeks) with no benefit, further improvement occurred at 12 weeks ($p < 0.05$ vs. 8 weeks). Interestingly, gender analysis showed much more benefit for males than for females ($p < 0.05$).



LHFQ Score.

In conclusion, permanent AV sequential pacing at best unichamber or biventricular mode impressively improves quality of life. Available data encourage this new therapeutic option in CHF patients.

2443 Effects of lead position on cardiac function in de novo dual-chamber implants: a randomised, prospective study of high septal versus apical lead positioning within the normal heart

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Background: Right ventricular apical pacing is known to produce localised areas of left ventricular (LV) hypertrophy due to abnormal contraction patterns. This produces dyskinetic wall motion resulting in systolic and diastolic dysfunction. A more physiological approach may be to position the lead on the interventricular septum in order to more closely mimic normal activation sequences. Whilst alternative pacing sites are becoming more readily accepted as an option for lead placement, little is known of the consequences of septal pacing in the normal heart, or more importantly whether this method can preserve cardiac function.

Methods: We studied 24 patients receiving first implant dual chamber pacemakers for high degree AV block with normal ventricles [Fractional Shortening (FS) > 30% determined by echocardiogram, no regional wall motion abnormality and no history of cardiac disease]. Patients were randomised to septal (n = 11) or apical pacing (n = 13). Echocardiograms were performed at 24 hours, 1 and 4 months post implant to measure LV systolic (LVIDs) and diastolic (LVIDd) internal dimensions and FS. All patients were ventricular pacing dependant.

Results: LVIDd was significantly lower in the septal group at 24 hours, 1 and 4 months poat implant, and LVIDs at 24 hours and 1 month. Data are shown as mean ± standard deviation (SD)

	LVId (mm)		LVIDs (mm)		FS (%)	
	Apical	Septal	Apical	Septal	Apical	Septal
24 hr	49 ± 4.3	44 ± 6.9*	36 ± 5.9	31 ± 4.6*	36.6 ± 9.9	38.5 ± 6.9
1 M	52 ± 5.1	43 ± 4.0*	36 ± 4.9	31 ± 4.2*	35.9 ± 7.8	37.8 ± 8.9
4 M	53 ± 5.9	43 ± 6.6*	37 ± 5.8	31 ± 5.9	36.2 ± 7.8	38.5 ± 7.8

*$p < 0.05$

Conclusion: These data suggest preserved systolic function in patients with septal leads as compared to the apically paced group. These data suggest that septal pacing in the previously normal heart preserves left ventricular function better than traditional apical pacing in the short to medium term.

2444 Optimal sequence rather than minimal asynchrony of activation improves ventricular function during ventricular pacing

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Abnormal electrical activation, as occurring during ventricular pacing and left bundle branch block (LBBB), reduces LV pump function. We compared two approaches to optimize LV function using ventricular pacing: minimal asynchrony and optimal sequence of electrical activation.

Methods: ECG and hemodynamics (aortic flowprobe, LV pressure and its 1st derivative LVdP/dt) were measured in anesthetized open-chest dogs during pacing (DDD AV interval 25 ms) from various sites. Experimental LBBB was induced by RF-ablation.

Results: In normal hearts (n = 7) QRS duration (measure of asynchrony of activation) was 47 ± 5 ms during sinus rhythm and increased to 110 ± 12 ms during pacing at the right ventricular (RV) apex. When pacing at the LV apex and LV base QRS duration was 8 ± 7%* and 15 ± 7%* longer than during RV apex pacing, respectively (* = $p < 0.05$). Stroke volume (SV) and LVdP/dtmax, however, were larger during LV apex (15 ± 16%* and 10 ± 12%*, respectively) and LV base pacing (11 ± 12%* and 3 ± 12%, respectively) than during RV apex pacing. Simultaneous pacing at RV apex+LV apex, RV apex+LV base and RV apex+LV base+LV apex decreased QRS duration by approximately 20% as compared with RV apex pacing and resulted in LVdP/dtmax and SV values similar to those during pacing at the LV apex alone. In hearts with LBBB (n = 5), QRS duration ranged from 82 to 100 ms. QRS duration could be reduced by as much as 19–30 ms when using AV sequential pacing at one or more LV sites and AV-intervals of 40–100 ms. However, optimal LV function was obtained when using AV intervals 20–50 ms shorter than used to obtain the shortest possible QRS duration.

Conclusions: During cardiac pacing in normal and LBBB hearts more synchronous electrical activation may improve LV function, but the best LV function is obtained by optimizing the sequence of electrical activat-ion, e.g. to activate the LV wall before or simultaneous with the RV wall.

2445 Haemodynamic improvement by transvenous left ventricular pacing with a new over the wire lead (Easytrak) in patients with congestive heart failure

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Multisite pacing has been recently introduced to improve clinical outcome in patients (pts.) with end-stage cardiomyopathy. Benefit of right ventricular (RV), left ventricular (LV) or biventricular (BIV) pacing is still controversial, although acute data favour LV or BIV being superior to RV pacing.

Methods: In a new approach of stimulating the left ventricle through coronary branch veins emptying into the great cardiac vein and coronary sinus (CS), a new Over The Wire (OTW) coronary venous pacing lead ("Easytrak")was implanted in 30 patients with congestive heart failure (NYHA II-III) during EP study. After coronary venogram, OTW was advanced through a new designed guiding catheter for access to CS. In 6 pts., cardiac output (CO) was determined by thermodilution, and RV, LV and BIV pacing under VDD pacing with 4 different atrioventricular intervals (AVI) (40, 80, 120 and 160 ms) were compared to baseline.

Results: LV coronary veins could be reached in 23 of 30 pts (77%). Pacing threshold (PT) at apex was 2.8 ± 0.4 mV, at mid ventricular level 3.2 ± 0.5 mV and at base 5.0 ± 0.5 mV ($p < 0.05$ vs. apex). If more than one vein was tested best PT was 1.7 ± 0.5 mV. R wave amplitude was >7 mV in all cases. CO increased from 3.9 to 4.3 l/min at VDD pacing with AVI of 40 ($p < 0.03$), 80 ($p < 0.05$) and 120 ms ($p < 0.02$) under LV pacing only. With LV AVI 160 ms, RV, and BIV pacing, no significant increase was observed.

In conclusion, the new OTW pacing lead seems to be a useful tool for left ventricular multisite pacing. Access to different pacing sites was achieved with acceptable PT. Hemodynamic benefit for LV pacing could be demonstrated, promising improvement of LV performance in severe congestive heart failure.

BRUGADA'S SYNDROME: CLINICAL AND GENETIC ASPECTS

2446 Novel mutations in SCN5A causing long-QT and Brugada's syndromes and their functional consequences on human cardiac voltage-gated sodium channel

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Introduction: Familial long QT syndrome (LQTS) and Brugada syndrome are two distinct hereditary cardiac diseases causing ventricular tachyarrhythmias (torsade de pointes) or idiopathic ventricular fibrillation and sudden death.

In this study we report the electrophysiological characteristics of two novel mutations in SCN5A (the cardiac sodium channel gene) causing LQTS (E1784K) and Brugada syndrome (R1512W).

Method: The mutant channels were expressed in a mammalian expression system and studied using the patch clamp technique.

Results: The E1784K mutation found in LQTS patients is located in the C-terminal region of the sodium channel and showed a persistent inward sodium current (1.5% at −20 mV) and a faster recovery from inactivation, for example at −120 mV, the time constant of recovery from inactivation was 6.4 ± 0.6 ms (n = 4) compare to 12.7 ± 0.4 ms (n = 5)for wild-type hH1. No effect on steady-state inactivation parameters were observed.

The R1512W mutation found in a patient with Brugada syndrome is located in the III-IV linker of the sodium channel. The R1512W mutation produced a slowing of both inactivation and recovery from inactivation. For example, at a holding potential of −120 mV the time constant of recovery from inactivation was of 16.3 ± 1.8 ms compare to 12.7 ± 0.4 ms for wild-type hH1. This slowing of recovery from inactivation seen with this Brugada syndrome mutation could reduce the availability of sodium channels after each stimulation, and could change conduction velocity.

Conclusion: We conclude that the different clinical manifestations of these two mutations, originate most probably from the distinct electrophysiological abnormalities of the mutated cardiac sodium channels.

2447 A single SCN5A mutation causing both long-QT and Brugada's syndrome

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SCN5A, the gene that encodes the human cardiac Na^+ channel a-subunit, is mutated in LQT3 and in Brugada syndrome. The two syndromes display readily distinguishable ECG patterns but share the clinical feature of a high incidence of nocturnal sudden cardiac death. We have screened SCN5A in a large 8-generation kindred (n = 209) characterized by a high incidence of nocturnal sudden death, QT-interval prolongation and the Brugada syndrome ECG occurring in the same subjects. ECGs could be obtained from 119 individuals of whom 79 adults ($\geq$16 y) had a definite genetic status (gene carriers n = 43, non-carriers n = 36). In affected individuals heart rate is relatively slow ($P < 0.02$), PR and QRS durations are slightly prolonged, right precordial R-wave amplitudes are low and QT intervals are markedly prolonged ($p < 0.0001$ for all parameters). ST-segment elevation in the right precordials leads was present as well ($p < 0.0001$). 25 family members died suddenly, 16 of them typically between 04:00 and 07:00 A.M.

Linkage analysis in a subset of the family revealed complete linkage between 8 affected, 3 possibly affected and 12 unaffected sibs and SCN5A-linked markers, generating an estimated LOD score of $\geq$6 at 0% recombination. SSCP analysis of the complete coding region of SCN5A identified an aberrant conformer in exon 28 which co-segregated with the ECG abnormalities. The aberrant conformer was absent in unaffected family members and in 100 alleles from unrelated controls. DNA sequencing of exon 28 of affected family members revealed a TGA insert at position 5537, predicted to cause an insertion of aspartic acid (1795insD) in the C-terminal domain of the protein. The insertion was linked to the phenotype and was identified in all electrocardiographically affected family members.

Conclusions: LQTS3 and Brugada syndrome are allelic disorders but may share a common genotype.

2448 Incomplete penetrance and variable response to sodium channel blockade in Brugada's syndrome

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The Brugada syndrome is an inherited cardiac disease characterized by a typical electrocardiographic pattern of ST segment elevation and right bundle branch block, and by a high incidence of ventricular fibrillation occurring in the absence of structural heart disease. Recently, mutations in SCN5A gene, encoding for the cardiac sodium channel protein, have been demonstrated to underlie the disease in approximately 10% of families. It has been suggested that the Brugada Syndrome is associated with high recurrence of cardiac arrest, implying an almost complete penetrance (i.e. the ratio between clinically versus genetically affected individuals) and that that pharmacological challenge with sodium channel blockers unmasks the typical abnormality in 100% of the gene carriers with normal ECG (concealed Brugada Syndrome).

Two families were referred to our attention after sudden cardiac death of two young males (23 and 30 yrs respectively). DNA samples were obtained from 29 family members and screened for mutations in the SCN5A gene. Two novel missense mutations were identified in exon 18 (family 1) and exon 17 (family 2). Nine asymptomatic gene carriers were identified among the 16 members of family 1. Nine gene carriers were identified among the 13 members of family 2: a deceased patient, in whom the mutation was demonstrated using the DNA extracted from paraffin-embedded tissue from a cardiac biopsy, seven asymptomatic individuals, and a young man with history of three aborted cardiac arrests. Among 18 gene carriers only the symptomatic patient of family 2 (1/18, 5.5%) presented the typical ECG pattern at rest. The flecainide test (2 mg/kg) was performed in 10 gene carriers (5 in family 1 and 5 in family 2) and a positive electrocardiographic response was observed only in 2/10 (20%) cases.

Our data demonstrate for the first time a very low penetrance in the Brugada syndrome and a lack of correlation between the genetic status and the response to flecainide test in asymptomatic gene carriers.

2449 Evaluation and follow-up of patients with right bundle-branch block and ST-segment elevation in right precordial leads

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The etiology of the syndrome characterized by right bundle branch block (RBBB) and persistent ST segment elevation in V1-V3, and the mechanism of the ventricular arrhythmias are controversial. Although the syndrome is classicly considered to be associated with no structural heart disease, several authors found few patients with the same ECG pattern and a right ventricular cardiomyopathy involving the specialized conduction system. The aim of this study was to prospectively assess the clinical characteristics and follow-up of patients with RBBB and ST elevation in V1-V3 admitted to our Institute. Between 1997 and 1998 we identified 7 consecutive patients with this ECG pattern (all males; age 55 $\pm$ 15). The first patient died suddenly because of a VF. The second had syncope. The third patient was resuscitated from a VF. The others had lipothymia and/or thoracic pain. The last 6 patients were prospectively analysed. They underwent 2-D echo, coronary angiography, left ventricular angiography, right ventricular angiography and endomyocardial biopsy (all but one), electrophysiological study, signal-averaged ECG and baroreflex sensitivity (BRS) evaluation. A right ventricular cardiomyopathy was found in 4 patients. One of them also had a dilated cardiomyopathy and a mitral valve prolapse and 2 of them also had left ventricular hypertrophy. Mitral valve prolapse or left ventricular hypertrophy were the only abnormalities in the remaining 2 patients. Fibrosis was found in all the 5 patients in whom the endomyocardial biopsy was performed. One of them also had hypertrophy and atrophy of myocardial cells and another had only hypertrophy of myocardial cells. VF was induced in 4 patients. Sick sinus syndrome was found in 1. Three patients had a supra-His conduction defect. One patient had prolonged His potential and HV interval. Late potentials were positive in 4 patients. No patient had a depression of BRS. A defibrillator (ICD) was implanted in 3 patients; 2 of them and another 2 patients were treated with betablockers; one patient did not receive any therapy. During a follow-up of 10 $\pm$ 6 months, no patient had arrhythmic events.

In conclusion, in all our patients with RBBB and ST elevation in V1-V3 we found a structural heart disease. Long-term follow-up is needed to assess whether patients with RBBB, ST elevation in V1-V3 and an organic cardiac disease are at risk for malignant ventricular arrhythmias as those without any structural heart disease.

2450 Novel mutations in the cardiac Na^+-channel α subunit gene (SCN5A) in patients with Brugada's syndrome

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Brugada syndrome is characterized by a distinct electrocardiographic (ECG) pattern consisting of right bundle branch block (RBBB) with persistent ST-segment elevation in the right precordial leads, and sudden death by ventricular fibrillation. Mutations in SCN5A, the gene encoding the cardiac Na^+ channel alpha subunit, have been shown to cause this syndrome.

Methods: DNA analysis was performed on 8 patients with typical Brugada syndrome (ECG pattern and resuscitated sudden death). The 28 exons of SCN5A were analyzed by PCR-SSCP and abnormal conformers were sequenced. Mutant proteins were expressed in a mammalian cell line and Na^+ current kinetics were evaluated to confirm the pathogenicity.

Results: Mutations in SCN5A was evidenced in 4 of the 8 patients. A 1-bp insertion at position 2849 resulted in an in-frame stop codon that eliminates the domains DIII and DIV, and the carboxy-terminal portion of the channel. Two missense mutations (T632M and R1512W) were found in the cytoplasmic loops linking two domains, DI-DII, a region involved in protein kinase activation, where no mutation has been identified so far, and DIII-DIV, a loop important for the fast inactivation where the delKPQ has been identified in LQT3 patients. The third missense mutation (R1432G) induced the substitution of a highly conserved arginine by a glycine in the extracellular loop between transmembrane segments S5 and S6 of domain III. When expressed, the mutant proteins altered the Na^+ current kinetics. There was no evident phenotypic difference between the patients with identified mutations and the others.

Conclusion: The complete screening of SCN5A led to the identification of mutations in only 4 of 8 patients. This confirms the involvement of SCN5A in Brugada syndrome, and suggests that other genes are probably responsible for this syndrome.

CLINICAL CHARACTERISTICS OF PATIENTS WITH ATRIAL FIBRILLATION

2451 Atrial fibrillation in the 1990s: a shift towards non-rheumatic cardiac causes

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The clinical presentation and causes of atrial fibrillation (AF) in the 1990's may differ from AF seen 2–3 decades ago. It was the objective of this prospective study to characterize the underlying conditions of patients with electrocardiographically documented AF, observed in general practice in France (The ALFA Study). This study started june 1st 1993. The work-up included thyroid function tests, 12 lead ECG and M mode and 2D echocardiogram. AF was subdivided into paroxysmal (<7 days), chronic (last episode > 1 month) and recent onset AF (persistent > 7 days and <1 month).

Results: The study population comprized 756 patients with a mean age of 68.6 ± 11.4 years (range 19 to 95 years). There were 436 men (57.7%) and 320 women (42.2%). The relative prevalences of paroxysmal, chronic and recent onset AF were 22.1%, 51.4% and 26.4% respectively. Symptoms were present in 670 (88.6%) patients. Cardiac disorders present in 534 patients (70.6%), included hypertension (39.4%), coronary artery disease (16.6%) and myocardial diseases (15.3%) as the most common disorders. Rheumatic valvular heart disease were present in 115 patients (15.2%) and non-rheumatic valvular disease (mitral valve prolapse) in 25 patients (3.3%). The paroxysmal group differed by a high incidence of palpitations (79.0%) and a low incidence of detectable heart disease (53.9%). The chronic group was characterized by an older age, a higher percentage of organic heart disease (76.9%) and of congestive heart failure (42.6%).

In conclusion, this large-scale study highlights some of the changes that have occurred in the past decades particularly a shift in cardiac causes towards non rheumatic AF and a large proportion with lone AF in the paroxysmal group.

2452 Influence of gender on the clinical characteristics of atrial fibrillation

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Little is known on the influence of gender on the clinical presentation of AF. It was the objective of the ALFA Study to prospectively characterize the various subsets of patients with electrocardiographically documented AF, observed in general practice in France (The ALFA Study). This study started June 1st 1993. The work-up included thyroid function tests, 12 lead ECG and M mode and 2D echocardiogram. AF was subdivided into paroxysmal (<7 days), chronic (last episode > 1 month) and recent onset AF (persistent > 7 days and <1 month).

Results: The study population comprized 756 patients with a mean age of 68 ± 11.4 years (range 19 to 95 years). There were 436 men (57.7%) and 320 women (42.2%). The mean age was significantly ($p < 0.0001$) higher in the female population (71.4 ± 11.4 years) than in the male population (66.5 ± 11 years). Evaluated by decades, the male/female ratio decreased after 60 years of age. Symptoms were present in 670 (88.6%) patients and were slightly although significantly ($p < 0.004$) more frequent in the female population (92.5%) than in the male population (85.8%). Underlying heart disease was present in 534 patients (70.6%) and was significantly ($p < 0.001$) more common in women (76.9%) than in men (66.1%). Rheumatic heart disease represented a common cause in women (25.0%), but not in men (8.0%).

In conclusion, this large-scale study showed interesting differences between men and women regarding age distribution, symptoms and the prevalence and type of underlying heart disease in a population of patients with AF in general practice in France.

2453 Development of atrial fibrillation in patients with advanced chronic heart failure: clinical characteristics and prognostic significance during long-term follow-up

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Atrial fibrillation (AF) in patients with chronic heart failure (CHF) leads to loss of atrial contribution to ventricular filling, inappropriate increases in ventricular responses, and tachycardiomyopathy. It could thus be speculated, that the onset or development of AF in patients with CHF would be related to an adverse prognosis, and that it would easier develop in patients with more advanced disease.

Methods: We studied 325 patients, who at baseline had sinus rhythm and moderate to severe CHF (mean age 67 ± 8 yr, 75% male, LV ejection fraction 0.23 ± 0.07, 73% in NYHA class III, 27% in NYHA class III/IV or IV). During a mean follow-up of 3.4 yr (range 2.0–5.4 yr), 30 patients (9%) developed AF. At baseline, patients who developed AF in the course of the study were older (mean age 70 yr for those who developed AF, vs. 66 yr for those who remained in SR throughout the study, $p < 0.007$), but LVEF, NYHA class, and etiology of CHF were the same. Further, onset of AF was related to a slightly lower systolic blood pressure (mean 120 mm Hg vs. 127 mm Hg, resp., $p = 0.049$), and lower plasma norepinephrine concentrations (median 403 pg/ml vs. 488 pg/ml, resp., $p = 0.038$), but the two groups were otherwise remarkably similar. On multivariate analysis, all these 3 factors, and N-terminal atrial natriuretic peptide, were significantly related to the development of AF. During follow-up, 14 of the 30 patients (47%) who had developed AF in the course of the study died, compared to 145 of the 295 patients (49%) who remained in SR throughout the study (p = NS between groups).

Conclusion: In CHF, elderly patients have a higher chance of developing AF, but this chance does not appear to be related to more severe CHF. In addition, the development of AF in the present study was not associated with a poorer outcome.

2454 A registry of chronic atrial fibrillation: an overview of epidemiology and prognosis in clinical practice in France

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The follow-up (F-U) of 250 patients (pts) with chronic documented atrial fibrillation (AF) consecutively enrolled in a prospective registry between Sept 1994 and July 1995 is evaluated. Only 7 pts were lost to F-U, which is ≥3 years in the remaining 243. Out of the 250 pts, 157 (63%) were males. Mean age was 70 years, and only 58 pts were ≤60 years. AF was paroxysmal in 122 pts, permanent in 89, and converted to sinus rhythm in 39. No etiology was found in 127 pts (51%), whereas 53 had hypertension, 31 a coronary heart disease, 24 a valvular disease, and 17 a cardiomyopathy. History of previous neurologic event (stroke or transient ischemic attack) was present in 24 pts, other embolic events in 2, heart failure in 36. Anticoagulant was given in 134 pts, aspirine or ticlopidine in 56, no antithrombotic agent in 60. An antiarrhythmic drug was used in 147 pts.

During the F-U, death occurred in 24 pts (9.6%), a neurologic event in 18 pts: 16 embolic (6.4%) and 2 haemorragic, and signs of heart failure in 29 pts. Permanent AF was predictive of death or heart failure (17 & 18% vs 4 & 7.6%, $p < 0.01$ & <0.05) but not of neurologic event. Lone AF gived much less death or heart failure (4 & 3%) than valvular or coronary heart disease (22 & 39%, $p < 0.01$). The only etiology associated with a higher risk of neurologic event is hypertension: 9/53 = 17% vs 4.5% in normotensive pts ($p < 0.05$). Previous heart failure is associated with a higher risk of death or heart failure in the F-U, but not of neurologic event. Sex, previous neurologic event or therapy have no significant impact on the F-U in this registry.

2455 Atrial fibrillation – compliance with national guidelines

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Atrial Fibrillation(AF) is the most common arrhythmia and is associated with increased risk for stroke, congestive heart failure and increased mortality. Recent audits showed that there are significant differences in attitudes regarding anticoagulation treatment in patients with AF. National guidelines have been recommended to ensure a more uniform approach to this group of patients.In Sweden, National guidelines for management of AF were published in 1992.

Aims: To explore the compliance between National guidelines and clinical practice in management of AF according to anticoagulation treatment.

Methods: The medical records of 160 consecutive hospital treated patients with AF 5 yrs after the national guidelines were published. The records were reviewed with respect to indications and contraindications for chronic anticoagulation treatment and risk factors for stroke.

Results: The following clinical variables were considered as risk factors for stroke: Age > 65 yrs, previous ischemic attack/stroke, hypertension and diabetes. 23 patients had contraindications for anticoagulation treatment and 31 patients had no previous record of AF. Out of the 110 patients with riskfactors for stroke, previously known AF and no contraindications only 30 (27%) were treated with warfarin/coumadine and 46 (42%) received aspirin. All patients prescribed aspirin had doses below the recommended (320-mg a day). Although 34 patients(31%) had a moderate or high risk of stroke and no known contraindication to anticoagulation treatment they did not receive warfarin or aspirin. There was no difference in treatment between genders.

Risk factors	Anticoagulation	Aspirin	Untreated	Total
1	14	26	22	62
2	13	16	10	39
3	3	4	1	8
4			1	1
Total	30 (27%)	46 (42%)	34 (31%)	110

Conclusions: Clinical practice for patients with AF vary significantly despite published national guidelines. In addition there seems to be an underuse of anticoagulation treatment in the presence of risk factors for stroke.

2456 Prevalence, associated factors and mortality of atrial fibrillation in a large French cohort

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We studied the prevalence of AF according to age, in men and women, in a large French cohort. Factors associated with AF were also considered. We analyzed the relation between AF and CV and non-CV mortality.

Methods: The cohort was composed of 116384 men and 78805 women aged 30 to 95 years, who had a routine medical examination at the IPC Center from 1972 and 1988. Mean follow-up period was 14.5 years. 235 men and 63 women had an AF at the time of the examination.

Results: In both sexes, prevalence of AF increased with age. Before the age of 50 years the prevalence of AF was 0.05% in men and 0.01% in women, reaching 6.2% and 5.6%, respectively, after 80 years. Factors positively associated with the presence of AF, after adjustment for age, were myocardial infarction, ischaemia on ECG, hypertension, diabetes, obesity, alcohol, gamma-GT, and diuretics. Factors negatively associated with AF were vital capacity, expiratory volume, cholesterol, and the ratio of serum albumin/globulins. In men, AF increased the risk of cardiovascular mortality independently of the presence of cardiopathy and other factors. The risk ratio (RR) for cardiovascular mortality was 2.8 (1.7–4.8) ($p < 0.0001$) in presence of AF among men with cardiopathy. This was due to an increased risk of coronary mortality [RR: 3.5 (1.6–7.4)] and cerebrovascular mortality [RR: 2.7 (1.0–7.5)]. Among men with a lone AF, the risk of CV mortality was not significant. In women, the risk of cerebrovascular mortality tends to increase in presence of AF [RR: 3.5 (0.7–17.2)]. AF was not associated with non CV mortality in both sexes.

In conclusion, among the independent associated factors, alcohol and respiratory insufficiency are significant. In women, AF only seems to increase the risk of cerebrovascular mortality. In men, AF was found to be an independent risk factor for CV mortality only, due to an independent effect on coronary and cerebrovascular mortality.

EUROPEAN EXPERIENCE WITH SURGERY OF ATRIAL FIBRILLATION

2457 Long-term results of Maze surgery for drug-refractory paroxysmal atrial fibrillation without structural heart disease

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Background. If drug-refractoriness of paroxysmal atrial fibrillation (PAF) occurs, His bundle ablation followed by chronic pacing is frequently done, but this is an indirect therapy. Surgical channeling and exclusion of atrial areas inhibits PAF without damage of sinus node function.

Objectives. To examine the effectiviness and safety of MAZE surgery to abolish symptomatic drug-refractory PAF.

Methods. MAZE III surgery was applied on selected patients (pts) with symptomatic long-standing, drug-refractory PAF after exclusion of structural heart disease. These pts were candidates for His bundle ablation. Clinical characteristics, quality of life and follow-up results were collected to determine long-term surgical results.

Results. MAZE surgery was applied in 41 pts with a mean age of 49 ± 8 years. Death or stroke did not occur during a mean follow-up of 31 ± 16 months. At discharge 35/41 (85%) pts were free of PAF, and 6/41 (15%) had PAF or atrial tachycardias. During follow-up 39/41 (95%) pts remained free of PAF. Two of 41 (5%) underwent His bundle ablation and pacing for drug-refractory postoperative PAF. Three of 41 (7%) pts showed sinus node incompetence: 1 pt with persisting nodal rhythm after surgery, 2 with sinus pauses arising late after discharge. Pacing was needed in 1 patient. Quality of life, determined in the most recently operated pts (n = 9), improved significantly. Also the averaged maximal workload and peak VO_2 increased clearly after surgery.

Conclusion. This pilot study demonstrates safety and usefulness of MAZE III surgery in selected pts who are candidates for His bundle ablation and chronic pacing.

2458 Intraoperative radiofrequency ablation of atrial fibrillation in patients with structural heart disease

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In patients (pts) with chronic atrial fibrillation (AF) and structural heart disease, radiofrequency (RF) ablation was used to compartmentalize both atria, as a modification of the MAZE III procedure. The primary indication for surgery was mitral valve (MV) disease. MV repair was performed in 30 pts, MV replacement in 45 pts, ASD closure in 2 pts and tricuspid valve (TV) replacement in 1 pt. In 15 pts combined MV surgery and aortic valve replacement was carried out, 24 pts needed TV repair and 24 pts underwent concomitant CABG. There were 48 females and AF (>1 yr) was documented in all pts. The mean (± SD) values for age and left atrial dimension were 68 ± 9 yr and 48 ± 8 mm. The extra corporal circulation time was 230 ± 69 min, and the aortic cross clamp time 114 ± 37 min including 17 ± 5 min to perform the left sided MAZE. There were 4 in-hospital deaths (D). During a follow-up (FU) of 21 ± 9 months 9 pts died (3 cardiac D), 4 non-cardiac D, 2 unclassified D. 50 pts were in sinus rhythm, 8 pts in atrial flutter and 3 in AF. In 4 pts a DDD pacemaker was implanted. Echodoppler measurements in 65 pts showed biatrial transport in 50 pts and only right sided atrial transport in 1 pt.

Conclusion: 1. The RF modified MAZE simplifies the MAZE and is safe; 2. RF ablation can eliminate AF and reestablish atrial transport; 3. The RF-MAZE should be considered in all pts with chronic AF undergoing MV surgery.

2459 Surgical radiofrequency ablation for atrial fibrillation: effectiveness of the epicardial approach

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Chronic atrial fibrillation (AF) in pts with mitral valve disease has a poor rate of conversion to sinus rhythm (SR) if not treated. Surgical incisions, endocardial cryoablation and endocardial radiofrequency (RF) have proven effective. We here report our experience with epicardial RF ablation of the left atrium during mitral surgery.

Methods: Since February 1998, 26 pts underwent mitral valve surgery and concomitant surgical treatment of chronic AF using an original technique with a RF multipolar catheter. Right and left pulmonary veins encirclings are performed epicardially usually before CPB. After cardioplegic arrest the valve procedure is carried out. Two endocardial linear lesions, between the two encirclings and from the left encircling to the mitral anulus, are then performed. In 12 pts having suture of the left appendage, the last ablation line involved the base of the auricle. Mean duration of the ablation procedure was 12 minutes, but most of it was performed before aortic cross clamping (ACC).

Results: Mean AF duration was 39.1 ± 52.1 months, mean left atrial diameter and mean cardio-thoracic index were 53.2 ± 18.7 cm and 0.58 ± 0.03 respectively. No significant prolongation of CPB (124.4 ± 24.1 min) and ACC time (76.2 ± 22.2 min) was needed. Bleeding was not increased (252 ± 136 ml). After operation sinus rhythm was present in 25/26 pts. Ten pts (38.5%) underwent electrical cardioversion for atrial flutter or other SV tachycardias in 6 cases, for AF in 4. No pt died. No procedure-related complication was recorded. Mean postoperative hospital stay was 7.6 ± 5.9 days. At follow-up (7.4 ± 3.5 months), 19/26 pts (73%) were in SR, and 17/19 pts (89.5%) recovered biatrial contractility (at 2.9 ± 3.2 months).

Conclusion: Epicardial radiofrequency catheter ablation of the left atrium during mitral valve surgery is a safe and effective approach to treat chronic AF. These findings may suggest a widening of the indications for AF surgery.

2460 Curative ablation of chronic permanent atrial fibrillation by the induction of contiguous left atrial lesion lines between the mitral annulus and the pulmonary veins: results, complications and long-term follow-up in 25 patients

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A new left atrial approach for intraoperative catheter-guided radiofrequency (RF) ablation of permanent atrial fibrillation (AF) was performed in 25 pts. (age: 63 ± 7 yrs) during operative mitral valve repair or replacement. AF was documented in all pts. for 1–14 yrs. (mean 4.3 ± 2 yrs.) Left atrial size measured 47–63 mm. Linear lesions in the left atrium were induced temperature-guided with a specially designed hand-held electrode probe (10 mm tip, Sulzer Osypka). from the posterolateral mitral annulus to the left inferior pulmonary vein and continued via the upper left pulmonary and the upper right pulmonary vein to the lower right pulmonary vein.

Results: The antiarrhythmic part of the surgical procedure was completed in 21 ± 4 minutes (total bypass time: 107 ± 12 min.). Postoperatively, all patients had sinus rhythm. Between days 2 and 6 after surgery 13 of 25 pts. relapsed to AF (n = 5) or developed atypical atrial flutter (n = 8). Treatment with sotalol (80 mg tid for three months) and/or electrical cardioversion restored sinus rhythm or DDD-pacing in all but 1 pt.. During long term follow-up (1–21 mo., median: 6 mo.) 18/24 pts. (75%) were in sinus rhythm or DDD-pacing, 2 pts. in AF and 4 pts. in atypical atrial flutter. One pt. died on the first day after surgery due to recurrent ventricular fibrillation, 1 pt. developed stroke 4 weeks after surgery despite sinus rhythm and effective anticoagulation.

Conclusions: Curative treatment of chronic permanent AF can be achieved by the induction of continuous left atrial lesion lines using intraoperative radiofrequency application (freedom from AF during long term follow-up: 22/24 pts). Because of the high efficiency of the procedure and the short intervention times, the technique may deserve widespread use. The results of this study may also have implications for the development of a curative percutaneous treatment strategy.

2461 Quality of life after Maze surgery for atrial fibrillation

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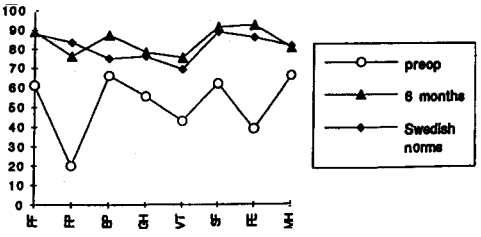
In 45 patients (33 male, 12 female) with paroxysmal (P) (n = 28) or chronic (C) (n = 17) atrial fibrillation (AF) undergoing maze surgery, the quality of life were evaluated pre- and six months postoperatively by using SF 36. The mean duration of PAF and CAF was 10.2 years (2–25 years) and 2 years (1–6 years), respectively.

Results: Preop., all scores were significantly lower compared to the general Swedish population (GSP) ($p < 0.0001$). The lowest score was obtained for RP (20 ± 36) and RE (39 ± 44) i.e. problems with work or other daily activities. Six months postop. the level of all items were significantly increased ($p < 0.001$) and did not differ significantly compared to the norms for GSP.



Conclusion: Patients with idiopatic PAF or CAF has a very low quality of life. Already six months after maze surgery, the patients resume the same level of quality of life as the general population.

2462 Value of the electrophysiological evaluation of sinus and atrial activity after the Maze surgery: prediction of atrial fibrillation recurrences

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The maze procedure may restore sinus rhythm (SR) in those patients with atrial fibrillation (AF) who undergo cardiac surgery. However, some patients may develop sinus dysfunction and interatrial conduction disturbances after surgery, and further recurrences of AF.

Methods: we have studied 23 patients (15 female, 8 male), mean age of 61 ± 22 years during a 10 months mean follow up. The underlying cardiopathy were: reumathic heart disease (70%), degenerative (22%), neoplasic (4%) and congenital (4%). The duration of the AF was <1 year in 8 patients (30%) and >1 year in 15 (70%). We performed an electrophysiological study (EPS) previously to discharge and another second EPS at the end of the follow up period.

Results: At hospital discharge 13 patients (57%) were in SR, 8 (35%) in AF and 2 (8%) were not studied. The EPS before hospital discharge showed a cycle length of 780 msec (530–1000), a Sinus Node Recovery Time (TRNS) of 985 msec (880–1200). All the patients showed intraatrial conduction disturbances and 3 of them interatrial conduction disturbances. At the end of the follow up period, 8 patients (36%) were in sinus rhythm. The EPS showed these mean data: a cycle length of 1000 msec, a TRNS of 1200 msec, a Sinoatrial Conduction Time (TCSA) of 250 msec, an Interatrial Conduction Time (TCIA) of 200 msec.

In Conclusion: The number of patients in SR at hospital discharge (57%) decreases during the follow up to 36%. The duration of the AF is a determinant factor in these results, because no patient with a duration of AF > 1 year persisted in SR. The data of the PES at discharge was not useful to predict the recurrence of AF.

ADVANCES IN PHYSIOLOGICAL PACING

2463 The registry of the European working group on cardiac pacing

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In 1996 a total number of 190,189 pacemakers (PM) (first implants 130,957) were registered in 2,774 hospitals of 20 European countries for a population of 442.95 million(M): an implantation rate per M population: total 429, first implants 296.

The PM implantation rate per M varies considerably from country to country: for the total number of PM: median 355; first implants median 283. For 1996 the rate of first implants per M was: Austria 444; Belgium 626; Croatia 157; Czech R 467; Denmark 301; FR Yugosl 67; France 528; Germany 423; Greece 286; Italy 346; Lithuania 94; Moldova 13; Netherlands 275; Norway 235; Poland 196; Slovak R 280; Spain 262; Sweden 382; Switzerland 328; UK 263.

For the number of PM implanting hospitals per M, we have obtained the following figures: median 4.34 min 0.23 max 19.5.

The% of PM modes in the different countries gives the following values: VVI-VVIR pacers: median 51.3 min 28.1 max 91; AAI-AAIR: median 2.4 min 0.28 max 13.7; DDD-DDDR: median 39.2 min 6 max 61.8. The%VVI(R) pacing in SSS was: Austria 44.7; Belgium 29; Croatia 70; Czech R 38.7; Denmark 16; FR Yugosl 16; France 27.5; Germany 49.7; Italy 35.1; Moldova 60; Netherlands 41.3; Poland 44; Slovak R 88; Spain 58; Sweden 27; UK 38.6.

For 1996 15 countries have reported on ICD's. The total number of ICD's per M was: Austria 13.3; Belgium 24.1; Croatia 0.8; Czech R 8.2; Denmark 24; FR Yugosl 0.4; Germany 23.8; Italy 10.5; Netherlands 10; Norway 14.6; Poland 0.9; Slovak R 4.3; Spain 7.4; Switzerland 14..4; UK 6.

The number of ablations per M in 1996 is known for 9 countries: Belgium 130.6; Croatia 2.5; Czech R 25.3; FR Yugosl 5.3; Norway 59.3; Poland 5.2; Slovak R 38.1; Switzerland 67.2; UK 42.1.

2464 The effects of long-term right ventricular apical pacing on cardiac sympathetic innervation: an I-123 metaiodobenzylquanidine cardiac scintigraphic study

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The aim of this study was to investigate whether there are MIBG scintigraphic abnormalities in paced patients where the ventricular stimulus originates from the apex of the right ventricle and is fully paced.

Methods: We studied 11 patients, mean age 68 ± 8 years, who had been paced in DDD mode for a long period (3.6 ± 1.1 years) (Group A) and 8 patients, mean age 69 ± 9 years, with a recent pacemaker implantation (40 ± 17 days) (Group B). Twelve healthy individuals, aged 63 ± 11 years, served as a control group. None of the patients had any condition that might affect myocardial adrenergic innervation. All patients underwent planar and SPECT myocardial imaging 4 hours after intravenous infusion of 5 mCi I^{123}-MIBG. The heart to mediastinum (H/M) ratio was calculated in order to quantify cardiac MIBG accumulation, while the SPECT study was performed in order to investigate the regional distribution of adrenergic innervation (AI). All Group A patients underwent a SPECT Tl^{201} myocardial study during the same week as the I^{123}-MIBG study.

Results: The H/M ratio was smaller in Group A than in Group B ($p < 0.01$) or the controls ($p < 0.001$). In Group A, 9/11 patients had a regional alteration in adrenergic innervation, compared with 0/8 from Group B ($p < 0.01$). Also, 9/11 patients in Group A had abnormal MIBG SPECT studies (inferior apical and inferior-lateral wall), while only 3/11 had a positive Tl^{201} SPECT study in the same two areas ($p < 0.05$).

Conclusions: Long term stimulation from the apex of the right ventricle appears to lead to disturbances of adrenergic innervation of the ventricular myocardium. This provides another reason to seek alternative pacing sites which could ensure a more normal activation sequence.

2465 Chronic right ventricular apex pacing can suppress hypertrophy in the septum of hypertrophying dog hearts

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Asynchronous electrical activation, induced by ventricular pacing (VP), causes enhanced mechanical load in late activated and diminished mechanical load in early-activated regions. We have recently shown that these conditions ultimately lead to reduced wall thickness in early-activated regions and increased wall thickness in late-activated regions of normal hearts. Because pacing is advocated as therapy in hypertrophic cardiomyopathy we investigated whether VP induces a similar remodeling in canine hearts with pressure overload hypertrophy (POH).

Methods: POH was induced by aortic banding in puppies. At age 9 months 7 dogs were paced for 6 months at physiological heart rate (DDD, AV-interval 25 ms) at the right ventricular (RV) apex (POH-pace group). Four POH dogs remained in sinus rhythm and served as control (POH-control group). 2D-echocardiography and X-ray marker detection were used to measure left ventricular (LV) cavity and wall volume and the relative changes in volume of 5 LV wall sectors (apical and basal septum and LV anterior, posterior and lateral wall).

Results: During the last six months of the protocol LV wall volume increased in the POH-control group, varying from 27 ± 9% in the apical septum to 30 ± 5% in the LV lateral wall (mean ± S.D.). In the POH-pace group the increase in regional wall volume in 4 out of 5 sectors ranged from 31 ± 16% in the basal septum to 35 ± 17% in the LV anterior wall. In the apical septum, however, this increase was significantly smaller (17 ± 21%). In these hearts also myocyte diameter was smaller in the apical septum than in the LV lateral wall.

Conclusions: In hypertrophying hearts chronic pacing at the RV apex suppresses the development of hypertrophy specifically in the apical septum. In contrast to normal hearts VP does not lead to excess hypertrophy in late activated regions, suggesting different sensitivity of normal and hypertrophic myocardium to mechanical load.

2466 Long-term results with cardiac resynchronization for heart failure: the InSync™ trial

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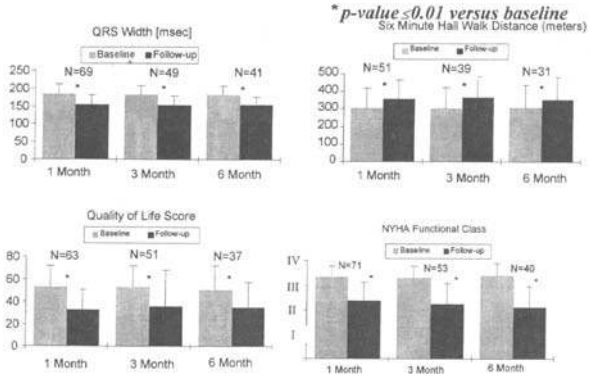
The InSync™ trial is a prospective, multicenter evaluation of Cardiac Resynchronization for patients with advanced Heart Failure (HF) and ventricular conduction delays. Patients with advanced dilated cardiomyopathy (NYHA class III/IV, EF < = 35%, LVEDD = > 60 mm) and conduction disturbances (QRS = > 150 ms) were included.

Methods: 71 patients (77% male, average age 67 ± 9 years) were enrolled in this global study. QRS width, 6 minute Hall Walk Distance (HWD), Quality of Life (QoL) questionnaire (Minnesota Living with HF score) and NYHA Class were examined at baseline, 1, 3 and 6 months after implantation and compared to baseline.

Analysis: Statistically significant improvements were observed for each endpoint at 1, 3 and 6 months.



Conclusion: These data from the InSync trial suggest that Cardiac Resynchronization may provide an effective additional therapy in symptomatic HF patients with ventricular conduction disturbances.

2467 Profile of cardiovascular mortality in the CTOPP study

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The Canadian Trial of Physiologic Pacing (CTOPP) randomized 2568 patients about to receive a pacemaker to either "physiologic" pacing (AAI, DDD, AAIR, DDDR) or "non-physiologic" (VVI, VVIR) pacing. Patients with chronic atrial fibrillation or significant co-morbidity were excluded. 1094 patients received the former and 1474 the latter. Over an average follow up of 3 years, all cause mortality was similar in the 2 groups. The aim of this sub-study was to examine the profile of cardiovascular (CV) mortality in our population.

Results: Total CV deaths were 15% of those randomised to VVI, VVIR vs 13% of those randomised to physiologic pacing. The percentages of patients dying of heart failure (HF), presumed arrhythmic death, myocardial infarction, stroke and pulmonary embolism, respectively, were similar in both groups. Of the 284 CV deaths noted among patients aged 70 or more, 68 (24%) were due to HF and 125 (44%) were presumed arrhythmic. Of the 75 deaths noted in patients aged less than 70, 15 (20%) were due to HF and 36 (48%) were presumed arrhythmic deaths.

Conclusion: At an average follow-up of 3 years, the CV mortality profile was similar for those patients receiving "physiologic" and "non physiologic" pacemakers. Furthermore, this profile was similar for those over or under the age of 70.

EFFECTS OF GENDER ON PROGRESSION OF CORONARY ARTERY DISEASE AND RESPONSE TO TREATMENT

2484 Disturbances of vascular endothelial function in pre-eclampsia

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Women who have experienced an episode of pre-eclampsia are susceptible to recurrent pre-eclampsia, and hypertension, in later life. The mechanisms which underlie this risk have not been identified. We hypothesised that vascular endothelial function is defective in women with previous pre-eclampsia, and may influence their future risk of hypertension related disorders.

We studied 103 consecutive women aged 18–43 yrs, with recent (>3 months) pre-eclampsia, and 48 age matched controls. Brachial artery flow-mediated (FMD, endothelium dependent), and glyceryl trinitrate-induced (GTN, endothelium independent) dilatation, were measured using high resolution ultrasound. Subjects were characterised for major vascular risk factors.

FMD was reduced in women with previous pre-eclampsia compared to controls (2.2 ± 0.4 vs 4.7 ± 0.6%, $p < 0.001$). In contrast, there were no significant differences in GTN induced dilatation (21.0 ± 1.3 vs 20.5 ± 0.7%, $p = 0.74$). Compared to controls, brachial artery diameter was higher in women with previous pre-eclampsia (3.49 ± 0.04 vs 3.28 ± 0.07 mm, $p = 0.01$), but there were no differences in brachial artery flow either at rest, or during reactive hyperaemia, between the two groups. Women with previous pre-eclampsia had higher diastolic and systolic blood pressure, and body mass index ($p < 0.01$), but similar total and HDL cholesterol, and smoking rates (p = ns) compared to controls. In a multivariate model, reduced FMD in women with previous preeclampsia was independent of vascular risk factors ($p = 0.01$), and differences in brachial artery diameter.

In summary, endothelium dependent dilatation is impaired in healthy young women with a previous episode of pre-eclampsia. Our findings support the hypothesis that basal endothelial nitric oxide activity is impaired in women with previous pre-eclampsia, and may contribute to their future risk of vascular disorders.

2485 Intracoronary 17β-oestradiol reduces plasma endothelin-1 levels in postmenopausal women with coronary artery disease

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Oestrogen (E) beneficially affects coronary reactivity by an endothelium-dependent mechanism in postmenopausal women with coronary artery disease, at least in part via nitric oxide. Postmenopausal E therapy is known to decrease systemic plasma levels of the potent vasoconstrictor endothelin-1 (ET), however the effects of intracoronary E administration on ET production is unknown. We therefore investigated the effects of a 20 min intracoronary 17β-oestradiol (E2; 60 ng/min) or vehicle control (VC; 0.001 ml 15% ethanol/min) infusion on ET-1 levels in 20 postmenopausal women [14 patients (mean ± SEM; aged 65 ± 2 years) and 6 controls (63 ± 3 years)] with coronary artery disease (CAD). Immediately before and after the E2 infusion, 2-minute intracoronary infusions of substance P (10 and 25 pmol/ml; SP10 and SP25 respectively) were given. A catheter was positioned the ostium of an irregular coronary artery for the infusions, and another into the coronary sinus for blood sampling. Blood sampling for analysis of plasma ET-1 levels took place at baseline, then at 5 minute intervals during the infusion of E2. Plasma ET-1 levels in the coronary sinus were significantly decreased after 20 min of E2 infusion compared to baseline (0.86 ± 0.16 vs 1.12 ± 0.18 pmol/l, $P = 0.05$; coronary sinus vs baseline). In the control group there was no significant change in ET-1 levels after VC compared to baseline. Levels of coronary sinus ET-1 after SP10 and SP25 were decreased after the E2 infusion (1.29 ± 0.17 vs 1.03 ± 0.15 pmol/l ($P = 0.04$) and 1.3 ± 0.15 vs 0.99 ± 0.17 pmol/l ($P = 0.024$); SP10 and SP25 before vs after E2 respectively). We conclude that intracoronary E may beneficially affect endothelium-dependent coronary reactivity in postmenopausal women with CAD at least in part via a decrease in ET-1 production.

2486 Hormone replacement therapy and the incidence of acute myocardial infarction: a population-based nested case-control study

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Epidemiological studies have consistently shown an association between a marked reduction on the risk of coronary heart disease (CHD) and hormone replacement therapy (HRT). However, these studies provided only information on the effects of the oral route of HRT administration. Therefore, we conducted a population-based nested case-control study using the General Practice Research Database in the UK.

Methods: A cohort of 164,769 women aged 50–74 years was followed from January 1, 1991 to December 31, 1995. Women with history of myocardial infarction (MI), other cardiovascular and cerebrovascular disease, neoplasms, coagulopathies, vasculitis and alcohol-related diseases were excluded from the source population. 1,242 potential cases of MI were identified. After the review (blind to exposure status) of medical records and all available information related to each identified event (including autopsy reports and death certificates for fatal cases) 1.013 first episodes of AMI cases were confirmed, 791 non fatal AMI and 222 CHD deaths, using WHO adapted criteria. 5,000 controls frequency-matched by age were randomly sampled. Prescriptions of HRT filled during the study period were obtained from the database.

Results: Prevalence of HRT use was 22%. 13% of cases and 17% of controls used HRT during the last six months prior to the index date. The odds ratio (OR) of AMI for HRT-users compared to non-users was 0.7 (95% C.I.: 0.6–0.9) after controlling for age, coronary risk factors, comorbidity, current use of aspirin and type of menopause. A trend of greater benefit with longer duration of HRT use was observed: ≤1 year, 0.8 (95% CI: 0.6–1.1); >1–3 years, 0.7 (95%CI: 0.6–1.0); >3 years 0.6 (95% CI: 0.4–0.9). The ORs for unopposed and opposed therapy were 0.6 (95% CI: 0.4–0.9) and 0.8 (95% CI: 0.6–1.0). 79% of women used oral therapy and 21% transdermal therapy. The ORs associated with oral conjugated oestrogens was 0.7 (95% CI: 0.6–0.9) and with transdermal oestradiol was 0.8 (95% CI: 0.6–1.3). The protective use of HRT was associated with medium doses of oestrogens and, appeared to diminish after 2–3 years of the cessation of use. The overall absolute risk of AMI was 1.6 per 1,000 person-years. In our cohort, 61 AMI cases were estimated to be prevented per 100,000 person-years by current-recent HRT use.

In conclusion, these results are consistent with those previously reported for oral HRT and suggest that the use of transdermal therapy has a similar protective effect than that reported with oral preparations.

2487 Gender differences in survival following acute myocardial infarction 1981–1995

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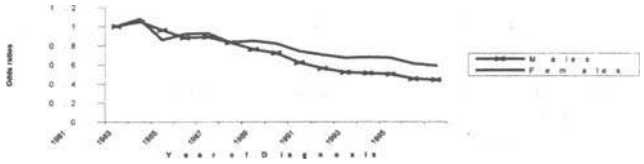
Background: There has been much debate about whether or not women receive different management than men after acute myocardial infarction (MI) and have a worse prognosis than men. We have examined case fatality in *all* patients admitted to hospital with acute MI in Scotland between 1981–1995 to determine whether or not gender differences in survival after MI do exist and persist.

Methods: Scotland (population 5.1 million) has a national Morbidity Record Database holding comprehensive, high quality data, which links all hospitalisations and deaths. A Scottish wide, retrospective, cohort study of all 178,077 individual MI patients admitted between 1981–1995 was carried out. Mortality up to 10 years was calculated with Cox-modelling for the effects of age, sex, socioeconomic deprivation, co-morbidity and year of treatment.

Results: 83075 women and 95002 men were hospitalised with acute MI during the period of study. Unadjusted 30 day, 1 year, 5 year and 10 year case fatality rates in all patients were 24, 33, 50 and 65%. Adjusted case fatality rates fell significantly in both men and women between 1981–1995 (figure). Men however, had a greater fall in case fatality rate than women and this gender difference in prognosis persisted over the period of study.



Acute myocardial infarction: case fatality at 30 days.

Conclusions: Women continue to have a worse survival than men after myocardial infarction. Further investigation and explanation of this alarming finding is required.

2488 Abciximab benefit in coronary intervention by gender and device: results of randomized trials

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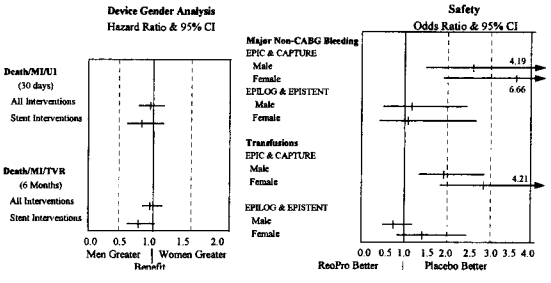
Platelet GP IIb/IIIa inhibition with abciximab (AB) reduces ischemic complications of percutaneous coronary intervention (PCI). Adverse outcomes of PCI may be increased in women.

Methods: We analyzed results for women (n = 2116) and men (n = 5744) in EPIC, EPILOG, CAPTURE and EPISTENT placebo-controlled randomized trials of AB therapy during PCI. Results: Women were older, had more diabetes mellitus or unstable angina presentation and less prior myocardial infarction (MI) or coronary bypass surgery (CABG) than men. Hazard ratios and 95% confidence intervals (CI) for death, MI, or urgent intervention (UI) to 30 days; death; MI or target vessel revascularization (TVR) to 6 months (A) as well as major non-CABG bleeding or transfusion requirement (B) are shown.



In conclusion, prophylactic AB improves outcomes following PCI with similar benefit and safety profiles in both men and women. Device-gender analyses for other GP IIb/IIIa inhibitors need to be performed.

2489 Coronary intervention in women: how do they fare in the long term?

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Coronary heart disease (CHD) is the leading cause of mortality in women in the United States, accounting for nearly 250,000 deaths each year. It is also a prominent cause of morbidity and disability among women, particularly in the older age group. Coronary revascularization in women is perceived to be associated with higher complication rates and lower success rates compared with men. We studied acute and long-term clinical outcomes following percutaneous coronary intervention (PTCA) in women with hemodynamically significant obstructive CHD. From 1/95 to 12/98, 1,028 women underwent PTCA at our center. Mean age at presentation was 66.5 ± 11.6 years (range 24–94 years). The majority presented with unstable angina (45%), while 26.4% presented with acute MI. Co-morbidities included: age ≥ 70, 44.1%; diabetes, 32.8%; prior MI, 25.3%; prior CABG, 16%; multivessel disease, 15.3%; EF < 40%, 17.3%. There was a history of smoking in 32.8% and CHF in 17.3%. Cardiogenic shock was present in 7.6%. On angiography, 53.2% of lesions were ostial or proximal, subtending large volumes of myocardium; one-third of all lesions represented LAD distribution. The lesion was in the native vessel in 96.6%. Stent (ST) was deployed in 33.5% of all PTCA procedures, either electively or for suboptimal result. Stented vessels were ≥3 mm in diameter. Post-ST high-pressure dilatations were performed (mean 16.1 atm). Adjunctive IABP support was used in 17.5%. Glycoprotein IIb/IIIa inhibitors were used in 12.8%. Patients received antiplatelet therapy following the procedure.

Results: Procedural success (≤20% residual; TIMI 3 flow) was obtained in 97.2% of women. Acute re-PTCA was required in 2.3%; 1.6% required CABG surgery before discharge. *There were only 2 in-hospital deaths in this series.* Vascular access site complications due to IABP use were seen in 5/180 patients (2.8%). Mean global LVEF at discharge was 43.9%*. Mean hospital stay was 2.46 days.

12-month Follow-Up [96.8% complete; Mean Follow-Up 6.74 months]

SAT	TLR-PTCA	CABG	Stroke	Death	EFS	Mean LVEF
7	87	39	18	46	782	49.0%;
(2.0%)	(8.5%)	(3.8%)	(1.8%)	(4.4%)	(76.1%)	*$p = 0.046$

SAT: subacute stent thrombosis; TLR: target lesion revascularization; EFS: event-free survival

Conclusions: (1) This large series demonstrates that percutaneous intervention is a safe and effective therapeutic option in women with hemodynamically significant CHD. (2) Procedural success was high and in-hospital adverse events were infrequent, despite unstable presentations and significant co-morbidities at baseline. (3) The incidence of SAT, access site complications and neurological events was low. (4) At 12-month follow-up, the rate of TLR was acceptable and major adverse cardiac event-free survival was high, with *significant* improvement in global LV systolic performance. (6) Our data suggests that an aggressive therapeutic strategy for prompt and effective salvage of jeopardized myocardium in women presenting with significant CHD can eliminate gender-related negative outcomes historically reported with coronary intervention in women.

PRIMARY AND SECONDARY PREVENTION IN CORONARY ARTERY DISEASE

2490 The association of socioeconomic factors with incidence, mortality, and one-year prognosis of first myocardial infarction

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Low socioeconomic status (SES) is usually associated with increased risk of coronary heart disease deaths. Reduction of socioeconomic health differentials has been one of the main goals of health policy in many countries, including Finland.

Methods: First ever myocardial infarction (MI) events (n = 8445) recorded by the FINMONICA MI register during 1983–1992 among men and women aged 35–64 years were included in the study. Data on SES were obtained by a record linkage of the MI register data with the files of Statistics Finland on the basis of social security number, unique to every citizen of Finland. Taxable income and education level were used as the indicators of SES.

Results: The age-standardized rate ratios and 95% confidence intervals of first MI events by taxable income among men were as follows:

Income	Incidence	Prehospital deaths	0–28 day deaths	0–365 day deaths
Low	1.67 (1.57–1.78)	3.39 (2.96–3.88)	3.18 (2.82–3.58)	3.18 (2.84–3.55)
Middle	1.84 (1.73–1.95)	2.33 (2.03–2.68)	2.30 (2.04–2.59)	2.34 (2.09–2.62)
High	1	1	1	1

The rate ratios are adjusted for age, study area, urban/rural residence, and study year. The findings in women were consistent with those in men.

Conclusions: The mortality from first MI events was more than three times higher in the lowest than in the highest income group. In part, the mortality difference was due to the difference in incidence, but mainly it was due to the considerable difference in prehospital sudden deaths.

2491 Prevalence of coronary heart disease within a population of 901,829 sampled in the UK, and level of secondary prevention of coronary heart disease among those identified

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Purpose: Several small studies have been published recently which document the prevalence of coronary heart disease (CHD) in different regions within the United Kingdom (UK). The present survey was undertaken nationwide to define the extent of CHD in the community and assist family doctors to audit whether measures for secondary prevention for individuals with CHD were being addressed in their practice.

Methods: 548 doctors working in 137 medium to large family practices took part. 12 research nurses spent 18 months collecting the data. The average total number of patients in each practice was 7215, with an average of 4 physicians in each practice.

Results: From a total number of 901,829 individuals, the medical records of 24,431 patients were identified as having CHD. The prevalence therefore was 2.7%, i.e., each physician looked after about 50 patients with established CHD. 64.6% of patients were aged 60–79, and 17.1% were 80 or older. 59.5% were male. The table shows the distribution of disease and the level of secondary prevention:

Angina pectoris	21,275	87.1%
Previous MI	10,164	41.6
CABG/PTCA	3,848	15.7
Heart failure	1,306	5.3
Continued smoking	5,722	23.4
Hypertension (>160/90 mm Hg)	9890	40.5
Diabetes mellitus	2,644	10.8
Multiple risk factors (2 or more)	8395	34.4
Cholesterol ever recorded	14,205	58.1
Cholesterol > 5.0 mmol/l	10,807	(76.1% of recorded values)
No record ever of cholesterol	10,226	41.9

Conclusions: High proportions of patients in the UK with established CHD have inadequate secondary preventive measures. 86% have high cholesterol levels, or have never had it measured; 23% continue to smoke and 40% have hypertension. The majority of the patients are middle aged or elderly. It is clear that secondary prevention of CHD in the UK offers a great opportunity for improved management. This data will be used to generate a model for health promotion in CHD to be applied at the level of the family practice.

2492 Familial aggregation of body mass index: a population-based family study in eastern Finland

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To investigate the familial aggregation of BMI a cross-sectional study of children at age of 15 and their biological parents was carried out in a rural community in eastern Finland.

Two hundred twenty four children were invited, 184 families agreed to participate (82%), from which 144 were included in the analysis. Comprehensive health and lifestyle questionnaires were completed by the participants before physical measurements.

Significant positive correlations of BMI were found between the mother and the offspring ($r = 0.31$, $p < 0.001$, $n = 140$), the father and the offspring ($r = 0.23$, $p = 0.017$, $n = 107$), the mother and the daughter ($r = 0.26$, $p = 0.044$, $n = 63$) and the mother and the son ($r = 0.36$, $p = 0.001$, $n = 77$). The adjustments for the parent's age, education and family history of acute myocardial infarction and the offspring's gender did not change these results. There was a higher proportion of the offspring in the highest quartile of BMI when the mother has obesity (OR = 3.1, 95% CI = 1.2–8.0, n = 140, mother obesity = BMI $\geq$ 27.3) and when one or both parents have obesity (OR = 2.8, 95% CI = 1.0–8.0 for one parent with obesity; OR = 4.6, 95% CI = 1.1–20.0 for both parents with obesity; n = 103; obesity = BMI $\geq$ 27.3 for mothers and $\geq$27.8 for fathers).

The study confirmed the aggregation of BMI in families. The stronger obesity association between the mother and the offspring may confirm the mother's key role in the primary prevention of obesity.

2493 Acute myocardial infarction is increasing in Spanish men

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Spain has the second lowest CHD mortality in Europe. Mediterranean diet and lifestyle are conventionally invoked as protective factors for this favourable pattern. However, this country has undergone many socio-economic changes over the last 20 years which could affect this pattern. The WHO-MONICA project was set up to monitor trends in CHD morbi-mortality and risk factors. The aim of this paper is to report on attack rate trends of acute myocardial infarction (AMI) from 1985 to 1996 for the ages 35 to 64 in Spain.

Methods and data are from the population-based register of the WHO-MONICA Project carried out in a metropolitan area of the Northeast of the country covering one million population. Sources of information were hospital discharge lists, death certificates, necropsy records and direct information from physicians, patients and relatives. More than 40 hospitals were monitored. All cases were validated through medical records, using the project diagnostic criteria and undergone external quality control. Rates were age-adjusted to the European standard population. Trends were calculated by linear regression.

Results: 11,443 cases were registered. Of these, 36% were classified as definite acute myocardial infarction. The average attack rate (MONICA-definition 2) of AMI was 107 per 100,000 (189 men, 28 women). Attack rates of AMI increased at a rate of 2.5% annually ($p < 0.06$) from 142 to 208 in men. No significant changes were observed in women. Rates increased more for recurrent (5%, $p < 0.008$) than for first events (2.1%, $p < 0.02$) and more for fatal (3.4%, $p < 0.02$) than for definite non-fatal events (2.2%, $p < 0.03$). 28-day case fatality did not significantly change over the period ($\beta = 0.008$, $p = 0.49$). Official country-wide hospital statistics also show a 29% increase of AMI admission rates for all ages between 1986 and 1995.

Conclusion: Overall AMI attack rates in middle aged men are increasing in Spain. Primary and secondary prevention programs are needed.

2494 Regional differences in cardiovascular disease mortality and major risk factors within Oslo: an ecological analysis

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Cardiovascular disease (CVD) mortality, ischaemic heart disease (IHD) mortality and all cause mortality vary considerably between different districts in Oslo. We examined the CVD risk factors and mortality according to socio-economic status (SES) in the 25 administrative districts of Oslo. This analysis is based on data from CVD surveys comprising 6897 men and 7323 women 40 years of age in the period 1985–88. The correlations between area-specific mortality rates for persons 45–74 years of age in 1991–95, area indicators of SES and CVD risk factors, were estimated. The proportion of the population being daily smokers, having low education, having high income, and the sex-specific mean cholesterol and systolic blood pressure levels of the areas, were used as independent variables in the regression analyses.

For both genders this ecological analysis demonstrates strong associations between mortality and major cardiovascular risk factors. The mortality rates as well as the cardiovascular risk factors are also highly related to the socio-economic indicators, with correlation coefficients (Pearson) of 0.74 for smoking and CVD mortality, and −0.78 for high income and ischaemic heart disease (IHD) mortality for both genders. Smoking explained 70% of the regional differences in all cause mortality for men and 46% for women, and for CVD mortality rates, 61% and 49% respectively. Corresponding figures for IHD mortality were 61% and 46%. Diastolic blood pressure and total cholesterol are closely related to the socio-economic indicators and to smoking in both genders.The relative strength of the cardiovascular risk factors on the all cause mortality, CVD mortality and IHD mortality in the multivariate analyses differ between males and females. This is particularly seen for total cholesterol which explains a larger proportion of the CVD mortality in women than men (42% v. 24%). Also physical inactivity shows strong correlation with mortality for both genders, with correlation coefficients of 0.69 for men and 0.64 for women with respect to CVD mortality.

Conclusion: Cardiovascular risk factors and life style habits on population level from the mid 1980s are strongly related to mortality, and explain a large proportion of the regional variations in mortality in Oslo in the 1990s. The mortality rates and risk factors are highly associated with area-based SES indicators. A gender difference in the preventive measures giving priority to men could affect risk factors on population levels and result in weaker explained variances of mortality for men than women.

2495 Air Force/Texas Coronary Atherosclerosis Prevention Study: relative benefit of primary prevention in subgroups with different absolute risk according to U.S. NCEP ATP-II and joint European guidelines

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Background: The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) demonstrated that, for generally healthy persons with average LDL-C and below average HDL-C, treatment with lovastatin, 20–40 mg/day, reduced the risk of a first acute major coronary event by 37% vs. placebo, in addition to diet and lifestyle measures.

Design/Methods: This was a randomized double-blind placebo controlled study of 6605 men and women; mean duration was 5.2 years. Post-hoc analyses were performed within subgroups according to those who would (Rx+) and would not (Rx−) be recommended for drug treatment by U.S. (NCEP-ATP II) and Joint European (Euro) guidelines.

Results: Only 17% and 20% of the cohort would have met the U.S. and European guidelines, respectively. The interactions between treatment and the subgroup factor were not significant (p = 0.384, p = 0.684, respectively).

Risk Subgroup	Treatment	N	Cases	Rate[1]	Relative Risk	(95% CI)[2]	P[3]
U.S. Rx+	Lovastatin	530	27	1.00	0.53	(0.33, 0.84)	0.006
	Placebo	566	53	1.87			
U.S. Rx−	Lovastatin	2774	89	0.62	0.57	(0.51, 0.88)	0.003
	Placebo	2735	130	0.93			
Euro Rx+*	Lovastatin	658	43	1.30	0.66	(0.45, 0.97)	0.034
	Placebo	652	63	1.96			
Euro Rx−**	Lovastatin	2608	70	0.52	0.61	(0.45, 0.82)	0.001
	Placebo	2592	113	0.85			
Overall	**Lovastatin**	**3304**	**116**	**0.68**	**0.63**	**(0.50, 0.79)**	**<0.001**
	Placebo	**3301**	**183**	**1.09**			

Note: 95 persons without SBP at baseline could not be classified based on the Joint European Guidelines; *high or very high risk; **low to moderate risk; [1]% per year or 100 person-years at risk; [2]Cox model stratified by site and gender; [3]between treatment group log rank statistic stratified by site and gender

Conclusions: Clinical benefit was consistent between subgroups and overall cohort for both Guidelines, despite different levels of absolute risk. [In such cases, the effect within the overall cohort is the best estimate within subgroups.] This suggests that in addition to current recommendations for persons at high risk, significant benefits can also be achieved with lovastatin treatment for persons at lower absolute risk, in addition to lifestyle and diet interventions.

COST-EFFECTIVENESS OF INTERVENTIONS

2496 Cost-effectiveness of simvastatin in diabetic patients with coronary disease: results from 4S

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Diabetes is a major source of morbidity, mortality and medical costs. Clinical results from the Scandinavian Simvastatin Survival Study (4S) demonstrated a 55% reduction in the risk of coronary death and nonfatal MIs in diabetic patients with coronary disease treated with simvastatin.

The purpose of this study is to investigate the cost-effectiveness of simvastatin in these patients, using prospectively collected outcomes data from 4S. Diabetic patients were identified using two different classifications schemes. First, according to Clinical History (202 Diabetic, 4242 Non-Diabetic) and second based on the new American Diabetes Association (ADA) Definition (483 Diabetic, 678 Impaired Fasting Glucose (IFG), 3237 Normal Fasting Glucose (NFG)).

There was a reduction in cardiovascular hospitalization due to simvastatin therapy in all subgroups. The difference was greatest for the diabetic group, regardless of the classification scheme used. Reductions in hospitalizations in the diabetic group resulted in substantial hospital cost savings that offset 67% to 76% of the drug cost using Swedish costs(depending on the classification used).

Cost effectiveness results for diabetic patients ranged from 1600 ECU per life year gained (based on clinical history) to 3200 ECU per life year gained (based on ADA criteria) using Swedish costs. In the other European countries evaluated, intervention with simvastatin maintains a favorable cost-effectiveness ratio independent of differences in local health care unit costs.

Conclusion: Regardless of diabetic classification scheme, treatment with simvastatin in all 4S subgroups resulted in cost per life year gained estimates that are well within the range generally considered to be extremely cost effective compared to other medical interventions. Based on the results of 4S, cholesterol lowering with simvastatin provides good value for money in both diabetic and non-diabetic patients with cardiovascular disease.

2497 Cost-effectiveness of stenting as strategy of coronary revascularization in diabetic patients with one-vessel disease

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Despite some subgroups of diabetic (D.) patients (P.) have poor outcome after coronary angioplasty (C.A.), a subgroup of diabetic P. have only one vessel disease. In these P., C.A. may be an efficient and cost/effective strategy.

The aim of the study was to evaluate the effectiveness (E.) and cost/effectiveness (C/E) of a successful revascularization by C.A. in a consecutive series of D. vs non-D. P., with and without stent implantation. An analytic model was used to determine incremental C/E. Effectiveness was defined as the absence of death, acute myocardial infarction or need of revascularization at 6 months follow-up.

A total of 302 P. were included and evaluated. Mean age of P. was 65 ± 8 years. There were 202 P. with stent implantation (33 D. and 169 non-D.) and 100 with balloon without stenting (25 D. and 75 non-D.).

The results were as follows:

Group	Effectiveness	Cost ($)/100 p.	C/E
D-Stent	70%	1.279.078	18.273
D-Balloon	56%	1.355.249	24.201
Non-D-Stent	83%	1.152.281	13.883
Non-D-Balloon	76%	1.061.533	13.968

Stenting in D. P. with one vessel disease, implied a net saving of 5.928 $ at 6 months follow-up. Nevertheless, in these contex stenting does not added significant effect in terms of costs and C/E for non-D. P.

In conclusion, in the population included with one vessel disease, a successful coronary balloon angioplasty is a low efficient strategy of treatment for diabetic P., in these setting stenting appears to be the most Cost/Effective percutaneous therapy.

2498 The cost and effects of combining stenting with abciximab derived from the EPISTENT study

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Objective: To assess the balance between the costs and effects of the combination of abciximab with coronary stenting compared to stenting without abciximab and compared to balloon angioplasty with abciximab.

Method: Estimates of costs and effects are based on data from the EPISTENT study (n = 2399) carried out in the US and Canada. Effectiveness is calculated in two ways: MI-free survival and survival free of major cardiovascular events (MACE-free survival). Costs were calculated per patient by multiplying data about resource utilization and events with Dutch estimates of unit costs (based on detailed data from the Benestent II and the Capture study). Account was taken of the use of abciximab, the index revascularisation (with bail out stents), MI's (Q-wave and non Q-wave), and subsequent revascularisations (PTCA, stent and CABG). Costs and effects are assessed after one and six months.

Results: At month 6 the additional costs per additional MI free survivor are estimated at EUR 41,509 for adding stents to abciximab and at EUR 13,572 for adding abciximab to stents. The corresponding upper 95% limits are EUR 1,483,392 and EUR 27,179. When considering the costs per MACE-free survivor the additional costs per additional MACE-free survivor are respectively EUR 12,862 (upper 95% limit: EUR 29,636) and EUR 15,164 (upper 95% limit: EUR 48,468).

Costs and effects at one and six months

	PTCA + stents (N = 809)	PTCA + abciximab (N = 796)	Stent + abciximab (N = 794)
Month 1: costs	EUR 6,939	EUR 6,526	EUR 7,734
Month 1: MI/MACE free	88.88%/85.78%	93.22%/89.32%	94.33%/93.32%
Month 6: costs	EUR 7,721	EUR 7,605	EUR 8,537
Month 6: MI/MACE free	87.64%/78.37%	91.33%/76.51%	93.58%/83.75%

Conclusions: At 6 months, a combination of the use of abciximab and stenting leads to an increase in event free survival at higher costs. How one should prioritize depends on the value attached to the prevention of MI's or the prevention of revascularisations.

2499 Comparing direct and indirect 1-year costs for elective percutaneous transluminal coronary angioplasty, stenting and directional coronary atherectomy: evaluation with a cost-analytic model

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Background: Coronary stenting and directional coronary atherectomy (DCA) has been shown to reduce the frequency of restenosis and the need for repeat revasularisations compared to conventional angioplasty (PTCA), however at higher primary interventional costs. To compare the additive costs of complications and reinterventions we develpoed a computerized analytic model, that deals with the direct medical costs as well as the indirect ones such as loss of productivity.

Methodes and results: The average interventional costs for the three procedures were obtained from a total of 300 elective 1-vessel-interventions in our clinic. The probabilities of early and late complications (death, bypass surgery, vascular complications and repeat interventions) in the first year after revascularisation were derived from a review of the literature since 1994 (STRESS, BENESTENT, BOAT, OARS). Average costs (± standard deviation) for one year were determined by using a Monte Carlo simulation of 10,000 intervenions for each procedure.

Calculating the direct medical costs, PTCA (4891 ± 4982 Euros) turned out to be less expensive than stenting (5253 ± 4516 Euros) and DCA (6100 ± 4076 Euros). The rate of restenosis for stent implantation theoretically would have to be less than 19% (DCA 1%), to reduce the costs to the PTCA level. If the indirect costs for a average collective of patients (average age 60 years, 50% employed) are considered as well, stenting (8625 ± 11407 Euros) is cheaper than PTCA (9074 ± 14990 Euros) and DCA (9220 ± 9929 Euros). Sensitivity analyses show that the sequence depends on the patient's age: For patients younger than 54.3 years, DCA is the cheapest treatment and for patients older than 63.9 years it is PTCA. For working patients under 65 years, stenting (60 years: 11998 ± 21009 Euros) and DCA (12338 ± 18057 Euros) are less expensive than PTCA (13256 ± 28420 Euros), as long as the restenosis rate of the angioplasty is above 30%.

Conclusions: Considering the direct 1-year medical costs, despite a higher rate of restenosis and an increased need for repeat revascularisations PTCA appears to be the cheapest interventional technique because of its low primary costs. If indirect costs caused by loss of productivity are taken into account, stenting and DCA are more cost effective, mostly because of the patient's reduced period of work inability.

2500 Cost-effectiveness of intravascular ultrasound guidance for stent implantation: results of the randomized Restenosis after Intravascular Ultrasound Stenting (RESIST) study

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Background: 155 pts were randomized to stent deployment with vs without Intravascular Ultrasound (IVUS) guidance. At 6 months, a non significant 6.6% difference in restenosis was observed (22.2% vs. 28.8%, p = 0.18) and at 18 months, a 12% difference in event free survival (EFS) (p = 0.059). Procedural costs and the cost/effectiveness ratio (CER) were calculated.

Methods: Procedural costs at stent implantation and total procedural costs including cost of repeat lesion revascularization procedures were calculated in Euros. CER per % of restenosis avoided and CER per % of EFS gained.

Results: Procedural costs at stent implantation were 17% higher in the group with IVUS, (2970 ± 680 vs 2530 ± 923 Euros, p = 0.001). This overcost was the result of the use of more balloons (1.68 vs 1.49 balloons per patient) plus the cost for IVUS catheters in the IVUS group. Event free survival at 18 months follow-up was 59/79 (75%) in the IVUS group, vs 48/76 (63%) in the control group and less lesion revascularization procedures were needed in the IVUS group (21/79 vs 31/76, p = 0.03). The total procedural cost in the IVUS group was 11% higher than in the control group (3223 ± 883 vs. 2896 ± 1253 Euros, p = 0.001). CER was 67 Euros per percent of restenosis avoided and 37 Euros per percent of EFS gained at stent implantation, and total CER was 49 vs 27 Euros for restenosis and EFS respectively

Cost	IVUS group	Control
At stent implantation	2970 ± 680	2530 ± 923
Total cost	3223 ± 883	2896 ± 1253

Conclusion: IVUS guidance in stent implantation led to a 17% over cost, that was reduced to 11% when including the costs for lesion revascularization procedures. The CER does not favour IVUS guidance.

2501 Assessment of cost and effectiveness in the treatment of congestive heart failure

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The launching of new potent drugs in the treatment of chronic diseases increase at the first glance the health care expenditure but optimise the efficiency by reducing the treatment of complications. To assess the costs-effectiveness of different treatment strategies in patients suffering on CHF a computer based model was developed to compare medical outcomes (number and severity of complications, duration of hospitalisation, number of visits, changing the NYHA-class) with cost consequences (basic and complication treatment). The model is mainly based on medical literature (AIRE, CIBIS, CONSENSUS, DIG, SAVE, SOLVD)

Method: A Markov disease model considering cohort specification (age, gender, NYHA-class), NYHA-dependent drug utilisation, complication rate (unstable angina, acute myocardial infarction, stroke, worsening of CHF, mortality) and complication-related direct costs (drugs, investigations, hospitalisations) was developed. To provide a realistic course of CHF the average age of CHF patients (66 years), the age-dependent mortality rate and the distribution of NYHA classes (I-IIa: 30%, IIb-III: 36%, III-IV: 34%) are taken into account for the simulation period of 5 years. The treatment in scenario A in mild and moderate CHF patients is digitalis + diuretics (DD) and in severe CHF patients DD + ACE-inhibitors (ACE-I). Cohort B is treated in mild and moderate CHF patients with DD + ACE-I and in severe CHF DD + ACE-I + a/b-blocker.

Results: The medication costs in scenario B are between 37 to 55%/year higher than in scenario A. On the other hand the total costs in scenario B are merely increased by 0.7 to 13%/year and the mortality rate is reduced by 26 to 39%.

Year	Drug cost A (SFr)	Drug cost B (SFr)	Total cost A (SFr)	Total cost B (SFr)	Mortality A (%)	Mortality B (%)
1	2738	3755	6752	6801	20.8	12.7
2	4666	6714	11493	12100	31.9	21.2
3	6306	9350	15518	16796	40.3	28.1
4	7765	11785	19088	21118	47.3	34.2
5	9077	14061	22294	25154	53.4	39.6

Conclusion: A more intensive treatment regime results in less cardiovascular events and mortality rate. In this example the additional expenditure per CHF patient is not completely compensated by prevented complication but causes nevertheless an optimised utilisation of the limited sources.

CORONARY HAEMODYNAMICS: THEORY AND CLINICAL APPLICATION

2502 Coronary microvascular dysfunction downstream from a severe stenosis effect on coronary reserve measurement following angioplasty

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Impairment of coronary flow reserve (CFR) may persist following coronary angioplasty (PTCA). We tested the hypothesis that this phenomenon reflects a pre-existing microcirculatory disorder. To this purpose, coronary blood flow velocity and distal coronary pressure were monitored before and after PTCA in 15 patients with single vessel disease and normal left ventricular function. Blood flow velocity was normalized by cross sectional area at the Doppler catheter tip to obtain a blood flow index (CBFI). Distal coronary pressure was measured by a fiberoptic guidewire. Maximal vasodilation was induced by intracoronary adenosine (2 mg). In the whole group, minimal microvascular resistance (defined as the ratio between distal coronary pressure and adenosine-CBFI) was 2.35 ± 1.99 mmHg/ml/min and did not change following PTCA (2.68 ± 2.11, ns). Although average CFR increased following revascularization from 1.75 ± 0.6 to 3.28 ± 1.67 ($p < 0.01$), it remained abnormally low (<3) in 7 patients. These patients, compared with the remaining 8, showed similar trans-stenotic pressure gradient, under maximal vasodilation, both before (43 ± 21 vs 50 ± 13 mmHg, respectively, ns) and following (8 ± 8 vs 8 ± 7 mmHg, respectively, ns) PTCA. By contrast, they showed higher values of minimal microvascular resistance both before (3.71 ± 1.16 vs 1.17 ± 0.78 mmHg/ml/min, respectively, $p < 0.01$) and following (3.97 ± 1.63 vs 1.55 ± 1.87 mmHg/ml/min, respectively, $p < 0.02$) PTCA. To verify whether this phenomenon was related to a higher extravascular compression or to a reduced cross-sectional area of maximally dilated microvessels, pressure-flow relationships were constructed in each patient, using maximal CBFI values (Y axis) obtained at two different distal coronary pressures (before and after PTCA). The slope of the line connecting the two points was defined as "maximal microvascular conductance", its intercept with X axis as "opening pressure" an index of extravascular tissue pressure. With respect to the remaining, the 7 patients with low CFR following PTCA had similar values of opening pressure (9 ± 6 vs 15 ± 12 mmHg, respectively, ns), but lower values of maximal conductance (0.23 ± 0.45 vs 2.65 ± 2.5 ml/min/mmHg, respectively, $p < 0.05$). Thus, following successful revascularization, a persistently low CFR may be observed in a sizeable number of patients. This abnormality may be caused by pre-existing elevated microvascular resistance and not be the consequence of PTCA. This phenomenon seems related to a reduced microcirculatory cross sectional area rather than than by an elevated extravascular compression.

2503 Fractional flow reserve of serial coronary stenoses: theoretical model and animal validation

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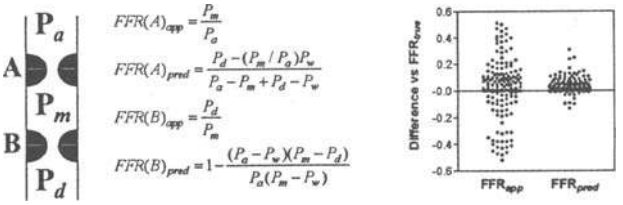
Background: Fractional flow reserve (FFR), an index of coronary conductance, equals the ratio of the hyperemic pressures distal and proximal to a stenosis. FFR has been well validated in case of isolated stenosis.

Objective: To determine, in case of sequential stenoses (A and B, fig 1), the FFR of each lesion separately, i.e. after removal of the other one.



Method and results: Apparently, the FFR (FFR_{app}) of stenoses A and B can be calculated by the mere ratio of the pressure immediately distal and immediately proximal to the respective lesions. However, this might underestimate the influence of coronary occlusive pressure (P_w) as well as the mutual influence of each lesion on the other one. Therefore, a theoretical model was developed to predict the FFR (FFR_{pred}) of each lesion separately. These equations (fig 1) were validated in 5 open chest dogs in which two stenoses in series of varying severities (n = 155) were created. FFR_{app} and FFR_{pred} were compared to the actual FFR (FFR_{true}) obtained after removal of the other stenosis. FFR_{true} correlated well with FFR_{pred} but not with FFR_{app}.

Conclusion: In case of sequential stenoses, it is possible to predict the FFR of each lesion separately, only when the influence of the second lesion and the influence of P_w are taken into account.

2504 Conflicting haemodynamic evaluation of intermediate coronary lesions by comparison of fractional flow reserve and blood flow velocity reserve

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Background: Fractional flow reserve (FFR) and coronary flow velocity reserve (CFR) are used to evaluate hemodynamic severity of coronary lesions. However, there is limited information regarding the direct comparison between both diagnostic techniques in intermediate coronary lesions.

Methods: Quantitative coronary angiography was performed in 82 patients (111 coronary lesions) to determine lesion severity. Distal coronary pressure and blood flow velocity were assessed with sensor equipped guidewires during baseline and maximal hyperemic conditions (12–18 mcg i.c. adenosine) to determine FFR and CFR. CFR was also measured in an angiographic normal reference vessel (CFR-ref). Agreement between FFR and CFR was determined at cut off values of 0.75 and 2.0 respectively.

Results: Coronary lesion severity varied between 43–79% diameter stenosis (mean: 60 ± 11%). Concordant results between CFR and FFR were obtained in 84 lesions (76%); discordant results were obtained in 27 lesions (24%) in 23 patients (28%). FFR was > or equal to 0.75 and CFR < 2.0 was documented in 12 lesions (Group A); FFR was < 0.75 and CFR > or equal to 2.0 in 15 lesions (Group B). Both groups had a normal CFR-ref. Clinical, hemodynamic and angiographic characteristics (risk factors, age, heart rate, aortic pressure and geometric lesion severity) were similar in both groups. Differences are presented in the table below.

Group	FFR	CFR	CFR-ref
A (n = 12)	0.83 ± 0.05	1.63 ± 0.22	2.60 ± 0.72
B (n = 15)	0.67 ± 0.07*	2.57 ± 0.47*	3.48 ± 0.73**#

*P < 0.0001 and **P < 0.05 compared to group A; #P < 0.003 compared to CFR

Conclusion: Discordant results between fractional flow reserve and coronary flow velocity reserve were observed in 24% of the intermediate coronary lesions. The hemodynamic significance of a coronary lesion, assessed by FFR only, may be obscured by a reduced CFR in the presence of a normal reference CFR. On the other hand, a normal CFR indicating a non-significant lesion, may accompany an abnormal FFR. These findings emphasize that combined pressure and flow velocity data are mandatory for accurate characterization of coronary lesion severity in approximately one quarter of the patients.

2505 Coronary pressure measurement to assess the individual haemodynamic significance of multiple, sequential stenoses within one coronary artery

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The presence of one stenosis in a coronary artery influences the hemodynamic behavior of another stenosis in the same artery, which confounds the calculation of both coronary and fractional flow reserve (FFR) of each lesion separately. Recently, it was shown in animals that the FFR of each individual lesion as it would be after treatment of the other lesion(s), could be predicted beforehand by the formulas:

$$FFR_{prox} = P_d - (P_m/P_a) \cdot P_w/P_a - P_m + P_d - Pw$$

$$FFR_{dist} = 1 - (P_a - P_w) \cdot (P_m - P_d)/P_a \cdot (P_m - P_w)$$

where FFR_{prox} and FFR_{dist} indicates the FFR of the proximal and distal stenosis, as it would be after elimination of the other stenosis; and where P_a, P_m, P_d, P_w indicate mean aortic pressure, coronary pressure between both stenoses, coronary pressure distal to both stenoses, and coronary wedge pressure, respectively, all measured during maximum hyperemia.

Methods: In the present study, these formulas were tested in 32 humans with at least 2 stenoses within one coronary artery. In 19 patients, the proximal stenosis was stented first, in 13 patients the distal first. Coronary pressures were measured by the 0.014″ Pressure Wire™ (used as primary guide wire in these procedures), before any intervention was done, after stenting of one lesion, and after stenting of both lesions.

Results: After stenting of one stenosis, the hyperemic gradient across the second stenosis increased significantly from 10 ± 7 to 19 ± 11 mmHg. On the other hand, the predicted FFR of a particular stenosis, calculated beforehand by the formula's, versus the true FFR of the same lesion as measured directly by the hyperemic distal to proximal pressure ratio after having eliminated the other stenosis, were very close together (r = 0.92; Δ% = 4 ± 4%).

In conclusion: When 2 or more stenoses are present within the same coronary artery, coronary pressure measurement accurately predicts the true hemodynamic significance and FFR of each individual stenosis as it will be after eliminating the other stenosis.

2506 Prevalence of microvascular dysfunction in patients with severe coronary artery disease

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Background. Coronary flow velocity reserve (CFVR) estimation is the current concept for assessment of physiological significance of an epicardial coronary artery stenosis and a complementary technique during coronary intervention. Recently, relative coronary flow velocity reserve (rCFVR), which is the ratio of CFVR in the stenotic coronary artery to the CFVR in the normal reference coronary in the same patient is preferred to CFVR as it is independent of many factors affecting absolute CFVR such as resting blood velocity, heart rate, arterial pressure, left ventricular hypertrophy, previous myocardial infraction. The purpose of the study was to investigate the frequency of microvascular abnormality in the reference vessel in order to address the significance of rCFVR.

Methods and Results: Intracoronary Doppler flow measurement was performed in the target and reference coronary arteries in 107 patients (87 males, 59 ± 10 years) who had angiographically severe stenosis of a single coronary artery. The CFVR was measured in the reference vessel and before, after interventions in the target vessel. Patients were divided into two groups according to the CFVR < 3.0 (group A) or CFVR ≥ 3.0 (group B) in the reference vessel.

CFvR	Before	After	Reference vessel
Altogether	1.93 ± 0.68	2.64 ± 0.86*	3.01 ± 0.78*#
Group A (n = 48, 45%)	1.75 ± 0.61	2.37 ± 0.86*	2.31 ± 0.37*+
Group B (n = 59, 55%)	2.07 ± 0.71	2.87 ± 0.82*	3.58 ± 0.51*#

*p < 0.0001 (after intervention and reference vessel vs. before intervention); #p < 0.0001; +p = NS (#,+ = reference vessel vs, after intervention)

Conclusion: Microvascular dysfunction exists in nearly half of reference vessels in patients with severe coronary stenosis. The CFVR presents in a large variety in the reference vessel in individuals. Therefore, rCFVR is a much more reliable parameter than CFVR in individuals in clinical decision making and assessment of coronary intervention.

2507 Effect of collateral and collateral-adjacent vascular resistance alterations on the coronary flow reserve of a collateral-receiving artery

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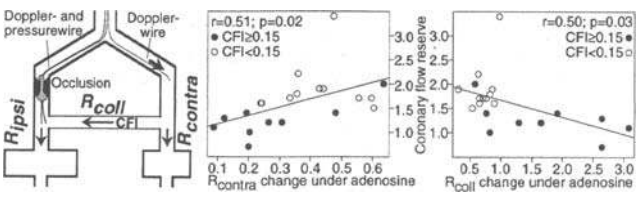
Background: It has been hypothesized that vascular resistance changes during hyperemia in the collateral (R_{coll}) as well as the collateral-supplying (contralateral, R_{contra}) and -receiving (ipsilateral, R_{ipsi}) areas may influence the coronary flow reserve (CFR) of an ipsilateral region (CFR < 1: coronary steal).

Methods: This study in 20 pts (60 ± 10 years) undergoing percutaneous coronary revascularization measured adenosine-induced CFR during *vessel patency* distal to the stenosis using an intracoronary (i.c.) 0.014″ Doppler wire. Subsequently and during *vessel occlusion,* simultaneous distal ipsilateral flow velocity and pressure (P_{occl}) as well as contralateral velocity measurements via a third i.c. wire were obtained before and during adenosine infusion (140 mg/kg/″; figure). From those measurements and simultaneous mean aortic pressure (P_{ao}, mmHg), a collateral flow index (CFI) as well as the vascular resistance indices R_{coll}, R_{contra} and R_{ipsi} were computed. CFI = (P_{occl} − 5)/(P_{ao} − 5). The study population was subdivided into a group with CFI ≥ 0.15 and a group CFI < 0.15.

Results: CFI ranged from 0.0–0.58. The coronary stenosis to be dilated was similarly severe in the two groups: 84 ± 13% versus 77 ± 11% (NS). R_{ipsi} remained unchanged during adenosine, and CFR was not associated with R_{ipsi}: CFR = 1.6 ± 0.6; r = 0.04.



Conclusions: Aside from the influence of the stenosis severity on the downstream CFR, hypermia-induced alterations of vascular resistances of the collateral bed itself and also of the collateral-supplying vascular area codetermine CFR directly and inversely, respectively. These interrelations of vascular areas do not occur in pts with poorly developed collaterals (figure), and they are manifest in the absence of ipsilateral resistance changes. This is the first study in humans to demonstrate comprehensively the validity of a theoretical model explaining the occurrence of coronary steal via collaterals.

MYOCARDIAL INFARCTION: NEW DEVELOPMENT IN DIAGNOSIS AND TREATMENT

2508 Mechanical thrombectomy during percutaneous intervention for acute myocardial infarction: experience with the angiojet® rheolytic system

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Objective: To prospectively assess the efficacy of the POSSIS AngioJet® rheolytic system in acute transmural myocardial infarction (MI) in patients with evidence of angiographic thrombus presenting within 24 hours of symptom onset.

Methods: 115 patients (mean age 61 ± 12 years, 67% males) from 9 US centers were included. 36% had prior MI and 13% presented with cardiogenic shock. Culprit lesions were: LAD (26%), LCX (11%), RCA (39%), left main(1%) or a saphenous vein graft(23%). Mean ejection fraction was 43 ± 12%. Adjunctive percutaneous revascularization was performed in 97%: PTCA alone (33%), coronary stenting (62%), and atherectomy (2%).

Results: Procedural success (achievement of <50% final diameter stenosis with TIMI 2 or 3 flow) was observed in 92%. Clinical success (procedural success and freedom from in-hospital MACE) was achieved in84%. Minimum lumen diameter increased from 0.52 ± 0.56 mm (83% diameter stenosis) to 1.44 ± 0.66 mm (52% diameter stenosis) after rheolytic thrombectomy, to 2.30 ± 0.66 mm (23% diameter stenosis) after final treatment. Angiographic thrombus area decreased from 63 ± 73 mm^2 to 20 ± 35 mm^2 after rheolytic thrombectomy. Procedural complications included distal embolization in 12% evident by angiography, perforation in 3%, and sustained no reflow in 5%. At 30-day follow-up no additional patients died, but 4% had recurrent MI and 3% required PTCA.

Conclusions: Rheolytic thrombectomy effectively removes intracoronary thrombus before definitive plaque treatment in patients with acute MI, with an acceptable complication rate.

2509 In vitro streptokinase resistance test for rapid prediction of coronary artery patency by angiography after acute myocardial infarction

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Early and sustained grade 2–3 flow according the Thrombolysis in Myocardial Infarction (TIMI) criteria, obtained after the 60-minutes (min) infusion of 1.5 MU streptokinase (SK) for acute myocardial infarction, was strongly related with reperfusion achievement and long-term prognosis (GISSI-2). SK thrombolytic efficacy is hampered by the presence of unsuspected antibodies or inhibitors in blood. In-vitro SK resistance screening (SK RES test), expressed as time > 50 sec for 100 U/ml SK to lyse a fresh autologous thrombus using a new bedside test (Thrombolytic Assessment System, TAS™) was prospectively assessed, before SK infusion, in 72 patients admitted for acute myocardial infarction within 12 hours after the onset of symptoms. We analysed the predictive value of SK RES test for reperfusion detected by angiography, assessing infarct-related coronary artery patency (TIMI 2–3) and left ventricular ejection fraction (LVEF) within the first 48 hours after thrombolysis.

Results: The incidence of potential RES was 19% (14/72 patients); in these patients, occluded or minimal perfusion (TIMI 0–1) occurred more frequently than in predicted responders. Odds ratio 4.5 (95% CI 1.5–13.6).

	SK RES test ≤ 50 sec	SK RES test > 50 sec	p value
Patients	n = 58	n = 14	
TIMI 2–3	84% (49/58)	36% (5/14)	0.0007
TIMI 3	81% (47/58)	21% (3/14)	0.0001
LVEF (%)	54 (45–60)	47 (37–53)	0.001

Median (25th–75th percentiles).

Conclusion. This pilot study provides the first evidence that a convenient bedside test assessing SK RES would efficiently screen patients for optimal angiographic and clinical response to SK.

2510 The acute coronary syndrome diagnosis and prognostic evaluation by troponin I is influenced by the test system affinity to different troponin complexes

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Cardiac troponins are established in acute coronary syndrome (ACS) diagnosis and risk assessment. Recently it was shown that cardiac troponins are released as T-I-C complex and than further degraded to T and I-C. It is not known whether the various affinity to the T-I-C and I-C complex of different troponin I test systems influence the diagnostic value of the test results in clinical practice.

Patients and Methods: We included 162 patients (61.28 SD11.05 years) with suspected acute myocardial infarction (AMI)in the study. In 109 patients AMI was confirmed during hospital stay by WHO criteria. Blood samples were taken at admission, after 1, 2, 4, 8, 12 and 24 h. Troponin I (TnI) was measured using the Opus®plus (TnI-O, cutoff 1.6 μg/L) and the Stratus® (TnI-S, cutoff 1.5 μg/L) analysers. TnI-O has high affinity to the binary (I-C) and TnI-S to the ternary (T-I-C) troponin complex. A 6 months follow up with respect to death and recurrent ACS was performed (combined primary endpoint).

Results: The sensitivity (SE), specificity (SP) and positive predictive value (PPV) for AMI diagnosis are listed below.

	0–2 hours	2–4 hours	4–8 hours
TnI-O/SE	75.2%	81.7%	89.0%
TNI-O/SP	92.5%	92.5%	90.6%
TNI-O/PPV	95.3%	95.7%	95.1%
TNI-S/SE	82.6%	90.8%	93.6%
TNI-S/SP	86.8%	88.7%	81.1%
TNI-S/PPV	92.8%	94.3%	91.1%

Logistic regression analysis with control for age, gender, diagnosis and mode of reperfusion therapy (PTCA or thrombolysis) shows prediction of the primary endpoint by TnI-S > 8 μg/L (optimal cutoff) at admission (Odds ratio 11.4, p = 0.0042). The use of the optimal cutoff for TnI-O resulted in an Odds ratio of 3.4 (p = 0.0552). Due to the small number of patients with unstable angina (n = 53), no significant prediction of outcome could be shown in those patients.

Conclusions: The affinity to the early released troponin T-I-C complex does not relevantly add on the AMI diagnostic properties of a TnI test system. Independent prognostic information could be obtained in patients with high TnI values at admission by the system with higher T-I-C affinity only. These patients have to be classified as having a longer delay between onset of symptoms and start of treatment. Therefore, in patients with acute coronary syndromes a troponin I test system with high affinity to the early released T-I-C complex provide a small but significant benefit in risk assessment.

2511 Plasma soluble P-selectin levels in acute myocardial infarction and its relationship with the success of thrombolytic therapy

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P-selectin, an integrated membrane protein in platelets and endothelial cells, mediates adhesive interactions between platelet (plt), leukocyte and endothelium to form thrombi. The purpose of this study was to investigate plasma level of soluble(s) P-selectin in patients (pts) with acute myocardial infarction (AMI) and the effect of successful thrombolysis on P-selectin levels.

Methods: A total of 32 AMI pts (26 male,mean age:54 ± 12) within the first 6 hours of chest pain were enrolled prospectively. Criteria for exclusion were inflammatory or neoplastic disease or an infectious disease within the last six weeks. Levels of P-selectin were determined by enzyme-linked immunoabsorbent assay on plasma taken from systemic veins of pts with AMI, stable angina (SA, n = 18), and the healthy controls (n = 15). Samples were obtained before, three and 24 hours after initiation of reperfusion therapy. Peak creatin phosphokinase (CPK) levels, plt and white blood cell (WBC) counts were also determined. Tissue plasminogen activator was used as thrombolytic therapy. Seven pts showed recurrent angina or failure to reperfusion.

Results: The plasma sP-selectin levels were significantly higher in the AMI group than the other 2 groups (86.7 ± 8.7 ng/ml, p < 0.05). The plasma sP-selectin levels were similar in SA and control groups (29 ± 4 vs 25 ± 7 ng/ml, p = ns). In pts with AMI we observed a strong correlation between the sP-selectin levels and peak CPK levels (r = 0.72, p < 0.05) and a moderate correlation with the WBC count(r = 0.064, p < 0.05.) A significant increase in sP-selectin levels was observed at 3 hours after successful thrombolysis (p < 0.005) and was followed by a decrease near to the baseline level late after reperfusion. But, pts with failed reperfusion showed sustained high levels of sP-selectin at 24 hours of the thrombolytic therapy (p < 0.05).

Conclusion: Plasma sP-selectin level is elevated in pts with AMI and it increases further following reperfusion therapy. This increase in sP-selectin levels is probably induced by the activation of endothelial cells, WBC, or plts after myocardial ischemia and reperfusion during AMI. Therefore sP-selectin can be considered as a systemically detectable indicator of the local coronary plt-WBC-endothelium interaction leading to AMI. As the elevated sP-selectin levels are sustained in pts with failed reperfusion, the serial p-selectin level expression may be used as an indicator of successful thrombolysis in AMI.

2512 Basic fibroblast growth factor, a potent promoter of angiogenesis, is a useful predictor of the progression of ventricular remodelling in acute myocardial infarction patients

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It has been recently reported that bFGF, a strong angiogenic peptide, enhances myocardial collateral development in an animal model of experimental coronary occlusion. The aim of our study is to clarify the role of bFGF in the early and late phase of acute myocardial infarction (AMI) in patients.

Methods: 27 patients with first attack of AMI, and no previous history of any other disease, were examined for plasma levels of bFGF, measured by ELISA, and compared to corresponding levels of 20 Normal controls (NC) with mean values: 1.61 ± 0.25 pg/ml. All pts were divided in 2 sex and age-matched groups. Group A: pts with minor AMI, EF > 45% and no subsequent LV dysfunction. Group B: pts with large infarct size, EF < 45% and heart failure. Plasma samples were collected at the time of hospital admission (O hours) and 6 h, 12 h, 18 h, 24 h, 48 h, 3 days, 4 d, 7 d, 15 d and 30 d thereafter. The mean latency period between symptom-onset and admission was 2.0 ± 1.0 h. All pts received thrombolysis.

Results are expressed as mean values ± SEM in pg/ml as follows:

Pts	0 h	6 h	12 h	18 h	24 h	48 h	3 d	4 d	5 d	7 d	15 d	30 d
A (13)	3.23 ± 1.9 ◇	1.55 ± 0.3	2.52 ± 0.9 *	1.20 ± 0.2 *	1.20 ± 0.2 *	1.74 ± 0.5	1.26 ± 0.2 *	1.32 ± 0.2 *	2.12 ± 0.6	5.9 ± 2.7 ◇	5.61 ± 3.6 ◇	5.7 ± 2.6 ◇
B (14)	5.15 ± 0.7 ◇	2.44 ± 0.4	2.11 ± 0.3 *	2.45 ± 0.4 *	2.0 ± 0.34 *	2.34 ± 0.4 *	2.55 ± 0.4	2.51 ± 0.3	2.96 ± 0.4	13 ± 6.3 ◇	13.8 ± 6.3 ◇	13.9 ± 3.3 ◇

p < 0.05 compared to corresponding values of: a) NC (◇) b) the relevant first plasma sample (*) (Wilcoxon test).

Conclusions: Both groups developed an initial high bFGF level but only in group B this increase was significant compared to NC. This may imply that acute hypoxia, due to reduced vascular flow, could be the same stimulus for this rise in both groups. This early peak is followed by a gradual decrease in both groups, probably due to thrombolytic therapy, and a late rebound of bFGF values. This rebound is significant compared to NC only in group B, leading in increased collateral vessel formation probably as an attempt to alter the progression of heart failure. Therefore, bFGF could be used as an early predictive marker for the quality of ventricular remodeling following AMI.

2513 In-hospital and long-term outcome of right ventricular infarction in a defined community population: the Mayo Clinic coronary care unit experience

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Background: Right ventricular myocardial infarction (RV-MI) is a complication of non-anterior wall MI that is often fatal if unrecognized. The short-term and long-term outcome of RV-MI remains ill defined in the current era of aggressive reperfusion therapy although recent studies have suggested a benefit for primary PTCA with RV-MI.

Methods: We analyzed 910 consecutive patients admitted to the Mayo Clinic CCU from Rochester, MN with acute MI from January 1988 until March 1998. We have compared the in-hospital and long-term mortality of patients with clinically determined RV-MI (n = 42) to those without RV-MI (n = 868).

Results: The in-hospital mortality rate of RV-MI (28.6%) was increased compared to Non-anterior MI without RV-MI (7.2%) and anterior MI (11.4%), p < 0.001. Patients with RV-MI had increased utilization of primary reperfusion therapy: RV-MI 67% vs Non-Ant MI 42% vs Ant MI 50%, p = 0.002. The use of beta-blockers differed between groups: RV-MI 48% vs Non-Ant MI 65% vs Ant MI 69%, p = 0.02. Median time from symptom onset to reperfusion therapy did not differ among groups. The pre-discharge EF in RV-MI (53%) was not significantly different from Non-Ant MI (53%) but was different than Ant MI (45%), p = 0.001. The odds ratio (OR) of in-hospital mortality, even after multivariate adjustment, remained increased in RV-MI: 3.64 (1.62–7.82), compared to anterior MI (p = 0.002). The relative risk (RR) of long-term mortality, after multivariate adjustment, was not increased in the RV-MI group: RV-MI RR 1.30 (0.78–2.14), p = 0.31 compared to Non-Ant MI without RV-MI. The RR of long-term mortality was reduced in Non-Ant MI without RV-MI compared to Ant MI: 0.79 (0.62–1.00), p = 0.05.

Conclusions: While the in-hospital morbidity and mortality of RV-MI remains increased, despite aggressive use of primary reperfusion therapy, the long-term survival of RV-MI is comparable to Non-Ant MI. The increased in-hospital mortality is not explained by a lack of aggressive utilization of reperfusion therapy, but may in part be explained by decreased utilization of beta-blocker adjunct medical therapy.

ALTERNATIVE TREATMENT OPTIONS FOR STABLE ANGINA

2514 Aggressive lipid lowering versus coronary angioplasty in subgroups of the AVERT trial: post hoc analyses

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Background: PTCA has been shown to relieve symptoms better than medical therapy with a slightly higher event rate, but no clinical trial has included aggressive cholesterol lowering as part of medical therapy.

Methods: The Atorvastatin Versus Revascularization Treatments Trial (AVERT) randomized 341 patients referred for PTCA to atorvastatin 80 mg/day or to PTCA followed by usual care. Included were patients with 1 or 2 vessel disease, an LDL-cholesterol of 3.0 mmol/L or more, and an exercise level of 4 mins (treadmill) or 20 W/min (bicycle) without 2 mm or more of ST depression. Excluded were patients with CCS angina class > 2, left main of 3 vessel disease, ejection fraction < 40%, PTCA within 6 months, unstable angina or MI within 2 weeks, or previous bypass surgery. All patients were followed for 18 months, at which time mean LDL-cholesterol had decreased by 46% and 18%, to 2.0 and 3.1 mmol/L in the atorvastatin and PTCA groups respectively. The primary efficacy parameter was the composite incidence of cardiac death (n = 2), nonfatal MI (n = 9), CVA, CABG (n = 11), PTCA (n = 39), or hospitalization for worsening angina with objective documentation (n = 36).

Results: Overall, 22 atorvastatin and 37 PTCA patients experienced an endpoint event (13% vs 21%, p = 0.048). The event rate was higher with 2 vessel (31/148, 20.9%) than 1 vessel disease (28/193, 14.5%), but was lowered by atorvastatin compared to PTCA in both groups: 24.4% to 17.1% with 2 vessel and 18.2% to 10.6% with 1 vessel disease. Events were more common in symptomatic than in asymptomatic patients, 18.9% vs 8.9%, but were lowered by atorvastatin in both subgroups. ST depression was induced by exercise in 158 of the 341 patients (46%). The event rate was less with atorvastatin, 8.6% vs 19.3%, in patients with inducible ischemia.

Conclusions: Although retrospective subgroup analyses are of limited value, particularly in a small trial such as AVERT, the advantage of atorvastatin over angioplasty/usual care extended to 1 and 2 vessel disease, to asymptomatic and class 1–2 patients, and to those with inducible ischemia. Aggressive cholesterol lowering with atorvastatin can delay or eliminate the need for angioplasty in a broad spectrum of patients with stable coronary disease.

2515 ACE inhibition with ramipril improves left ventricular function at rest and post-exercise in patients with stable ischaemic heart disease and preserved left ventricular systolic function

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Angiotensin-converting-enzyme inhibition counteracts myocardial ischemia as well as myocardial and vascular remodeling. Experimentally it attenuates diastolic dysfunction caused by myocardial ischemia, and may have clinical significance in patients with stable ischemic heart disease and preserved left ventricular systolic function.We aimed to assess the effects of a 6-month ramipril intervention on left ventricular function at rest and post exercise in patients with stable ischemic heart disease and preserved left ventricular systolic function.

Methods: Patients (n = 98, age 65 ± 9 years, 37% women) with stable ischemic heart disease and preserved left ventricular systolic function were randomized to ramipril 5 mg/day (n = 32), ramipril 1.25 mg/day (n = 34), or placebo (n = 32). Resting and post maximum exercise echocardiography/Doppler examinations were performed at baseline and after 6 months.

Results: Changes over 6 months in resting transmitral E-wave deceleration time (Edt) and Edt adjusted for heart rate (Edt/RR) differed between the ramipril 5 mg, ramipril 1.25 mg, and placebo groups, indicating a favourable effect of ramipril: Edt 24 ± 82 (ramipril 5 mg), −1 ± 69 (ramipril 1.25 mg), and −29 ± 64 ms (placebo), respectively, P = 0.012; Edt/RR 30 ± 105, 2 ± 61, and-28 ± 69 ms, respectively, P = 0.015. Changes over 6 months in the difference between resting and post exercise Edt/RR also varied between groups, indicating a favourable effect of ramipril: −53 ± 137 (ramipril 5 mg), −28 ± 118 (ramipril 1.25 mg), and 35 ± 101 ms (placebo), respectively, P = 0.029. Resting atrioventricular plane displacement improved in the combined ramipril groups compared to the placebo group: 0.2 ± 0.8 mm vs −0.2 ± 1.3, P < 0.05.

Conclusions: Ramipril treatment during 6 months, in patients with stable ischemic heart disease and preserved left ventricular systolic function, improved resting left ventricular function and reduced the exercise induced diastolic filling abnormalities usually seen in these patients.

2516 Efficacy and safety of trimetazidine in patients with persistent stable angina pectoris under β-blocker therapy: TRIMPOL II multicentre study

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The aim of the study was to assess the antianginal efficacy of trimetazidine, a metabolic agent which improves cardiac metabolism in ischemia, in patients with persistent angina pectoris despite metoprolol.

Methods: 227 patients with stable effort angina despite metoprolol (50 mg b.i.d.) were included in this multicenter double-blind randomized placebo controlled trial with a follow-up period of 12 weeks. All patients had proven coronary artery disease and stable angina (>3 months). Before inclusion all patients had two stable (<20% variability) positive treadmill exercise tests separated by one week. At inclusion patients were randomized to trimetazidine (20 mg t.i.d.) + metoprolol (50 mg b.i.d.) or placebo + metoprolol for a 12-week treatment period.

Exercise treadmill testing was again performed at four and twelve weeks. Main criteria of evaluation were improvement at 12 weeks in the following: exercise time to 1 mm ST segment depression, total walking time, work capacity, time to onset of angina.

Results: 227 patients (114 trimetazidine, 113 placebo, mean age 54.8 years), with no statistically significant inter-group differences in demographic characteristics, completed the 12-week treatment period. Results are shown in the table below:

	Trimetazidine + Metoprolol ($W_{12} - W_0$)	Placebo + Metoprolol ($W_{12} - (W_0)$	Inter-group differences
Increase time to 1 mm ST-segment depression (%)	28.5%*	12.6%*	p < 0.01
Increase total walking time (%)	16.6%*	7.6%*	p < 0.01
Increase work capacity (%)	15.6%*	4.8%	p < 0.01
Time to onset of angina	27.4%*	12.2%*	p < 0.01

*p < 0.01

In conclusion, after a 12-week treatment period, trimetazidine significantly improved all ergometric and electrocardiographic parameters compared to placebo in patients with stable angina pectoris treated with metoprolol.

2517 Temporary sympathectomy for refractory angina

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Purpose: Post-revascularisation angina which is refractory to conventional treatment is a growing clinical problem which has yet to be addressed adequately. Repeat coronary artery bypass surgery, palliative angioplasty and transmyocardial laser therapy are often attempted but are expensive and have an associated increase in mobidity and mortality. Permanent cardiac sympathetic denervation is an effective technique that is presently being re-evaluated following advances in the technique of thoracoscopic surgery, however there are difficulties associated with nerve regeneration, future treatments should the pain recur and concerns regarding patients with poor left ventricular function.

Methods: We report our first 54 consecutive patients who underwent temporary left stellate ganglion block (LSGB) for severe angina following failed revascularisation using 15 mls of 0.5% bupivacaine. All patients had typical angina and were taking maximally tolerated oral antianginal medication. Patients completed standardised HAD and Seattle Angina questionnaires. Stellate ganglion block was performed as per usual operator practice and temporary cardiac sympathetic denervation was confirmed using power spectral analysis of heart rate variability (HRV).

Results: There were no serious adverse complications. Only one patient was admitted overnight due to nausea and all other patients were treated as outpatients. Patients were initially evaluated one week after their procedure, and then followed until their pain recurred. Daily GTN usage was reduced from 6.6 ± 5.1 to 1.9 ± 3 ($p < 0.001$). Canadian Class Status was reduced from 3.4 ± 0.6 to 1.4 ± 1.6 ($p < 0.001$). The average length of time completely painfree in patients with changes in HRV suggestive of effective cardiac sympathetic denrvation was 5.6 ± 5.0 weeks compared to 0.3 ± 0.5 weeks in patients with no such alterations ($p < 0.001$). Quality of life was also significantly improved.

Conclusions: This pilot study suggests that temporary left stellate ganglion block is capable of ameliorating severe angina for much longer than the local anaesthetic effect of bupivacaine. It offers the prospects of this therapy being developed as an outpatient treatment for refractory angina. A double blind randomised placebo controlled study is underway funded by the British Heart Foundation.

2518 Comparison of prognostic surveys used in the Multicentre Study of Enhanced External Counterpulsation (MUST-EECP)

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Because of the need for non-invasive therapy in patients with chronic angina pectoris refractory to conventional therapy, a multicenter placebo-controlled trial of enhanced external counterpulsation (EECP) was begun in the United States in 1995 with enrollment concluded in May 1997. Immediate improvement in various ischemic parameters was noted in the actively treated group (AC) compared to the inactive or sham group (IC), but it was unclear whether long-term clinical benefits would be present as reported previously in observational non-randomized studies.

Methods: To assess long-term clinical benefit, two separate protocols were employed. In *Method 1*, mail and telephone surveys were instituted by nurse coordinators in 80 patients who were at least 3 months post-treatment.

In *Method 2*, 125 patients were enrolled in a quality of life evaluation using 1) SF-36, and 2) Quality of Life Index – Cardiac Version III (QLI). Post-treatment mail surveys were collected at 3, 6, 9 and 12 months by an independent consulting firm.

Results: In *Method 1*, 40 patients were in the AC and IC groups with a mean follow-up time of 12 months. Hospitalization rates for both groups were similar, but improvement in symptoms was more significant in the AC group (28/40 v s 15/40, $p < 0.01$).

In *Method 2*, the AC group had significantly greater improvement than the IC group in 1) SF-36: Bodily Pain ($p < 0.01$), and Health Transition ($p < 0.05$), and 2) QLI: Health and Functioning ($p < 0.05$) at 12 months.

Conclusion: In the MUST-EECP trial AC patients reported significant improvement compared to IC patients in health status regardless of the follow-up methodology.

2519 Draft guidelines for the management of refractory angina on behalf of the UK Refractory Angina Group

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Refractory angina is a clinical diagnosis. It is based on the presence of symptoms of angina that are thought to be caused by coronary insufficiency and which are not controllable by a combination of anti anginal medication, angioplasty or coronary artery bypass surgery. The presence of demonstrable myocardial ischaemia is desirable but is not an absolute requirement for including a patient in the guideline process.

What follows is the "consensus" algorithm from the Refractory Angina Group in November and is now presented for peer review/consultation. This is a draft proposal and that individual practitioners will have to take account of local resource provision.

1. Diagnosis requires a cardiological and cardiothoracic surgical opinion that further revascularisation is unfeasible. Regular angiographic review is recommended to exclude "new" revascularisable disease.
2. Outpatient assessment to include: Review of pain history, drug history and physical exam.
3. Outpatient counselling to include explanation of management plan, lifestyle advice.
4. Rehabilitation. Involving exercise programme, lifestyle advice, relaxation training.
5. Psychotherapy. Based on established psychological assessment methods.
6. Transcutaneous electrical nerve stimulation. Based on Mannheimer protocol.
7. Temporary sympathectomy. Unilateral left stellate ganglion block, T3/4 paravertebral block in stages. Based on the Liverpool protocol.
8. Spinal cord stimulation.
9. Opioids.
10. Destructive sympathectomy.
11. Laser myocardial revascularisation. Only as part of a formal clinical trial.

Angina alone is not an indication for cardiac transplantation.

Recommendations: Closer links between cardiologists and pain specialists is essential. Clearly a great deal of research is required. Where RCTs are unfeasible there is an overwhelming case for comparative studies.

SIGNAL TRANSDUCTION IN ISCHAEMIC PRECONDITIONING

2520 Mechanical stretch mimics preconditioning and ameliorates the detrimental effect of angiotensin II in vivo

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Volume overload protects against myocardial infarction and this protection is completely blocked by gadolinium (Gd^{3+}), a stretch receptor antagonist. Angiotensin II (AII) mimics preconditioning (PC) in vitro limiting the infarct size. The aim of this study was to investigate whether AII infusions and/or mechanical stretch from hypertensive response are PC analogues in vivo.

Methods: Anesthetized rabbits (n = 7–10/group) were used to study PC with the following standard protocol: 5 min of intervention (AII infusion or aortic constriction) – 10 min of reperfusion (rep) – 30 min of ischemia – 120 min of rep. Pressor (5 μg/ml) or non-pressor (1 μg/ml) doses of AII were either infused intravenously (IV) or directly into the left atrium (LA) and blood pressure was continuously monitored. The infarcted (I) and the risk areas (R) were delineated with the aid of Zn-Cd fluorescent particles and tetrazolium chloride staining. Infarct size is expressed as I/R ratio in % as mean ± 1 SEM.

Results:

	Intervention	Pressor response	Infarct size
Group A	AII 5 μg/ml IV	Hypertension	31.2 ± 4.8
Group B	AII 5 μg/ml LA	Hypertension	$52.2 \pm 6.9^{*}$
Group C	No intervention	Normotension	39.6 ± 6.1
Group D	AII 1 μg/ml IV	Normotension	42.1 ± 5.9
Group E	AII 1 μg/ml LA	Normotension	$48.9 \pm 3.5^{*}$
Group F	Aortic constriction	Hypertension	$17 \pm 3.7^{**}$
Group G	Aortic constriction + Gd^{3+}	Hypertension	48.8 ± 4.2

$^{*}p < 0.05$ vs *A*. $^{**}p < 0.001$ vs G.

Conclusion: AII fails to mimic PC in vivo; direct LA administration of pressor or non-pressor doses of AII increases infarct size. By contrast, hypertensive response from IV pressor doses of AII ameliorates the direct AII toxicity on myocardium. Mechanical stretch by itself due to aortic constriction can mimic PC, an effect blunted by Gd^{3+}.

2521 Mechanism of early ischaemic preconditioning by nitric oxide is guanylate cyclase dependent but independent of protein kinase C or sarcolemmal/mitochondrial ATP-sensitive potassium channels

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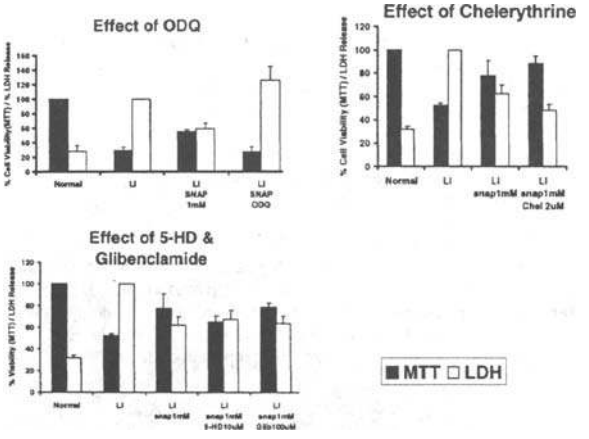
Nitric oxide (NO) can mimic early ischaemic preconditioning (PC) in cultured neonatal rat cardiocytes but the mechanism of this protection is unknown.

Methods: Pre-treatment for 90 minutes with the nitric oxide donor s-nitroso-N-acetyl-L-penicillamine (SNAP) followed by 30 minutes under normal culture conditions protected against subsequent 6 hours of lethal ischaemia (LI). We studied the effect of the specific guanylate cyclase inhibitor ODQ 10 μM, the PKC inhibitor chelerythrine 2 μM, together with glibenclamide 100 μM and 5-hydroxydecanoate (5-HD) 10 μM (blockers of sarcolemmal and mitochondrial ATP-dependent K^+ channels respectively) on SNAP-induced protection. Cell viability was quantified by LDH release and MTT bioreduction. Glibenclamide, 5-HD, ODQ and chelerythrine did not alter tolerance to ischaemia when given alone.



Results & conclusion: SNAP produced a significant increase in MTT conversion and a reduction in LDH release ($p < 0.01$) compared to SI alone. This protection was abolished by ODQ ($p < 0.01$) but unaffected by the presence of chelerythrine, glibenclamide or 5-HD. This suggests that early PC by NO is guanylate cyclase dependent but independent of PKC or mitochondrial/sarcolemmal ATP-dependent K^+ channels.

2522 The inhibition of p38α during index ischaemia may underlay ischaemic preconditioning

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Activation of protein kinase C (PKC) and more recently mitogen-activated protein kinases (MAPKs) have been associated with the cardioprotective effect of ischaemic preconditioning. We examined the interplay between these two kinases in a characterised model of ischaemic preconditioning in cultured rat neonatal cardiocytes, were expression of active PKC-δ results in protection. Two members of the MAPK family, p38 and p42/44, were activated transiently during preconditioning with 90 min simulated ischaemia and 30 min re-oxygenation. Surprisingly, overexpression of active PKC-δ, rather than augmenting, completely abolished this activation. We therefore determined if a similar effect occurred during lethal simulated ischaemia. Lethal ischaemia activated only p38 MAPK (280 ± 45% activation, $p < 0.01$), which was attenuated by overexpression of active PKC-δ. Moreover preconditioning, which gives rise to a similar level of protection, caused a strikingly similar inhibition of ischaemia-induced p38 activation (111 ± 26% activation, $p < 0.01$). To determine if this reduced p38 phosphorylation was the cause, or an effect, of preconditioning, we used SB203580, a p38 inhibitor, in attempt to protect myocytes against lethal ischaemia alone. SB203580 significantly reduced ischaemic injury (CK release 38.0 ± 3.1%, LDH release 77.3 ± 4.0% and MTT bioreduction 127.1 ± 4.8% of control, $n = 20$, $p < 0.05$). Cells infected with adenoviruses encoding wild-type p38α or p38β, show differential activation of p38 ($p < 0.001$) during sustained simulated ischaemia, since p38α remains activated (148 ± 36% activation) whereas p38β is deactivated (36 ± 10% activation, $p < 0.01$). Prior preconditioning prevented this activation of p38α (84 ± 15% activation, $p < 0.05$). Hence inhibition of p38α during index ischaemia may represent a common mechanism for preconditioning-induced cardioprotection.

2523 Mechanisms of delayed cardioprotection in a human cardiocyte cell line

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Evidence of delayed preconditioning or second window of protection (SWOP) in man is limited. We investigated the mechanisms of SWOP in an adult human cardiac myoblast cell line (Girardi cell) model, with particular reference to the role of the mitochondrial K_{ATP} channel. Girardi cells were grown to confluence and submitted to a variety of interventions: Group 1 were preconditioned (PC) by incubation in ischaemic buffer (KCl 16 mmol, lactate 20 mmol, pH 6.5) in an hypoxic chamber (argon 95%, carbon dioxide 5%) for one hour. Group 2 were preincubated with the P38 kinase inhibitor, SB203580, 30 minutes prior to PC. Group 3 were incubated with adenosine, a known trigger for PC, 100 uM for 20 mins. All groups were allowed to recover for 24 hours prior to being subjected to lethal simulated ischaemia (LSI), consisting of 3 hours incubation in ischaemic buffer with a pH of 6.3 in the hypoxic chamber. A further group of preconditioned cells were treated with the mitochondrial K_{ATP} channel blocker 5-hydroxydecanoate sodium 50 uM (5-HD), 30 mins prior to LSI. Lactate dehydrogenase enzyme release into medium was assayed as an index of cell injury and expressed as percent of total releasable LDH.

Group	Ischaemic injury index [mean (SEM)]
ischaemia	36.4 (1.1)
PC	12.1 (0.9)*
PC + SB203580	28.6 (2.8)
PC + 5-HD	31.9 (4.8)
Adenosine	11.9 (2.0)*
Adenosine + SB203580	25.3 (2.9)

*$p < 0.001$ vs ischaemia by one way ANOVA

Conclusion: In this human cardiac cell model, adenosine and PC provide delayed cardioprotection against LSI. These effects appear mediated via a P38 kinase signalling pathway and effected by the opening of the mitochondrial K_{ATP} channel.

2524 Myocardial protection during serial balloon angioplasty (PTCA): ischaemic preconditioning?

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Myocardial preconditioning is a powerful technique for reducing infarct size in animal models. Serial balloon inflation during PTCA is a potential human model but it is not clear if ischaemic tolerance on subsequent inflations is due to collateral recruitment or preconditioning. Patients with LAD disease underwent 2 balloon inflations of >3 min separated by >5 min reperfusion. Balloon occlusion pressure (Pocc) was measured with a 0.014" pressure wire positioned distal to the balloon. Collateral flow index was calculated on the basis of simultaneous measurements of mean aortic (Pa) and coronary sinus pressure (CSP): (Pocc-CSP)/(Pa-CSP). Myocardial ischaemia was assessed with degree of ST shift, from the surface ECG chest lead with greatest deviation. The patient on a scale from 0–10 graded pain severity.

		Collateral Flow Index		ST Deviation		Chest Pain	
Patient	Age	Occ 1	Occ 2	Occ 1	Occ 2	Occ 1	Occ 2
1	56 m	0.09	0.19	7.5	2.5	10	5
2	68 m	0.16	0.15	0.7	0	0	0
3	57 m	0.15	0.18	1.5	0.9	6	6
4	58 m	0	0	10.2	6.7	10	7
5	56 f	0	0	0.8	0.8	6	6
6	56 m	0.2	0.25	0.8	0	9	5
7	58 m	0.38	0.37	1.8	1.5	9	8
8	56 f	0.32	0.29	0.3	0.3	3	2
9	52 m	*0*	*0.02*	*9*	*7.2*	*5*	*4.5*
10	51 m	*0*	*0*	*6.7*	*3.3*	*3*	*1.5*
	Mean	*0.13*	*0.146*	*3.93*	*2.32**	*6.1*	*4.5**
	SD	± 0.1	± 0.1	± 3.9	± 2.7	± 3.4	± 2.6

(*$P < 0.01$ Occlusion 2 v Occlusion 1, paired t-test)

Conclusions: 1. We demonstrate that ischaemic parameters improve significantly during the second balloon occlusion, 2. This protection is achieved without significant collateral recruitment providing evidence for preconditioning in man.

2525 Attenuation of the maximum ST-segment depression, the value of CK-MB Isoenzyme and the ejection fraction in the first Q anterior wall myocardial infarction: a new method of confirming spontaneous ischaemic preconditioning?

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Background: In the induced models of ischaemic preconditioning which have a protective effect for the ischaemic myocardium (repeated stress tests, pacing tachycardia, PTCA) an attenuation of the maximum value of ST-segment depression (ASTD) was noted.

We studied ASTD as an indicator of the spontaneous adaptation to ischaemia during 3 successive ischaemic attacks (A1, A2, A3) in the first Q myocardial infarction (AMI), the total izoenzyme CK-MB value [$\sum$(CK-MB)] and the ejection fraction of the left ventricle (EF).

Methods: Eighty pts (61 m/19 f, mean 59 ± 4 yrs), at the onset of AMI, immediately upon entering the coronary unit were subjected to 24 h ECG Holter monitoring (ECGH) and the maximum ST-segment depression value was measured during A1, A2, A3, with periods of spontaneous reperfusion. All pts were divided into group A with a statistically significant ASTD and group B with no significant ASTD. During the 7 days following AMI, the Σ(CK-MB) value has been analyzed; the EF was measured by echocardiography. Fibrinolythics therapy was not applied to the pts and during ECGH they did not receive beta-blockers. Coronarography had not shown a significant difference between A and B in the severity of the coronary disease.

Results:

Group	n	Average values of max. STD (mm)			$\sum$(CK-MB) (iu/l)	EF (%)
		A1	A2	A3		
A	36	2.62 ± 0.2	1.73 ± 0.1*	1.46 ± 0.1*	64.18 ± 8.1**	48 ± 5**
B	44	2.86 ± 0.1	2.81 ± 0.2	2.94 ± 0.2	99.48 ± 6.2	27 ± 5

*p < 0.001 vs. A1; **p < 0.001 vs. group B

Conclusion: Pts in group A showed significantly lower average $\sum$(CK-MB) value and significantly higher average EF value, compared to group B ($p < 0.001$). This could confirm the importance of ASTD as a clinical indicator of the existence of spontaneous adaptation and ischaemic preconditioning in some pts with their first Q AMI.

THE HEART IN HYPERTENSION: NEW ASPECTS OF CARDIOVASCULAR STRUCTURE AND FUNCTION

2526 Macrophage chemoattractant protein-1 and macrophage inflammatory protein-1a serum levels in hypertensive patients with or without significant hyperlipidaemia

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Objective: The activation of monocytes with infiltration into the vessel wall is an early event in atherogenesis. C-C chemokines may play a role in the recruitment and activation of monocytes/macrophages in this disorder. This study investigates the differences in serum activity of representative C-C chemokines, such as macrophage chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1a (MIP-1a), between hypertensive patients with significant hyperlipidemia and hypertensive patients without this condition.

Methods: Serum levels of MCP-1 and MIP-1a were determined by Elisa assays in 38 patients (29 men and 9 women) with moderate hypertension and 15 age-matched healthy controls. Patients (n = 18) with total cholesterol (TC) ≥ 240 mg/dl and LDL-C ≥ 160 mg/dl were classified as group A, while patients (n = 20) with values less than the above, as group B. All patients did not receive any medications before blood sampling for laboratory measurements.

Results: Data (mean ± SD) are shown in the table:

Pts	Age (yrs)	SBP (mmHg)	DBP (mmHg)	TC* (mg/dl)	LDL-C* (mg/dl)	MCP-1** (pg/ml)	MIP-1a*** (pg/ml)
Group A (n = 18)	58.2±6.3	172±6.1	103±4.8	261.2±11.7	169.9±7.9	198.4±29.3	24.3±4.1
Group B (n = 20)	56.7±7.1	170±6.8	105±4.2	218±12.3	138.3±8.7	150.7±33.2	19.8±3.9
Controls (n = 15)	54.3±5.9	125±4.3	88±3.8	208.5±14.8	133.2±9.1	116.2±24.3	15.4±3.1

* p group A vs B < 0.01, ** p group A vs B < 0.01, p group A vs controls < 0.001, p group B vs controls < 0.05, *** p group A vs B < 0.05, p group A vs controls < 0.005, p group B vs controls < 0.05

In group A, MCP-1 and MIP-1a values were significantly correlated with LDL-C ($r = 0.49$, $p < 0.05$ and $r = 0.56$, $p < 0.01$, respectively). No correlation was found between smoking and C-C chemokine serum activity in study population.

Conclusions: MCP-1 and MIP-1a serum levels are elevated in hypertensive patients, especially in those with significant hyperlipidemia. This elevation may reflect the initiation and progression of inflammatory atherosclerotic process triggered by arterial hypertension and enhanced by its coexistence with hyperlipidemia.

2527 Effects of short-term with an ACE inhibitor or an angiotensin II antagonists on vascular content of ICAM-1 in spontaneously hypertensive rats

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Objective: It has been demonstrated that intercellular adhesion molecule-1 (ICAM-1) plays a role in leukocyte extravasation through the endothelium. Since ICAM-1 contributes to the trapping of monocytes on local vascular walls, it may participate in the process of atherogenesis. We have evaluated the effects of an ACE inhibitor, enalapril (ENA) and of an angiotensin II receptor blocker, candesartan cilexetil (CAND), administered either at hypotensive or at non-hypotensive dosage, on structural alterations of mesenteric small resistance arteries in SHR as well as on vascular content of ICAM-1.

Design and Methods: One hundred and three rats were included in the study: 16 SHR were treated with low-dose (ld, 1 mg/kg/day) ENA, 14 with low-dose (ld, 0.5 mg/kg/day) CAND, 16 with high-dose (hd, 25 mg/kg/day) ENA, 21 with high-dose (hd, 15 mg/kg/day) CAND, while 18 WKY and 18 SHR were kept untreated (unt). Treatment was from age 4 to 12 weeks. Systolic blood pressure (SBP) was measured non-invasively every week. Mesenteric small arteries were dissected and mounted on a micromyograph (Mulvany's technique), and the media:lumen ratio (M/L) was calculated. The small mesenteric arteries content of intercellular adhesion molecule-1 (ICAM-1) was evaluated by ELISA on tissue homogenate.

Results: The results are summarized in the Table. SBP was significantly reduced only by the high doses of ENA or CAND. M/L was significantly greater in unt SHR than in unt WKY. A significantly smaller M/L was observed in SHR treated with the high doses of ENA or CAND, in comparison with untreated SHR and with SHR treated with the low doses of the drugs. ICAM-1 vascular content was greater in unt SHR than in unt WKY, and was almost normalized by treatment with both low and high doses of ENA or CAND.

Table	SBP (mm Hg)	M/L (%)	ICAM (ng/g of tissue)
unt'WKY	155 ± 15***	9.2 ± 1.9***	135 ± 69***
unt SHR	246 ± 25	14.0 ± 2.4	366 ± 233
SHR ENA ld	218 ± 18	13.2 ± 2.1	193 ± 55*
SHR CAND ld	221 ± 27	13.7 ± 2.2	149 ± 80**
SHR ENA hd	157 ± 20***#	10.7 ± 1.7***	149 ± 43**
SHR CAND hd	175 ± 19***	11.8 ± 1.9**	133 ± 72**

(* = p < 0.05, ** = p < 0.01, *** = < 0.001 vs. SHR unt; # = p < 0.001 vs. CAND hd)

Conclusions: ENA and CAND at either low or high doses were able to normalize the vascular content of ICAM-1, while only the high, hypotensive dose was able to induce a reduction of vascular structural alterations. Our data suggest that ENA and CAND could be effective in preventing the adhesion of inflammatory cells, and, consequently, may exert an antiatherogenic action, even at non hypotensive doses.

2528 Effects of hypertension in heart failure following myocardial infarction

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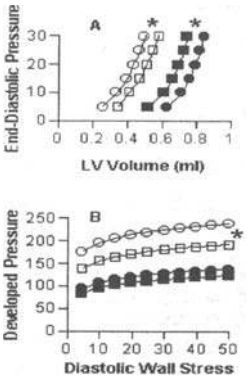
Hypertension (HTN) induces concentric left ventricular hypertrophy (LVH) and thus increases LV contractile function and decreases wall stress. Large myocardial infarction (MI) results in overall LV dilation and decreased LV contractile function. We tested whether in heart failure post-MI HTN was able to induce additional compensatory LVH and increase contractile function.

Male, Dahl salt-sensitive (SS) and salt resistant (SR) rats underwent coronary ligation or sham operation. 4 weeks of high-salt diet induced HTN in SS rats (>160 mmHg systolic blood pressure) but no HTN (NHTN) in SR rats. LV pressure-volume relationship (PV) were established in isolated, red-cell perfused hearts. Four groups were studied: Sham + NHTN (□, n = 8), Sham + HTN (○, n = 8). MI + NHTN (▫, n = 12), and MI + HTN (●, n = 8). Infarct sizes were similar in MI + NHTN and MI + HTN groups (48 ± 4% vs 46 ± 3% of LV, ns). In non-infarcted hearts HTN resulted in concentric LVH (HW/BW = 4.4 ± 0.1 vs 5.5 ± 0.2 mg/g, Sham + NHTN vd Sham + HTN, $p < 0.05$) as indicated by a leftward shift in the PV curve. In post-MI heart failure HTN resulted in further eccentric LVH (HW/BW = 5.3 ± 0.2 vs 6.0 ± 0.2 mg/g, MI + NHTN vs MI + HTN, $p < 0.05$) as indicated by a rightward shift in the PV curve (Fig A). HTN elevated contractile function in Sham rats ($p < 0.05$), but did not increase systolic function in MI + HTN compared to MI + NHTN rats (Fig B).



Conclusion: Dilated hearts post-MI still possess the ability to hypertrophy secondary to HTN. However, HTN does not increase contractile function and results in further LV dilation post-MI.

2529 Is dietary salt intake a determinant of left ventricular diastolic function in young women with mild essential hypertension?

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Previous studies have shown dietary salt intake as an independent determinant of left ventricular hypertrophy (LVH) in established essential hypertension; however, diastolic dysfunction might occur with or without LVH. This study was designed to examine the relation of dietary salt intake with the LV diastolic filling at the onset of hypertension in previously untreated young women with mild essential hypertension.

Methods: 42 young female patients (mean age 30.4 ± 2.7 yrs) with mild essential hypertension (group 1) and 36 age-matched female normotensive control subjects (group 2) underwent 24 hour blood pressure monitoring in parallel with 24 hr urinary sodium excretion and plasma renin activity. 2-D guided M-mode echocardiography with pulse-wave Doppler was performed to evaluate the structural and diastolic filling properties of left ventricle. Logistic regression analysis was performed to identify the independent determinants of left ventricular diastolic filling.

Results: In group 1 patients, the higher the urinary sodium excretion, the greater were the ratio of velocity time integrals A/E (VTI A/E) ($r = 0.57$, $p < 0.001$), maximal velocities (V max A/E) ($r = 0.48$, $p < 0.05$) and atrial filling fraction ($r = 0.54$, $p < 0.01$). On the contrary, group 2 patients showed an inverse correlation of sodium excretion with the diastolic filling parameters (all $p < 0.01$). Sodium excretion was related to plasma renin activity but in reverse in hypertensives ($r = -0.43$, $p < 0.05$). Logistic regression analysis identified sodium excretion (group 1: VTI A/E: $p < 0.0001$; group 2: VTI A/E: $p = 0.001$) and heart rate (group 1: VTI A/E: $p = 0.007$; group 2: VTI: A/E $p = 0.06$) as independent determinants of diastolic function in both groups. LV mass, enddiastolic volume index and endsystolic wall stress were not related to diastolic function parameters in either group.

Conclusion: Dietary salt intake assessed by sodium excretion over 24 hrs is a powerful determinant of LV diastolic dysfunction at the onset of hypertension, and even before the manifestation of LVH in young women.

2530 Exercise echocardiography is an optimal non-invasive stress test for the diagnosis of coronary artery disease in hypertensive subjects

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The aim of the study was to compare efficacy and side effects profile of electrocardiographic exercise stress test (EST), exercise echocardiography (EE) and dobutamine echocardiography (DE) applied for the diagnosis of coronary artery disease (CAD) in hypertensive patients (pts) with angina.

Methods: Study group included 197 pts, age 53 ± 9 years, 65 women, with treated (stage I and II) arterial hypertension, without history of myocardial infarction. Maximal exercise was performed on treadmill with Bruce protocol. EKG was evaluated continuously and wall motion was assessed before and just after the end of exercise. DE was performed with continuous i.v. infusion up to 40 μg/kg/min. with atropine 0.25–1.0 mg added in 44% of pts. Positive EST result was defined as ≥1 mm ST depression. Positive EE and DE result was defined as a new or increased wall motion abnormality after stress, calculated as a wall motion score index (WMSI). Left ventricular hypertrophy (LVH) evaluated with M mode echocardiography and defined as LV mass index > 117 g/m^2 in men and >104 g/m^2 in women was present in 45% pts.. Significant CAD (stenosis > 50%) was present in 59% pts.

Results:

	EST		EE		DE	
LVH	+	−	+	−	+	−
Sensitivity (%)	80	75	87	77	80	68
Specificity (%)	66*	56#	100*	94#	100*	96#

EE/DE vs. EST * - $p < 0.01$, # – $p < 0.001$.

Sensitivity differences were not significant. Specificity and sensitivity of evaluated methods were not different according to the presence of LVH. Maximal double product was significantly higher at EE than at DE (23852 ± 6408 vs. 20607 ± 5400 mm Hg/min., $p < 0.0001$) WMSI was also higher at EE than at DE (1.17 ± 0.14 vs. 1.12 ± 0.09, $p < 0.001$), what facilitated image interpretation. Systolic blood pressure increased above 240 mm Hg or declined more than 5 mm Hg from resting values more common at DE than at EE (7% vs. 2%, $p < 0.05$). New arrhythmia was induced with both DE and EE (18% vs. 13%, p = ns). Side effects like anxiety (7%), headache (7%) and paresthesia (37%) were reported at DE but not at EE.

Conclusions: In hypertensive patients with the symptoms of angina both stress echo methods are highly accurate and significantly more specific than exercise electrocardiographic test, independently from the presence of LVH. Treadmill exercise is associated with lower frequency of significant blood pressure variation and is better tolerated than infusion of dobutamine. Exercise echocardiography should be regarded as a method of choice in the diagnosis of coronary artery disease in hypertensive patients

2531 Coronary calcium as a predictor of coronary events in hypertensive patients: three years follow-up

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Coronary calcium (CC), easily detected by dual slice spiral CT (CT) is a marker of coronary artery disease. This study was aimed to investigate the predictive value of CC for cardiovascular events in hypertensive patients.

Methods: Five hundred forty four hypertensive patients (53% male, mean age 65 ± 6 years) were selected as a side arm of the INSIGHT protocol (International Nifedipine Study Intervention as a goal for Hypertension Therapy). All underwent CT and were followed for a period of 3 years (mean 27.6, median 36.0 months).

Results: Eighty three patients developed one or more cardiovascular events: In 59 the first event was coronary (acute MI: 18; sudden death: 3; angina: new; 4 worsening; 7, unstable: 16; coronary angiography: 9; PTCA: 1; CABG: 1) and vascular in 24 (TIA: 7; CVA: 17). Among 148 patients who had no CC (Total calcium score = 0) 9 (9.4%) developed event – 5 coronary and 4 vascular, while of the 387 patients who had CC (total score > 0) 74 (19.2%) had events – 54 coronary and 20 vascular. Results from Cox regression analysis, where the first cardiovascular event was considered as the terminal event, and age, sex, BMI, smoking, diabetes mellitus, hypercholesterolemia, family history of CAD, LVH, proteinuria and presence of CC as covariates demonstrated that the following factors significantly increase the probability of developing an event:

		RR	95% CI	P value
Coronary event:	Presence of CC	3.7	1.5–9.4	0.005
	Male gender	3.3	1.7–6.5	<.001
Vascular event:	Proteinuria	5.8	2.4–14.4	<.001
	LVH	2.6	1.0–6.7	0.039
	Family history of CAD	3.0	1.0–9.4	0.050

Conclusions: The presence of CC on dual slice CT quadruples the risk of developing a coronary event within 3 years. This technique is helpful in stratifying hypertensive patients.

NEW TRENDS IN MITRAL VALVULAR SURGERY

2532 Determination of plasma brain natriuretic peptide concentrations may improve the timing of surgical intervention in patients with chronic mitral regurgitation

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The long-term prognosis in patients who have had mitral valve surgery for chronic MR is not good. These poor results often reflect irrevesible LV impairment which is sustained and not detected prior to surgical referral. BNP synthesis and secretion is increased in a number of conditions associated with LV dysfunction and could potentially be used as a marker of early LV disease in chronic MR.

We studied 22 patients with isolated non-rheumatic chronic MR and echocardiographic evidence of at least moderate MR and 8 normal volunteers. Eleven patients were symptomatic and 10 of these were on the waiting list for valvular surgery. Plasma BNP was measured, after extraction, by radioimmunoassay. All subjects had normal renal function.

Mean plasma BNP (±SD) in all patients was higher in patients than normals: 20.9 (16.9) vs 3.4 (0.9) pmol/l; p 0.007. Plasma BNP in patients in NYHA I was 12.6 (7.0), NYHA II/III 17.1 (6.0) and NYHA IV 42.6 (23.6) pmol/l; p = 0.002 I vs IV, p = 0.019 II vs IV and p = 0.189 I vs II. Only 2 patients had normal BNP concentrations (<5.2 pmol/l) and both were asymptomatic. Two asymptomatic patients had levels >20 pmol/l with normal LV end-systolic dimensions (ESD) and both have subsequently developed symptoms within 6 months of follow-up. Those patients with increased LVEDD and normal LVESD (n = 14) had similar concentrations to those with normal LVEDD and ESD (n = 8): 17.95 (11.2) vs 17.8 (8.0); p = 0.89. There was no correlation between BNP levels and LV dimensions, fractional shortening or left atrial size: r = 0.083, r = 0.002, r = 0.051.

Plasma BNP concentrations are elevated in patients with isolated chronic MR prior to the development of symptoms or echocardiographic evidence of LV impairment. These results suggest that serial measurements of plasma BNP may be useful as a means of assessing progressive LV dysfunction in patients with MR but longitudinal studies are required to determine whether surgical intervention on the basis of BNP levels alters the long-term prognosis in these patients.

2533 Double orifice repair: a new approach for the surgical correction of myxomatous mitral regurgitation with bileaflet prolapse (Barlow's disease)

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Myxomatous disease with prolapse of both mitral leaflets is a surgical challenge. Repair of mitral regurgitation (MR) due to elongated subvalvar apparatus, redundant leaflets and dilated mitral annulus (fig 1), requires complex surgical procedures associated with unpredictable results. Double orifice repair is a new method of reconstruction particularly suitable for the correction of MR in Barlow disease.

Methods: Since 1993, we observed 62 consecutive pts (mean age 51 yrs) with Barlow disease. Regurgitation was due to elongated chordae and prolapse of both leaflets in 42 pts; in 20 pts, chordal rupture was also associated. Forty-nine patients were in NYHA class I and II while 13 were class III or IV. Pre-op planimetric valve area was 6.9 ± 1.46 cm^2. All patients underwent double orifice mitral repair (creation of two orifices by suturing the free edges of the leaflets in the middle portion (fig 2).

Results: There were no perioperative deaths. Post-op TEE showed no MR in 39 pts, mild in 21, and moderate in 2 pts. No patient had postoperative SAM. Planimetric post-op valve area was 3.3 ± 0.59 cm^2, no gradient across the valve was ever detected. Follow-up was complete (92 pt-yrs). There were no late deaths. One patient was reoperated for recurrent MR due to endocarditis and underwent mitral valve replacement (freedom from reoperation 89 ± 11% at 4 years). At latest follow up all patients but one are in NYHA class I or II, and echocardiography demonstrates stability of the repair and regression of ventricular volumes.

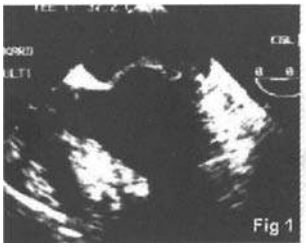
Fig 1

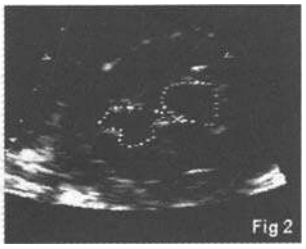
Fig 2

Conclusions: The double orifice repair technique is a simple and reproducible method for the surgical correction of myxomatous MR. The simplicity of the technique opens the perspective for percutaneous repair of mitral regurgitation.

2534 Simplified repair of mitral valve billowing and prolapse (Barlow): assessment of 84 consecutive patients

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Background: Mitral valve repair in patients with billowing and prolapse (Barlow) can be a demanding surgical procedure. We evaluated a simplified repair technique, addressing the essential physiologic components of repair.

Patients and Methods: 1,705 patients underwent mitral valve surgery in our hospital between 01.1994 and 06.1998. 84 patients (4.9%) had a mitral valve billowing and prolapse syndrome (Barlow). Of the 84 patients 60 were male (71.4%), the mean age was 53.5 ± 13.1 years (range 22 to 80). Mitral repair was performed in 65 patients (77.4%) using modified Carpentier techniques (=complete resection of the middle scallop of the posterior leaflet, a folding plasty with the remaining lateral scallops, combined with a triangular resection of the anterior leaflet) and an annuloplasty with a Carpentier-Ring. 19 patients had to undergo mitral valve replacement (22.6%), including 6 patients with non-successful initial intraoperative repair attempts and 1 patient who had emergency mitral replacement on the first postoperative day after valve repair due to SAM. Follow-up information was obtained by telephone interviews with cardiologists, family physicians and patients.

Results: There were 2 hospital deaths (2.3%) and one late death (1.2%). All 3 patients had a mitral valve replacement. In the group of 65 repair patients there was no hospital and no late death. Analyzing the percentages of successful mitral valve repair operations, our results increased from 65.2% in 1994 to 93.4% in 1996 and 100% in 1998 – due to our modified and simplified repair techniques. Echocardiography showed satisfactory mitral valve function in all patients. No residual regurgitation was found in 74 patients (88.1%), mild regurgitation in 7 (8.3%) and moderate regurgitation in 3 patients (3.6%). At the time of follow-up, 93.0% of all patients were in NYHA functional class I or II, all describing their quality of life as "normal". There were no late reoperations, no thromboembolic, bleeding or other complications.

Conclusion: Our data suggest that mitral valve repair in patients with prolapse and billowing (Barlow) is possible in evely patient.

2535 The natural history of mitral valve disease after aortic valve replacement

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The aim of this study is to describe the progression of mitral valve disease (MVD and the need for late mitral valve replacement (MVR) in pts after aortic valve replacement (AVR) without mitral valve surgery.

Patients & Methods: 52 pts (83 males, 69 females; mean age at follow up 66 ± 13 years, range 28–93) were followed after AVR for a mean of 9.0 ± 6.5 years. The etiology for AVR was rheumatic in 40.1% of pts. Pre- and postoperative data were derived from the clinical and/or angiographic transthoracic echocardiographic records.

Results: At the time of AVR, 68 pts (44.7%) had MVD; 21 (13.8%) mitral stenosis (MS) [16 (105%) mild, 4 (2.6%) moderate and 1 (0.65%) severe]; 47 (30.9%) mitral regurgitation (MR) [24 (15.8%) mild, 14 (9.2%) moderate and 9 (5.9%) severe]. 8/68 (5.26%) had combined mitral disease. At follow-up, 141 pts (92.7%) had MVD including 44 pts (28.9%) with MS [28 (18.4%) mild, 14 (9.3%) moderate and 2 (1.3%) severe] and 97 pts (63.8%) with MR [36 (23.7%) mild, 28 (18.4%) moderate and 33 (21.7%) severe]. 24 pts (15.8%) who had no evidence of MS preoperatively had so at follow up. In the group with baseline MS, 4/16 pts (19%) with mild disease progressed to moderate disease; the remaining 71.4% were unchanged. 53 pts (34.9%) who did not have MR preoperatively had so at follow up. In 17/47 pts with baseline MR (36.1%), disease progression was noted, while 57.4% showed no change. Despite the high rate of MVD at follow up, 80.8% of pts were in functional class I and II. Only 5 pts (3.3%) underwent MVR, none combined with AVR, after a mean of 20.25 years (range 4–26).

Conclusions: MVD is a common echocardiographic finding in patients late after AVR. Nevertheless, the majority of pts (81%) are clinically stable. Since mitral valve surgery was needed in only a few pts, we conclude that pts with mild and probably moderate MVD undergoing AVR, should not have concomitant mitral valve surgery.

2536 Curative treatment of atrial fibrillation in patients with simultaneous mitral valve replacement with intraoperative radio frequency ablation

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Introduction: The original MAZE procedure has become the gold standard in the operative therapy in patients with chronic atrial fibrillation. For simplification of the operative procedure we analyzed the efficiency of a continuous right and left atrial ablation line application by using radio frequency ablation (rfa) for the treatment of atrial fibrillation in patients with mitral valve replacement (MVR).

Methods: In 10 patients (pts; 5 m and 5 f, age range 45–74 years, mean 62 ± 10 years) suffering from mitral valve disease atrial fibrillation was documented for 18 ± 14 months. A continuous ablation line was performed through a right atrial transseptal approach starting at the posterior mitral valve annulus and incorporating all pulmonary veins. Electric isolation of the right atrial isthmus was performed using a new manual electrode. All pts received an additional MVR.

Results: Perioperative survival is 100%. The duration of intraoperative rfa was between 17–33 min. (mean 24 ± 5 min). No perioperative complications occurred. Eight pts had a sinus rhythm at the time of hospital discharge, 3 of them a previous cardioversion. In 4 pts with high grade AV-block a dual chamber pacemaker was implanted.

Conclusions: Electric isolation by an ablation line between the mitral anulus and the pulmonary veins and electric isolation of the right atrial isthmus can terminate chronic atrial fibrillation by interruption of the reentry circle. This procedure may become a new standard in therapy for patients with mitral valve replacement and chronic atrial fibrillation.

2537 Early and long-term results after surgery for ischaemic dilated cardiomyopathy associated with mitral regurgitation

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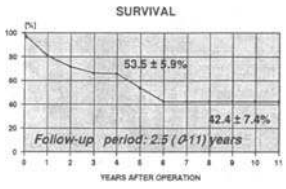
Background: The pathogenetic mechanism of chronic mitral regurgitation is considered to be due to the combination of papillary muscle dysfunction, left ventricular and annular dilatation and myocardial dyskinesia. These processes lead to remodelling of the fibrous skeleton of the heart, which is an important part of remodelling of the left ventricle. We have reviewed our group of 163 operated patients with chronic ischemic dilated cardiomyopathy (IDCM), ejection fraction (EF) below 30%, and mitral regurgitation (MR).

Methods: There were 149 male (91%) and 14 female patients, aged 34–70, with the mean age of 56.1 years. The mean EF was 22.6 ± 4.9%, and the mean left ventricular diastolic internal diameter 7.0 cm. Among those, 70% (115/163) had signs of congestive heart failure before surgical therapy. All patients had undergone myocardial revascularisation and Reductive Annuloplasty of Double (mitral and tricuspid) Orifices (RADO). Our technique preserves normal shape and flexibility of the mitral and tricuspid valve, corrects remodelling of the fibrous skeleton on the base of the heart and changes the geometry of the left and right ventricle.

Results: Postoperative mortality-30 days was 4.9% (8/163). Closing date of the follow-up study was February 15, 1998. The figure shows 10-year survival.



Conclusion: We conclude that this severe group of patients with IDCM, IMR and EF below 30% can be operated with low operative risk. After RADO and optimal myocardial revascularisation, a significant improvement in all hemodynamic parameters was observed, as well as good long term results. We recommend RADO as a very important associated procedure during myocardial revascularization in patients with IDCM associated with MR.

RARE FORMS OF CARDIOMYOPATHY: A CLINICAL CHALLENGE

2538 Abnormal cardiac energetics measured in vivo by ^{31}P magnetic resonance spectroscopy in the MELAS syndrome

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The MELAS (Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes) syndrome results in most cases from a maternally inherited A-to-G point mutation in the gene for $tRNA^{Leu\ (UUR)}$ at nucleotide 3243 (A3243G) in the mitochondrial genome (mtDNA). Genetic variability contributes to the marked phenotypic variability which is characteristic of mtDNA disorders. Cardiomyopathy is the predominant phenotype in some families.

Methods: Using ^{31}P MRS we measured phosphocreatine (PCr)/ATP in 8 subjects carrying the A3243G mtDNA mutation (3 clinically affected and 5 carriers from 4 families) and 18 normal subjects. Family A had a family history of a cardiomyopathy and families B to D did not. Patients lay prone in a 2T magnet. MRI was used to position the heart in the centre of the magnet. 1D slice-selective chemical shift imaging was used to obtain ^{31}P spectra from 1 cm slices parallel to the chest wall. Saturation slabs were used to remove signal from skeletal muscle. Position of cardiac spectra were identified from the images and areas of PCr, ATP and 2, 3 DPG peaks were calculated. PCr/ATP was corrected for blood contamination and saturation. Left ventricular dimensions were measured with echocardiography and EF and LV mass index (LVMI) calculated.

Results: PCr/ATP in the subjects was significantly reduced as compared to controls (1.9 ± 0.7 v 2.9 ± 0.3, $p < 0.01$). PCr/ATP was significantly lower in family A (1.3 ± 0.6) as compared to patients B to D (2.4 ± 0.2, $p = 0.025$). EF was normal in all 8 patients. There was no significant correlation between LVMI and PCr/ATP.

Conclusions: This study shows that there is a deficit of cardiac energy metabolism in the MELAS syndrome in the absence of LV hypertrophy or contractile abnormalities. This suggests that cardiac metabolic changes may precede the development of mechanical dysfunction. It is thought that abnormal mitochondria may produce free radicals which may further damage their function. Our findings provide a rationale for treatment aimed to prevent further deterioration in cardiac mitochondrial function in the MELAS syndrome, in particular in subjects with high levels of the A3243G mutation and a family history of cardiomyopathy.

2539 Clinical profile and long-term follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary myocardial disease frequently familial in origin. Systematic investigation of family members might better define its clinical spectrum and natural history.

A total of 365 subjects in 37 families were studied. In 19 families the proband died suddenly at a young age and ARVC was diagnosed at autopsy. In the remaining 18 families the proband had ventricular arrhythmias and the diagnosis was confirmed by endomyocardial biopsy. Protocol of investigation included basal ECG, 24 hour ambulatory ECG, signal-averaged ECG, exercise stress test, and 2-D and Doppler echocardiography. Ventricular and coronary angiography as well as RV endomyocardial biopsy were performed in 47 patients (pts).

Of the 365 subjects, 151 (41%) were affected, 157 (43%) were unaffected, 17 (5%) were carriers and 40 (11%) were classified as uncertain. The mean age of affected pts at diagnosis was 31 ± 13 years (range 4–64). By echocardiography 59% had mild, 35% moderate and 6% severe form of ARVC. Of affected pts, 60 had ventricular arrhythmias. Of these, 49 were treated with antiarrhythmic drugs and 2 with implantable cardioverter defibrillators. Analysis of the pedigree showed that males are more frequently affected than females ($p = 0.02$). Of the 28 families who underwent linkage analysis, 6 (22%) mapped to chromosome 14q24.3, 4 (14%) to chromosome 2q32.1–32.3 and 4 (14%) to chromosome 1q42–q43. No linkage was found in 14 (50%) families. Exercise performance was restricted in all affected pts. During a mean follow-up was 8.5 ± 4.6 yrs (range 2–18), 1 pt died and 15 developed an overt form of ARVC.

In conclusion, ARVC is a progressive disease with clinical findings appearing predominantly during youth. Systematic evaluation of family members can lead to early identification of ARVC. Several genes seem to be involved as to suggest genetic heterogeneity. Early diagnosis, exercise restriction and drug treatment may turn ARVC into a favourable clinical outcome. Affected family members appear to have a good prognosis over the mean follow-up of 8.5 ± 4.6 yrs.

2540 Identification of arrhythmogenic right ventricular cardiomyopathy from the surface ECG: parameters for discrimination from idiopathic right ventricular tachycardia

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Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an important disease underlying ventricular tachyarrhythmias and sudden death in young pts with apparently normal hearts. The major differential diagnosis is idiopathic right ventricular outflow-tract tachycardia (RVO-VT). A clear separation of the diseases is clinically relevant, because ARVC has a less favourable prognosis and therefore requires detailed diagnostic evaluation and effective antiarrhythmic treatment.

To assess the diagnostic value of different ECG findings for electrocardiographic distinction between ARVC and RVO-VT, 12-lead ECG and signal-averaged ECG recordings from pts with ARVC (n = 151 pts), RVO-VT (n = 142 pts) and a normal control group (n = 417) were analyzed qualitatively and quantitatively, using a graphic tableau:

	ARVC	RVO-VT	Control
T-wave inversion > V2	54.3%*	33.0%	1.4%
max. QRS-duration (V_{1-3})	114 ± 19 ms*	104 ± 13 ms	98 ± 11 ms
max. QRS > 110 ms (V_{1-3})	51.7%*	21.0%	12.9%
Epsilon potential	22.5%*	2.8%	0%
Late potential (25 Hz)	41.4%*	11.7%	3.0%
QRS-dispersion	40 ± 13 ms*	34 ± 10 ms	33 ± 9 ms
QT-dispersion	54 ± 21 ms	47 ± 16 ms	40 ± 13 ms

* = $p < 0.001$ for ARVC vs. RVO-VT and control

Conclusion: In pts with ARVC, all ECG parameters showed limited sensitivity. However, the presence of right precordial QRS prolongation, epsilon-potentials or late potentials were highly specific and may be helpful to distinguish ARVC from idiopathic RVO-VT

2541 Long-term follow-up of 34 adults with isolated ventricular non-compaction: poor prognosis due to fatal arrhythmias, congestive heart failure and systemic emboli

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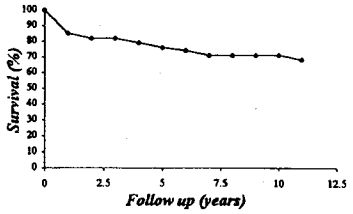
Background: Isolated ventricular non-compaction (IVNC) of the left ventricular myocardium is an increasingly detected congenital heart disease due to arrest of compaction of the loose meshwork of myocardial fibers during intrauterine life. Echocardiographically, typically there are excessive trabeculations and intertrabecular spaces perfused from the cavity. The clinical features in adults are: congestive heart failure (CHF) due to diastolic, ventricular arrhythmias and systemic emboli.

Methods and results: We obtained a prospective long-term follow-up of 34 adults with IVNC diagnosed in our echocardiography laboratory from 1984 to 1998. The age at diagnosis was 43 ± 18 years. The left ventricular ejection fraction was 35 ± 11%. The average follow-up was 3.9 ± 3.3 years. Ventricular tachycardias occurred in 5 patients (pts; 15%), CHF in 16 pts (47%), systemic emboli in 11 pts (32%). 11 pts (32%) died 3.4 ± 2.9 years after diagnosis.



In 7 pts, the cause for death was known: sudden cardiac death (4 pts), emboli (pulmonary emboli + cerebrovascular accident: each in 1 pt) and CHF (1 pt). 4 pts (12%) underwent heart transplantation because of untreatable CHF within 1 year of diagnosis. The youngest pt was a 16 year old male with palpitations as the only symptom; the oldest pt a 73 year old female CHF.

Conclusions: The prognosis of adults with IVNC is poor with a high rate of death (32%) or heart transplantation (12%) on long-term follow-up. Ventricular arrhythmias, systemic emboli and CHF are common. Early heart transplantation and oral anticoagulation may improve outcome.

2542 Influence of frataxin on the cardiomyopathy of patients with Friedreich's ataxia

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Concentric hypertrophic cardiomyopathy has been recognized as specific for the diagnosis of Friedreich's ataxia (FA) and is present in almost all patients with typical FA. FA is an autosomal recessive, progressive neurodegenerative disorder caused by unstable GAA repeat expansion in the first intron of frataxin gene (chromosome 9q13). Recently, it was reported that the size of this repeat may be associated with clinical severity of cardiomyopathy in FA patients.

Methods: In order to investigate the influence of the GAA repeats on cardiac hypertrophy in FA patients from the German population we analysed clinical data of 70 patients including ECG and echocardiography (49% men, mean age = 32 ± 11 years, onset = 15 ± 8 years). The size of repeats of both alleles was determined using PCR and agarose gel electrophoresis. DNA of 100 blood donors without FA was used as control group.

Results: According to the median of repeats all FA patients were divided into 2 groups (Gr. 1: patients with repeat value below than the median; Gr. 2: patients with repeat value above than the median). Interventricular septal thickness was significantly smaller in Gr. 1 of FA patients (10.8 ± 1.8 mm) compared to Gr. 2 (12.3 ± 2.4 mm; $P < 0.02$). Moreover, a positive correlation was demonstrated between the number of repeats on longer allele and ratio interventricular septal thickness/posterior wall thickness ($r = 0.96$; $P = 0.054$).

In conclusion, increased size of GAA repeats is associated with left ventricular wall hypertrophy in FA patients. These data suggest that the unstable GAA repeat expansion might influence cardiac hypertrophy in FA patients.

2543 Are sporadic cardiac myxomas a DNA repair-deficient disease?

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Objective: A recently discovered feature of the neoplastic cells is the elevated mutational rate which is reflected in the instability of the microsatellite DNA (microsatelite instability, MIN). MIN is an early event in DNA repair-deficient diseases and its implication in the pathogenesis of sporadic cardiac myxomas has not been previously investigated. The aim of our study was to analyse the incidence of MIN in sporadic cardiac myxomas, as a possible pathogenetic mechanism of these rare neoplasms.

Methods: Eleven surgically excised sporadic cardiac myxomas were assessed for MIN using 30 highly polymorphic microsatelite markers (Research Genetics, Inc, USA) located on a wide range of chromosomal arms. DNA was extracted from myxoma tissue specimens as well as the respective normal tissue and subjected to polymerase chain reaction (PCR). PCR products were electrophoresed in a 10% polyacrylamide gel and silver stained. MIN was scored by comparing the electrophoretic pattern of the microsatellite markers amplified from the paired DNA preparations (pathological/normal tissue). The analysis in the MIN positive cases was repeated at least twice and the results were highly reproducible.

Results: Microsatellite analysis showed that 7 cardiac tumors (64%) exhibited MIN in at least one marker. Five specimens were classified as tumors with high MIN (unstable for $\geq$2 genetic loci), while the other 2 specimens as tumors with low MIN (unstable for <2 genetic loci). The highest incidence of MIN was found for the marker D17s855, which lies within BRCA1. Other markers with high incidence of MIN were D17s250 (proximal to BRCA1) and D17s579. MIN was more frequently detectable in chromosome 17 than the other studied chromosomes. No association was found between the presence of MIN and the age, the tumor location or the tumor size.

Conclusions: MIN is a highly detectable phenomenon in sporadic cardiac myxomas indicating the presence of a decreased fidelity in DNA replication and repair in myxoma tissue. This observation suggests that sporadic cardiac myxomas may be a DNA repair-deficient heart disease.

PULMONARY HYPERTENSION: NEW PHARMACOLOGIC APPROACHES

2554 Vasoconstriction in pulmonary hypertension by potassium channel blockade

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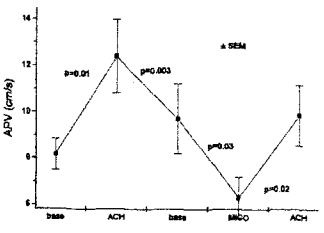
Potassium channels are supposed to be involved in the regulation of the basal vascular tone in pulmonary hypertension (PH) based on experimental evidence. Objective: A clinical evaluation of the interaction of endothelium-dependent residual vasodilatatory reserve with potassium channel blockade in PH.

Methods: In 8 patients with severe pulmonary hypertension (mean pulmonary artery pressure 54 $\pm$ 9 mmHg; pulmonary vascular resistance 17 $\pm$ 7 mmHg l^{-1} min) local vasoreactivity was tested in a pulmonary branch artery by infusion of 10^{-5} M acetylcholine (ACH) at baseline and after blockade of K^+ channels (K^+blockade) using 10^{-5} M miconazol. Average peak blood flow-velocity (APV) was determined using a 0.014" Doppler guidewire. Local diameters were controlled by intravascular ultrasound.

Results: Significant changes of systemic hemodynamics could be avoided by local testing. Local diameter changes could be ruled out. A reduction of local flow velocity (8 cm/s to 4 cm/s, $p < 0.05$) was associated with K^+blockade. Absolute flow velocity increase following infusion of acetylcholine was not impaired by K^+blockade suggesting independent mechanisms.



Conclusions: Potassium channels are involved in maintaining the basal flow in patients with PH. Drugs with potassium channel blocking side-effects may be deleterious and potassium channel opening may be an important therapeutic target in the treatment of PH and may explain the positive experience with iloprost combining potassium channel opening and PGI2 stimulation. Functional testing by ACH may fail to diagnose the role of endothelial hyperpolarizing factor in PH.

2555 Efficacy and safety of UT-15, a prostacyclin analogue, for primary pulmonary hypertension

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Primary pulmonary hypertension (PPH) is a severe and potentially fatal disease. Chronic intravenous prostacyclin (PGI2) improves exercise tolerance, hemodynamics, and survival in PPH, but at the expense of infections and other complications due to the nature of the delivery system and instability of the drug. UT-15, a stable PGI2 analogue with a longer half life, may be given subcutaneously, obviating the need for a permanent central venous catheter. The primary objective of this study was to assess the safety of chronically administered continuous subcutaneous infusion of UT-15 in PPH. Twenty-six patients with PPH (NYHA Class III/IV) were enrolled in a multicenter, double-blind, placebo-controlled, 2:1 randomized, 8 week trial. UT-15 or placebo was initiated at 2.5 or 5.0 ng/kg/min and the dose was adjusted based on PPH symptoms or on adverse events attributable to the study drug. There were 5 men and 21 women with a mean age of 35 $\pm$ 20 years. Baseline hemodynamics (PVR 13.9 units and 15.2 units) and exercise capacity as measured by the six minute walk test (372 m and 384 m) were similar in the UT-15 (n = 17) and placebo (n = 9) groups. The mean infusion rate for the UT-15 group was 14.5 $\pm$ 2.6 ng/kg/min and for the placebo group was 38.9 $\pm$ 6.7 ng/kg/min. Two patients did not complete the study because of intolerable side effects. The most common side effects were: headache (76%), diarrhea (59%), nausea/vomiting (59%), flushing (47%), and jaw pain (35%). Of patients randomized to UT-15, 88% of the patients experienced pain and 94% erythema at the injection sites, which was adequately controlled with treatment. One patient (11%) randomized to placebo experienced pain and erythema at the injection sites. Walk distance improved by 28 $\pm$ 11 m (8%) in the UT-15 group while it declined by 6 $\pm$ 27 m (1%) in the placebo group. Pulmonary vascular resistance index declined by 5 $\pm$ 1 unit in the UT-15 group while it increased by. 3 $\pm$ 2 in the placebo group. UT-15 is a safe treatment of PPH and affects hemodynamics and exercise tolerance favorably.

2556 Effect of inhaled Iloprost® on pulmonary artery pressure: results of an acute haemodynamic study and one month follow-up

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Background: Currently prostacyclin is the gold standard for treatment of pulmonary hypertension. Prostacyclin leads to marked improvement in haemodynamics and outcome in primary pulmonary hypertension. The major shortcomings of Epoprostenol® are tachyphylaxis and the need for a central venous line. Iloprost® is a stable analogue of Epoprostenol® with longer half-life but similar pharmacological properties. Both Epoprostenol® and Iloprost® can be aerosolised with similar effects on haemodynamics compared to intravenous application. The role of inhaled Iloprost® in long-term treatment of pulmonary hypertension, however, is still unclear.

Methods: We investigated 11 patients (2 male, 9 female; mean age 46 $\pm$ 19 years) with pulmonary hypertension. Four patients suffered from primary and seven patients from secondary pulmonary hypertension. Before haemodynamics were studied patients underwent transthoracic echocardiography with assessment of pulmonary artery pressure by Doppler. Haemodynamics were studied using a Swan-Ganz-catheter. After assessment of pulmonary pressure and pulmonary vascular resistance 20 μg of Iloprost® were inhaled and haemodynamics were reassessed. The daily dose of inhaled Iloprost® was 100 μg. Doppler echocardiography was used as a follow-up tool.

Results: All but one patient responded to inhaled Iloprost® with a fall of pulmonary pressure or resistance. There was a good correlation between Doppler-estimated pulmonary artery pressure and invasively measured pulmonary artery pressure ($r = 0.704$, $p < 0.05$). After inhalation of Iloprost® there was a significant fall in right ventricular systolic pressure from 82 $\pm$ 21 to 62 $\pm$ 20 mmHg ($p = 0.01$), pulmonary artery systolic pressure from 84 $\pm$ 23 to 70 $\pm$ 23 mmHg ($p = 0.02$) and in pulmonary vascular resistance from 718 $\pm$ 460 to 548 $\pm$ 353 dyn.sec.cm^{-5} ($p < 0.05$). Iloprost® had no effect on right atrial pressure and on pulmonary capillary wedge pressure. No side effects were observed. After one month there was no change in Doppler estimated pulmonary artery pressure compared to pretest levels (75 $\pm$ 20 vs 73 $\pm$ 20 mmHg, p: n.s.).

Conclusion: In patients with pulmonary hypertension inhaled Iloprost® leads to acute improvement of haemodynamic parameters. Furthermore, Iloprost® has the potential to keep pulmonary pressure stable, although no further improvement was seen after four weeks. The reason for this is unclear. Therefore, further investigations are needed to elucidate the role of Iloprost® in the treatment chronic pulmonary hypertension.

2557 Sustained effect of beraprost sodium in patients with primary and secondary pulmonary hypertension

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Clinical and hemodynamic effects of long-term beraprost sodium treatment in patients with severe pulmonary hypertension were studied. Eight patients (1 male, 6 female; age 49 ± 8 years) with vascular lung disease (4 primary pulmonary hypertension, 3 chronic pulmonary tromboembolism, 1 Eisenmenger' syndrome), and severe hemodynamic impairment (RAP 6 ± 4 mmHg, PAPm 54 ± 7 mmHg, PCWP 5 ± 3 mmHg, CI 1.7 ± 0.4 L/min/m^2) received beraprost sodium (1–2 mcg/kg a day in 3 or 4 administrations) in adjunction to standard therapy (oral anticoagulants, digoxin, furosemide, enalapril, nifedipine). During the first 3 weeks the starting dose (20 mcg t.i.d.) was increased as tolerated, and in case of systemic hypotension (SBP < 100 mmHg) the dose of enalapril or nifedipine was reduced. Functional class (NYHA), effort tolerance (six minute walk test, 6MWT) and systolic pulmonary pressure by echo-Doppler study of tricuspid regurgitation (PAPs) were evaluated at baseline, at one and three months. During follow-up we had no drug-related major side-effects. One patient died for refractory congestive heart failure within 40 days.

Results:

	Baseline	1 month	3 month	p <
NYHA class	3.7 ± 0.4	3.1 ± 0.6	2.6 ± 0.5	^°°
6MWT, mt	200 ± 68	241 ± 80	299 ± 65	^°°
PAPs, mmHg	98 ± 21	88 ± 18	83±	^°°

^/^ = p < 0.01/<0.001 1 month vs baseline; °/°° = p < 0.01/<0.001 3 months vs Baseline

Conclusion: Beraprost causes a significant and sustained reduction in PAPs with a concomitant improvement in functional class and effort tolerance These promising data should be confirmed in a larger double-blind study in order to define the potential role of this oral-active PGI2 derivative as a therapeutic option in pulmonary hypertension.

2558 Endotoxin challenge markedly alterates regulation of the endogenous pulmonary endothelin system

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Recently, the pulmonary endothelin (ET) system has been shown to play a major role in sepsis-induced adult respiratory distress syndrome (ARDS). However, only rare data exist on the regulation of endogenous pulmonary endothelins under basal and septic conditions. We investigated, therefore, in isolated, blood-free perfused rat lungs pulmonary vascular release of big ET-1 and ET-1 under baseline conditions and after endotoxin challenge using different pharmacological approaches. Control lungs (n = 7) released 14.6 ± 1.5 pg/ml big ET-1 and 0.49 ± 0.07 pg/ml ET-1 over 2 h. Endotoxin challenge (n = 7) significantly (p < 0.05) increased big ET-1 (1.5fold) and ET-1 (1.4fold). A-127722, an ETA receptor-selective antagonist (100 nM, n = 7), did not affect peptides under basal conditions, but significantly decreased big ET-1 (0.6fold) without affecting ET-1 after endotoxin. A-192621, an ETB receptor-selective antagonist (500 nM, n = 6), markedly elevated basal ET-1 (2.6fold). This effect disappeared after endotoxin challenge; big ET-1 was not changed by A-192621. Inhibition of nitric oxide (NO) synthesis by L-NOARG (100 μM, n = 6) did not influence basal release of ET peptides, but lessened endotoxin-stimulated big ET-1 (0.45fold) without changing ET-1. ODQ, an inhibitor of soluble guanylyl cyclase (sGC) (20 μM, n = 6), and meclofenamic acid, an inhibitor of cyclooxygenase (COX)(50 μM, n = 6–10) had no effect on basal or endotoxin-stimulated peptide release. We conclude that basal pulmonary release of big ET-1 and ET-1 is modified neither by NO, sGC, nor by COX. Furthermore, elevation of basal ET-1 by ETB receptor blockade indicates stoichiometric binding conditions prevailing in pulmonary vasculature. Abolition of this effect after endotoxin challenge points to an alteration of the functional status of ET receptors during sepsis. We suggest that the decrease in endotoxin-stimulated release of big ET-1 by ETA and ETB receptor blockade, and by inhibition of NO synthesis is either due to hightened activity of endothelin-converting enzyme or alteration of receptor affinity for big ET-1. The present findings demonstrate a complex alteration of ET receptor status and/or regulation of peptide synthesis by endotoxin, which has to be considered when using ET antagonists in septic ARDS.

2559 Endothelin-A receptor antagonism improves pulmonary and systemic haemodynamics in patients with severe pulmonary hypertension

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Endothelin-1, a powerful vasoconstrictive peptide, has been implicated in the pathophysiology of pulmonary hypertension (PH) by various investigators. The purpose of this study was to evaluate the effect of a short-term administration of an endothelin A (ET_A) receptor antagonist in patients with severe chronic PH.

Methods: The study group consisted of 10 pts (NYHA II–IV) aged 28.2 ± 14.6 yrs with severe chronic PH and systolic pulmonary artery pressure (PAP) 112.2 ± 31.8 mmHg. One pt had primary PH, 2 pts primary PH in conjunction with an atrial septal defect, 4 pts secondary PH after correction of congenital heart defects, 2 pts secondary PH with uncorrected congenital heart disease, and 1 pt secondary PH due to ischaemic heart failure. After baseline haemodynamic measurements, all pts underwent continuous infusion of BQ-123, an ET_A receptor antagonist, for 60 min at 200 mmol/min in the right atrium with haemodynamic evaluation at 30 and 60 min of the infusion and 30 min after the end of the infusion. No adverse effects were noted.

Results: Significant improvement was noted on pulmonary vascular resistance (PVR), systemic cardiac index (Qs), pulmonary cardiac index (Qp) and effective cardiac index (Qeff), with no effect on mean PAP due to the improved cardiac index.

	Baseline	60 min BQ-123	Effect	p value
PvR (Woods units)	20.6 ± 11.7	17.1 ± 11.5	↓ 16.8%	<0.005
Qs (L/min/m^2)	2.9 ± 0.8	3.3 ± 1.0	↑ 15.3%	<0.05
Qp (L/min/m^2)	4.5 ± 5.6	5.9 ± 7.5	↑ 30.1%	<0.05
Qeff (L/min/m^2)	2.5 ± 0.8	2.9 ± 1.1	↑ 17.7%	<0.05
mean PAP (mmHg)	75.3 ± 23.0	73.5 ± 22.4	NS	NS

Conclusion: Short-term administration of ETA receptor antagonist significantly improves haemodynamics in pts with severe chronic PH. New avenues for further research on endothelin antagonists as treatment options in this prognostically poor patient population need to be pursued.

OXIDANT STRESS AND ANTIOXIDANT THERAPY

2560 Dipyridamole as an antioxidant agent ex vivo

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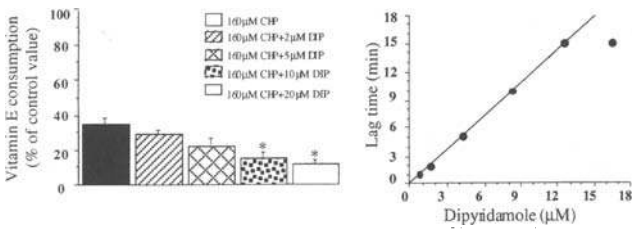
To test the antioxidant effect of therapeutic doses of dipyridamole on cellular membranes, red blood cells were chosen as an appropriate model to study oxidative stress induced by hydroperoxides because of their high content in heme-Fe^{2+}. The oxidative stress was induced by incubation with 160 μM cumene hydroperoxide (CHP) and expressed by three main factors: lipid peroxidation by means of kinetics of decrease in fluorescence emission of the probe incorporated in the cell membranes, vitamin E consumption and intracellular thiol content. The concentrations of dipyridamole tested (2–20 μM) did not exceed human pharmacological doses. After 7 minutes of incubation at 25°C with the oxidant and 20 μM dipyridamole thiol content was 50.1% ± 2.6 compared with 31.5% ± 2.4 (n = 10) in the absence of the drug. After 12 minutes vitamin E consumption was reduced to 11.7% ± 2.3 compared with 35.3% ± 3.4 (n = 11) in the absence of dipyridamole. Dipyridamole added five minutes after the oxidation reaction suppressed the fluorescence decay for a time proportional to the drug concentration.



In conclusion, at clinically realistic doses dipyridamole shows a definite, concentration-dependent anti-oxidant effect. It protects membranes from oxidation and spares the antioxidant power of red blood cells.

2561 Production of oxygen radicals during hypoxia and reoxygenation induces cellular damage and pH changes in cardiac myocytes: possible stimulation for post-ischaemic matrix remodelling

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Introduction: The common inducers of necrosis and programmed cell death (apoptosis) include oxygen free radicals, which are also implicated in the pathogenesis of myocardial ischemic reperfusion injury. In addition, ischemia-induced acidosis may contribute to activation of growth factors and, thus, to remodeling of the cardiac extracellular matrix. Therefore, the present study was designed to establish a reliable cell culture model of necrosis and apoptosis, to link production of oxygen radicals to biochemical parameters of cellular damage and to find protective mechanisms to maintain a physiological pH during ischemic reperfusion injury.

Methods: Neonatal rat myocytes were cultured in 2% oxygen for 24 hours to produce hypoxic conditions and then exposed to 20% oxygen for additional 12 hours to simulate reoxygenation.

Results: Hypoxia and reoxygenation stimulated the production of oxygen radicals, as indicated by decreased glutathione concentrations. Further, they decreased extracellular pH and increased lactate concentrations ($p < 0.05$). However, both pH as well as production of oxygen radicals depended on the beating rate of cardiac myocytes, since quiescent myocytes neither changed pH nor produced significant amounts of oxygen radicals during hypoxia. In addition, hypoxia lead to a 10-fold increase in LDH leakage ($p < 0.05$) and an almost complete loss in creatine kinase (CK) activity ($p < 0.05$). Furthermore, reoxygenation was followed by nucleosomal DNA fragmentation that was detectable by gel electrophoresis (DNA ladder) as well as significant induction of Fas receptor, cytochrome c and caspase 3, mediators of apoptotic cell death. In order to investigate whether acidosis is due to anaerobic glycolysis and lactate production we treated normoxic myocytes with hydrogen peroxide (H_2O_2). Dose-dependent studies documented the same acidosis with increasing doses of H_2O_2. In addition, anti-oxidants, such as carvedilol, BM 91.0228 or vitamin E maintaned a physiological pH during hypoxia and reoxygenation. Furthermore, they partially inhibited LDH and CK leakage and completely inhibited morphological features of apoptosis as well as DNA laddering. Finally, anti-oxidative treatment prevented the induction of Fas receptor, cytochrome c and caspase 3, following reoxygenation.

Conclusion: Taken together, these results suggest that hypoxia alone induces significant production of oxygen radicals, and, thus, may lead to necrosis and apoptosis. In addition, they document the acidic effect of oxygen radicals on extracellular pH, which can be prohibited by treatment with anti-oxidants.

2562 Protective effects of antioxidant enzymes during low-flow ischaemia and reperfusion in the aged rat heart

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Antioxidant enzymes (AOE) have protective effects in adult heart after no-flow ischemia. The aged heart is more vulnerable to low-flow ischemia, and has reduced AOE activities. We investigated the effects of AOE during both low-flow ischemia (LFI) and ischemia-reperfusion (I/R), in adult and in aged myocardium. In the LFI protocol, isolated hearts from 4 and 24 month old rats were subjected to an ischemic perfusion at 15% of their initial coronary flow without (4 I, n = 13; 24 I, n = 15) or with AOE (superoxide dismutase + catalase, 50 UI/ml) (4 I-E, n = 10; 24 I-E, n = 10). Active tension (AT) and coronary resistance (CR) were recorded at baseline, 30 and 60 min of perfusion. In the I/R protocol AT and coronary flow (CF) were recorded at baseline and after 30 min of reperfusion following 45 min of non-paced low-flow (15%) ischemia, without (4 I/R, n = 9; 24 I/R, n = 9) or with AOE (4 I/R-E, n = 7; 24 I/R-E, n = 8).

Results: Mean ± SEM in % of baseline value.

LFI	AT		CR	
	30 min	60 min	30 min	60 min
4 I	25 ± 4	17 ± 3	478 ± 80	655 ± 126
4 I-E	40 ± 5*	34 ± 5*	220 ± 33*	237 ± 37*
24 I	18 ± 2	18 ± 3	760 ± 112†	885 ± 108
24 I-E	28 ± 4*	18 ± 3	343 ± 128*	386 ± 100*

*$p < 0.05$ vs age-matched group, †$p < 0.05$ 24 mo vs 4 mo I and I/R group.

I/R	AT	CF
	30 min	30 min
4 I/R	77 ± 4	73 ± 6
4 I/R-E	73 ± 3	127 ± 18*
24 I/R	50 ± 7†	52 ± 9†
24 I/R-E	74 ± 5*	116 ± 13*

*$p < 0.05$ vs age-matched group, †$p < 0.05$ 24 mo vs 4 mo I and I/R group.

In conclusion: 1) AOE improve contractile and coronary dysfunction induced by prolonged low-flow ischemia in adult and aged hearts, but with a less sustained effect in the aged hearts 2) Reperfusion-induced contractile and coronary dysfunctions are greater in the senescent heart and 3) AOE significantly prevent these reperfusion-induced alterations in the aged heart, indicating a major role of oxidative stress during reperfusion in aged rats.

2563 Myocardial dysfunction is also induced by application of polymorphonuclear granulocytes at different times of ischaemia/reperfusion via release of reactive oxygen species

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It is well known that polymorphonuclear granulocytes (PMN), applicated in early reperfusion, significantly contribute to ischemia-reperfusion injury. In addition to this well-known fact, we investigated in the present study whether PMN applicated at different times of ischemia/reperfusion are also able to induce a myocardial dysfunction.

Isolated, perfused and pressure-volume work performing guinea pig hearts were exposed to a 30 min low-flow ischemia (1 ml/min), reperfused (5 ml/min) and PMN (1.000/μl perfusion buffer) were applicated as 1 min bolus during the 15th min of ischemia or in the 1st or 5th min of reperfusion in the presence of thrombin (0.3 U/ml perfusion buffer), respectively. Intracoronary PMN-retention (RET in percent of PMN applied) and recovery of external heart work (REHW-postischemic external heart work in percent of preischemic external heart work) were quantified. In further experiments, superoxide-dismutase (SOD) was added (10 U/ml perfusion buffer) to examine whether a potential PMN-induced myocardial dysfunction is mediated by release of reactive oxygen species during ischemia. Ischemic and reperfused hearts without PMN application in the presence of thrombin (REHW) or non-ischemic hearts with PMN application in the presence of thrombin (RET) served as controls.

Application of PMN during ischemia, the 1st or the 5th min of reperfusion significantly reduced REHW (62.6 ± 5%, 63 ± 4% or 66.8 ± 4%, respectively) as compared with control (91.6 ± 2%). RET significantly increased (70 ± 3%, 35 ± 4 or 41 ± 7, respectively) as compared with control (10 ± 3%). Coapplication of SOD led to a significant increase of REHW (81 ± 4%, 81.8 ± 2 or 83 ± 3, respectively), RET was almost unchanged by these measures, however.

We conclude that PMN are able to induce a reactive oxygen species-mediated myocardial dysfunction at all times of the ischemia-reperfusion process.

2564 Carvedilol inhibits hypoxia- and reoxygenation-induced necrosis and apoptosis in cardiac myocytes: evidence for cardioprotection by antioxidants

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Introduction: Necrosis and programmed cell death (apoptosis) are recognized as causes of cardiac myocyte loss with ischemia- and reperfusion-induced injury. The present study was designed to establish a reliable cell culture model of necrosis and apoptosis in-vitro, to link morphological findings to biochemical parameters of cellular damage and to compare the effects of carvedilol, a hybrid drug involving beta-1, beta-2 and alpha blocking as well as anti-oxidative properties, with its anti-oxidative metabolite BM 91.0228 and the non-selective adrenergic beta-blocker propranolol.

Methods: Neonatal rat myocytes were cultured in 2% oxygen for 24 hours to produce hypoxic conditions and then exposed to 20% oxygen for additional 12 hours to simulate reoxygenation. Drug treatment started 2 hours prior to hypoxia either with carvedilol (3 μM), BM 91.0228, propranolol or vehicle for the entire duration of hypoxia and reoxygenation.

Results: Hypoxia and reoxygenation significantly decreased intracellular glutathione concentrations, indicating stimulated production of oxygen radicals. In addition, in vehicle and propranolol treated cells hypoxia lead to a 10-fold increase in LDH leakage ($p < 0.05$) and an almost complete loss in creatine kinase (CK) activity ($p < 0.05$). This pattern of severe necrosis further increased after additional 12 hours of reoxygenation. Furthermore, in vehicle and propranolol treated cells reoxygenation was followed by nucleosomal DNA fragmentation that was detectable by gel electrophoresis (DNA ladder) as well as significant induction of Fas receptor, cytochrome c and caspase 3, mediators of apoptotic cell death. By contrast, carvedilol and BM 91.0228 partially inhibited LDH and CK leakage and completely inhibited morphological features of apoptosis as well as DNA laddering. Finally, both drugs prevented the induction of Fas receptor, cytochrome c and caspase 3, following reoxygenation.

Conclusion: Taken together, these results suggest that reoxygenation augments hypoxia-induced necrosis and apoptosis in cardiac myocytes. In addition, they indicate that the induction of Fas receptor, cytochrome c and caspase 3 may set the stage for this process. They further document that the anti-oxidative properties of carvedilol and BM 91.0228 prevent both necrosis and apoptosis. These effects could not be seen with non-selective beta-blockade alone, and, thus may indicate the cardioprotection of anti-oxidative therapy.

2565 Superoxide anion but not nitric oxide is released from neutrophils in the response to stimuli released from myocardium during coronary angioplasty

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Background. Activated neutrophils (PMN) are known to be a rich source of free oxygen radicals, including the superoxide anion (O_2^-), in the ischaemic and reperfused myocardium. Free oxygen radicals contribute to the development of myocardial reperfusion injury. Activated PMN have also been shown to release, in certain pathophysiological conditions, vasodilator nitric oxide (NO). PMN activation has been evidenced to occur as a result of myocardial ischaemia and/or endothelial injury during coronary angioplasty (PTCA). This may be related to PMN direct contact with the endothelium or a response to PMN-oriented stimuli.

Aim. To verify whether PTCA procedure results in the release of mediators capable of stimulation of O_2^- and NO production by PMN.

Methods. 18 patients (aged 38–65; mean 47 years) scheduled for PTCA of proximal stenoses in LAD were enrolled. Coronary sinus and arterial plasma samples were taken before balloon inflation (I), immediately after the first deflation (II) and 5 min. after the last deflation (III). Plasma samples were incubated with PMN obtained from healthy donors and O_2^- and NO production were measured by spectrophotometric assays.

Results.

	Superoxide anion nmol/5 × 10^6 PMN/10 min		Nitric oxide nmol/10^7 PMN/30 min	
Plasma from:	cor. sinus	artery	cor. sinus	artery
I	16.1 ± 2.1	15.8 ± 2.2	17.1 ± 4.2	22.4 ± 7.2
II	27.8 ± 2.8*#	16.1 ± 2.6	19.1 ± 5.1	20.8 ± 5.1
III	19.1 ± 1.9	16.9 ± 2.1	21.8 ± 5.9	21.5 ± 4.9

Mean values ± SEM, *$p < 0.05$ vs artery #$p < 0.05$ vs. I and III;

Conclusion: Mediators stimulating neutrophil O_2^- but not NO production are released to the coronary sinus after balloon deflation during PTCA.

GUIDANCE FOR PERCUTANEOUS INTERVENTIONS (PART II)

2575 30 months follow up of an IVUS-guided balloon angioplasty

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The CLOUT Study showed that quantification of arterial remodeling by means of IVUS allows oversizing of balloons resulting in improved angiographic outcome. The longterm outcome of this strategy was obtained at a clinical follow up (median time 2.5 years, range 25–75%: 1.8–3.3 years) in 97 of 100 pts from CLOUT without CABG.

Results:

Patients: Diabetes 21%, 41% prior MI, 61% multivessel disease. Mean reference vessel diameter:2.68 ± 0.48, mean balloon diameter: 3.38 ± 0.43, balloon/artery ratio: 1.30 ± 0.16. QCA analysis showed reduction of%diameter stenosis from 73 ± 16 to 19 ± 14. Final minimal area by IVUS was 4.3 ± 1.2 mm. At 30 month follow up 6.3% pts died (2.1% cardiac, 4.1% had MI and 27.5% had TLR, including 5.2% CABG and 22.3% re-PTCA). Thus cardiac death MI or TLR occurred in 28 (28.9%) pts. Non-TLR also was required in 19.6% pts. Independent multivariate predictors of TLR were diabetes ($p = 0.04$) reference segment plaque area ($p = 0.04$) and vessel size (EEM) ($p = 0.02$).

Conclusions: Despite improved procedural results with IVUS guided balloon sizing in the relative small vessels in CLOUT late adverse events still occurred frequently from recurrent disease at the target site and progressive disease elsewhere. Future strategies must therefore focus on even more aggressive approaches to reduce restenosis and stabilize atherosclerotic plaque.

2576 Hyperemic coronary flow after optimized intravascular ultrasound-guided balloon angioplasty and stent implantation

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Recent studies indicate the safe coronary luminal enlargement and "stent-like" long-term outcomes using upsized balloons guided by intravascular ultrasound (IVUS).The present study evaluates the acute physiological gain of adjunctive IVUS-guided balloon angioplasty and stent implantation.

Methods: After angiograpically guided balloon angioplasty in 20 patients with 1-vessel disease and normal left ventricular function, IVUS was performed to determine the size of the adjunctive balloon using the mean of the maximal luminal diameter and the maximal diameter of the external elastic membrane measured in the adjacent proximal and distal reference segments. Serial adenosine-induced hyperemic blood flow velocity measurements were performed, using a 0.014" Doppler guide wire, to determine the physiological lumen obstruction after standard balloon angioplasty, followed by IVUS-guided balloon angioplasty and stent implantation.

Results: Upsized balloon angioplasty (increase balloon size: 0.98 ± 0.26 mm; balloon:artery ratio 1.35 ± 0.21) resulted in an additional increase of arterial dimensions: minimal lumen diameter (MLD) 2.18 ± 0.38 mm to 2.73 ± 0.51 mm;%diameter stenosis (%DS) 34 ± 13% to 19 ± 22%; IVUS assessed minimal lumen area (MLA) 7.53 ± 1.55 mm^2 to 10.24 ± 2.22 mm^2 (all $P < 0.0001$). Major dissections (* type C) did not occur. Hyperemic blood flow velocity increased from 49.8 ± 20.1 cm/s to 59.1 ± 22.9 cm/s ($P < 0.05$) after IVUS-guided balloon angioplasty. Adjunctive stent implantation resulted in a further increase of MLD to 3.84 ± 0.51 mm,%DS to −9 ± 21% and MLA to 13.39 ± 1.80 mm^2 (all $P < 0.0001$), while hyperemic blood flow velocity remained unchanged (61.2 ± 24.7 cm/s, $P = 0.7$).

Conclusions: Upsized IVUS-guided balloon angioplasty increases arterial coronary dimensions and the distal hyperemic blood flow velocity. Adjunctive stent implantation does not yield a further gain in the hyperemic blood flow velocity, indicating the absence of a functional residual lumen obstruction after IVUS-guided balloon angioplasty. These findings may explain a stent-like clinical outcome reported after IVUS-guided balloon angioplasty.

2577 Predictors of coronary flow reserve before and after balloon angioplasty

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A coronary flow reserve (CFR) cut-off value of 2.5 after balloon angioplasty (BA) has been shown to be a predictor of 6-month clinical outcome. The influence of coronary risk factors (RF) and vessel geometry in predicting a cut-off value of coronary flow reserve of 2.5 before and after balloon agioplasty have not been studied in a prospective fashion.

Methods: 225 consecutive patients undergoing BA were evaluated as part of Debate I study. Intracoronary Doppler (ID) measurements of the target vessel were performed before and after BA. We investigated the predictive power of RF and quantitative angiographic measurements (QCA) on the binary distribution of the cutoff value of CFR before and after BA.

Results: By multivariate logistic regression, diameter stenosis before BA{(DS), odd ratio (OR): 1.20; confidence interval (CI): 1.06–1.35} was found as independent predictors of a CFR < 2.5 before BA. Post-BA, increasing age (OR: 1.06; CI: 1.02–1.10) and female gender (OR:2.99; CI:1.18–7.58) appeared to be independent predictors of a CFR after BA. No other angiographic (cross-sectional area, minimun luminal diameter, acute gain, lesion length, collateral supply, Ambrose lesion type classification and coronary segment) or patient demographics (diabetes mellitus, family history, hypertension, hypercholesterolemia) were independent predictors of a low CFR before or after BA.

Conclusion: 1) preintervention, the only determinant of CFR in significant lesions was the DS. 2) After BA, age and female gender appeared to have an influence attenuating the CFR. 3) CFR before BA or QCA mesurements post-BA did not predict CFR post-BA. 4) Aiming for an adequate CFR post-BA in the female and elderly groups lower values may be required. This should be taken into consideration while assessing the results of interventional procedures with intracoronary Doppler.

2578 Six-month quantitative angiographic and intracoronary ultrasound (ICUS) outcome obtained by ICUS-guided "stent-like" balloon angioplasty: a comparison with stent implantation

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We hypothesized that stent-like balloon angioplasty (BA) guided by intracoronary ultrasound (ICUS) may convey a favourable long-term outcome.

Methods: To test this hypothesis, we prospectively performed ICUS guided BA and 6-month angiographic and ICUS follow-up (fup) in 77 patients. Balloon sizing was performed using ICUS guidance where maximum balloon size was related to maximal vessel area at the lesion site. A "stent-like" result was defined as a minimal luminal area (MLA) > 70% of reference lumen area (Ref-LA) by ICUS, <30% residual diameter stenosis by QCA, and no dissection. When stent-like results were not achieved by BA alone, a stent was implanted to fulfill this criteria. Thirty eight patients (49%) underwent BA alone and 39 (51%) required stent implantation as well. Quantitative angiographic (QCA) and ICUS examinations were performed in all patients. Angiographic restenosis was defined as ≥50% diameter stenosis by QCA.

	ICUS-guided BA Stent	p-value	
QCA:			
Ref. Diam. pre (mm)	2.92 ± 0.54	2.88 ± 0.44	ns
MLD pre (mm)	1.12 ± 0.35	1.03 ± 0.30	ns
MLD post (mm)	2.14 ± 0.44	2.63 ± 0.42	<0.01
MLD fup (mm)	1.73 ± 0.55	1.57 ± 0.49	ns
ICUS:			
MLA post (mm2)	5.89 ± 1.99	8.21 ± 2.28	<0.01
MLA fup (mm2)	5.02 ± 1.98	4.68 ± 2.77	ns
Restenosis rate	23%	22%	ns

Conclusions: Although it was only possible to achieve a stent-like result using ICUS guided BA in 49% of cases, this stent-like result does convey a favourable 6-month angiographic and ICUS outcome similar to stent implantation.

2579 Intravascular ultrasound guided stenting does not further reduce in-stent restenosis

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Background: Intravascular ultrasound (IVUS) is claimed to be superior to quantitative coronary angiography (QCA) in stent implantation but, long-term results of IVUS guided vs. QCA with adjunct high pressure balloon deployment on intracoronary stenting are lacking. The purpose of the study was to compare the long-term effects of these modes of stent implantation on stent restenosis rate.

Methods and Results: From March 1994 to December 1997, 1122 patients had undergone intracoronary stenting, of which, 486 patients received IVUS guided (group A) and 636 patients received QCA guided high pressure balloon stent deployment (group B). In group A, 291 single stents (60%) and 195 (40%) multiple stents were deployed. In group B, 410 (64%) single stents and 226 (36%) multiple stents were deployed. IVUS guided stent deployment was defined as cross-sectional area in the stent > 80% of the average cross-sectional area of the proximal and distal reference segments. High pressure implantation was done with 16 ± 2 atmosphere to get residual stenosis of < 10%. The results were evaluated at a mean period of 8 ± 2 months. A total of 235 cases were found with in-stent restenosis (21%). Group A had 105 cases (39 cases with single in-stent restenosis and 66 cases with multiple stents). Group B had 130 cases (53 cases with single in-stent restenosis and 77 with multiple stents).

Stent restenosis	Single stent	Multiple stents	p
Group A (n = 105)	13.4%	33.8%	<0.001
Group B (n = 130)	12.9	34.1%	<0.001

Conclusion: IVUS guided stent deployment leads to a non significant reduction in angiographic restenosis rate compared to QCA with high pressure balloon deployment on long term evaluation. IVUS may be more cost-effective for plaque specific debulking prior to stenting.

2580 Coronary flow reserve immediately after stenting is not able to tell the late outcome

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Studies have shown that coronary flow velocity reserve (CFVR) after intervention may predict the long-term outcome. The purpose of this study is to evaluate the value of CFVR immediately after successful stenting in the prediction of late restenosis.

Methods and Results: Intracoronary Doppler were performed using a 0.014 inch FloWire® (Cardiometrics) in 68 patients (male 57, age 59.1 ± 10.3 years) who underwent intracoronary stent implantation. Intracoronary bolus injection of adenosine (12 μg for right coronary artery and 18 μg for left coronary arteries) was used to induce maximal coronary vasodilation. Baseline average peak velocity (bAPV), hyperemic average peak velocity (hAPV) and CFVR were measured pre-, immediately post- successful stenting and at 6-month follow-up. Patients were divided into two groups according to the CFVR after stenting (Group I, CFVR ≥ 2.5, n = 37 and Group II, CFVR < 2.5, n = 31). In-stent restenosis at 6-month were compared between the two groups. A significant improvement of CFVR was observed immediately after stenting (2.63 vs. 1.89, p < 0.001). A significant higher bAPV after stenting was found in Group II compared with Group I. A total of 19 (27.9%) of 68 patients occurred in-stent restenosis at follow-up (12 in Group I, 7 in Group II). No significant difference concerning restenosis rate was found between the two groups.

	Group I n = 37	Group II n = 31	p
bAPV (cm/s)	15.4 ± 5.6	24.9 ± 12.4	<0.001
hAPV (cm/s)	48.7 ± 18.4	44.8 ± 19.5	NS
CFVR	3.26 ± 0.57	1.88 ± 0.38	<0.001
Restenosis rate (%)	32.4	22.6	NS

Conclusion: Improvement of CFVR could be obtained after successful stenting. However, CFVR immediately after stenting is not able to predict the late outcome.

MODULATION OF ENDOTHELIAL FUNCTION

2581 Nitric oxide induces a cGMP-independent intracellular calcium rise in endothelial cells

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Nitric oxide has got various functions in biological systems. It serves as a neurotransmitter in the brain, and in higher doses as an antibacterial compound produced by macrophages. Moreover, endothelial cells release NO which regulates vascular tone and inhibits platelet aggregation and leukocyte adhesion to the vessel wall. NO diffuses from the endothelium to vascular smooth muscle cells, activating a guanylate cyclase, causing vasorelaxation. Elevated cGMP levels decrease intracellular calcium via cGMP dependent kinases.

The aim of this study was to investigate whether exogenous nitric oxide affects intracellular calcium levels in endothelial cells.

Therefore, using FURA-2 loaded porcine aortic endothelial mono-layers the influence of the synthetic NO donors S-nitroso-N-acetyl-D,L-penicillamine (SNAP) (half life of approximately 4 hours) and N-methyl-N(6-N-methylammoniohexyl)aminodiazen-1-ium-1,2-diolate (NOC-9) (half life of approximately 3 min) on intracellular calcium levels was measured. Both NO donors induced a calcium increase in endothelial cells which could be confirmed with an aqueous NO gas solution. The following investigations were performed with NOC-9. The calcium increase seems not to be due to a cGMP-dependent process since the specific inhibition of the NO-stimulated guanylate cyclase with ODQ did not diminish the NO-induced rise in calcium concentration and a treatment with the cGMP analogue 8-bromo-cGMP did not significantly increase intracellular calcium. The elevation of the intracellular calcium level is probably due to a calcium influx since the removal of extracellular calcium as well as an inhibition of receptor operated calcium influx with SKF-96365 significantly reduces the NO induced calcium increase. Thus, besides the well known negative feedback inhibition of NO on the endothelial NO-synthase these cells seem to express other targets for NO independent of the cGMP signal cascade.

2582 Elevated levels of uric acid potentiate endothelial dysfunction associated with hypercholesterolaemia

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In hypercholesterolemia, activation of the xanthinoxidase causes generation of vascular oxygen radicals, which results in reduction of NO-mediated vasodilation. On the other hand, xanthinoxidase also generates uric acid. Therefore, we assessed, whether elevated levels of uric acid in hypercholesterolemia are associated with impaired epicardial, endothelium-dependent vasodilation. In 28 normocholesterolemic and 23 hypercholesterolemic patients with an angiographically normal or minimally diseased (<30% focal stenosis) LAD or LCX, we tested the endothelium-dependent vasoreactivity by i.c. infusion of acetylcholine (Ach, 10^{-6} M).

Results: Hypercholesterolemic patients with a serum level of uric acid $\geq$ 6 mg/dl had a significantly greater vasoconstriction (31 $\pm$ 14%, n = 9) compared to patients with a serum level of uric acid < 6 mg/dl (9 $\pm$ 15%, n = 14; p = 0.002). There was a significant inverse relation between Ach-induced endothelial vasoreactivity and serum levels of uric acid in patients with hypercholesterolemia ($r = -0.72$; $p < 0.001$), whereas no significant correlation could be found in normocholesterolemic patients ($r = 0.27$; p = n.s.). There was no association between serum concentrations of cholesterol and uric acid ($r = 0.1$; p = n.s.).

Conclusions: Elevated concentrations of uric acid in patients with hypercholesterolemia are associated with an exaggerated paradoxical epicardial vasoconstriction to acetylcholine. Prospective studies are warranted to determine whether lowering of uric acid concentrations is associated with an improvement of endothelium-dependent vasodilation.

2583 Does endothelium-derived nitric oxide contribute to the coronary response to magnesium, the so-called natural, physiological calcium blocker?

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Magnesium (Mg) is considered a natural, physiological calcium blocker. Recently, it has been reported that some kinds of calcium blockers have exert an endothelium-derived nitric oxide (NO)-induced vasorelaxing effect. It is still unknown whether endothelium-derived NO is involved in the vasoresponse of human coronary arteries to Mg. We performed the present study to examine whether the coronary response to Mg changed after intracoronary infusion of NG-monomethyl-L-arginine (L-NMMA), an NO synthesis inhibitor.

Methods: Seventeen patients with normal coronary arteries were enrolled for this study. Magnesium sulfate (MgSO4) (0.2 mmol/min over 2 min) was infused into the left coronary ostium before and after intracoronary infusion of L-NMMA (200 μmol/5 min). Coronary blood flow (CBF) and coronary vessel resistance (CVR) were calculated by quantitative angiography and Doppler flow velocity measurements.

Results: Intracoronary infusion of MgSO4 caused dilatation of the epicardial coronary arteries (percent change from baseline, mean $\pm$ SEM, 6.3 $\pm$ 0.6%, $p <$ 0.0001 vs baseline), increase in CBF (31.1 $\pm$ 6.8%, $p < 0.0001$), and decrease in CVR (−22.2 $\pm$ 3.8%, $p < 0.0001$). After infusion of L-NMMA, the response of these parameters to MgSO4 did not change (coronary diameter: 4.9 $\pm$ 0.7%; CBF: 25.3 $\pm$ 6.7%; CVR: −19.4 $\pm$ 4.7%, all $p < 0.0001$ vs baseline).

Conclusions: These findings suggest that endothelium-derived NO may not contribute to the coronary dilatation induced by Mg.

2584 Long-term estradiol treatment improves vasoactive intestinal polypeptide-mediated vasodilatation in atherosclerotic coronary Watanabe-rabbit arteries

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The aim of this study was to investigate the influence of long-term treatment with 17-beta-Estradiol (E2) on the response to the two vasodilatatory peptides Vasoactive Intestinal Polypeptide (VIP) and Pituitary Adenylate Cyclase Activating Polypeptide (PACAP) in atherosclerotic coronary and cerebral arteries. Twenty five female ovariectomised Watanabe Heritable Hyperlipidemic rabbits were randomised to treatment for 16 weeks with either Placebo (n = 12) or E2 4 mg/day (n = 13). The chow used was semisynthetic in order to avoid the influence of phytoestrogens. Ring-segments of the posterior cerebral artery (PCA), the right proximal coronary artery (PROX) and the distal left coronary artery (LAD) were microdissected and mounted for isometric tension recordings in a myograph. The vessels were precontracted with Krebs buffer containing 30 mM Potassium. The dose-response relationship for VIP (10^{-10} to 10^{-6} M) and PACAP (10^{-10} to 10^{-6} M) were evaluated. E2 treatment significantly improved the maximal VIP-mediated dilatation (Emax, in percent of the precontraction) in PROX (45.8 $\pm$ 9.6% vs. 24.1 $\pm$ 3.7%, $p < 0.05$). There was no difference in Emax for the VIP-response in LAD (42.6 $\pm$ 3.6% vs. 33.8 $\pm$ 6.0%, p = 0.21) or CNS (60.2 $\pm$ 7.3% vs. 62.1 $\pm$ 4.8%, p = 0.82) between the two groups. There was no difference in Emax for the PACAP-mediated dilatation in neither PROX (47.9 $\pm$ 6.2% vs. 40.9 $\pm$ 4.0%, p = 0.35), LAD (32.1 $\pm$ 4.5% vs. 25.4 $\pm$ 3.3%, p = 0.24) or CNS (41.2 $\pm$ 6.9% vs. 37.8 $\pm$ 3.8%, p = 0.66) from the two groups. EC50 and pI2 for VIP and PACAP was not different between the two groups in any of the vessels. These results suggest that long-term treatment with E2 in atherosclerotic arteries improves the VIP-mediated, but not the PACAP-mediated dilatation in the proximal coronary arteries, where the atherosclerosis is most pronounced.

2585 Selective attenuation of relaxations mediated by the endothelium-derived hyperpolarizing factor in porcine coronary arteries following in vivo treatment with a balloon perfusion catheter

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Endothelium-derived hyperpolarizing factor (EDHF) and nitric oxide (NO) play a crucial role for vascular homeostasis. Endothelial dysfunction is a well-known phenomenon following coronary angioplasty (PTCA). Besides PTCA, balloon catheters are increasingly used with low pressure inflation for short-term occlusion of coronary arteries e.g. for brachytherapy or angioscopy. Whether these interventions induce long-term endothelial damage is unclear.

Methods and Results: We investigated vascular reactivity *ex vivo* in porcine coronary arteries 12 weeks following *in vivo* treatment with a novel balloon perfusion catheter. The catheter was advanced to the left descending coronary artery (LAD) and the balloon was inflated to completely occlude the LAD (30 min, 1.2 bar). Distal coronary flow was maintained using a roller pump system. After 12 weeks angiography failed to reveal any signs of stenosis. In isolated coronary rings preconstricted with U46619, sodium nitroprusside-induced relaxation was identical in all vessels investigated. Endothelium-dependent bradykinin-induced relaxation was not significantly altered in rings from the balloon-treated part of the LAD. However, following NO synthase inhibition using N^G-nitro-L-arginine, bradykinin-induced maximum relaxation was markedly attenuated in these rings (21 $\pm$ 7%), as compared to control rings (67 $\pm$ 6%, n = 12, $p < 0.001$). This relaxation was mediated by EDHF since it was completely abolished following preconstriction with KCl.

Conclusion: Even in the absence of any angiographic signs of stenosis, short-term treatment with a balloon catheter at low inflation pressure induces long-term functional disturbances of the coronary endothelium. Although the clinical relevance of these findings is uncertain, EDHF-mediated relaxation may be a particularly sensitive marker of subtle endothelial damage.

2586 Coronary vasomotor response to nifedipine is modulated by functional and morphological coronary alterations

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Despite the known coronary vasodilator potential of nifedipine the impact of endothelial dysfunction and/or intimal hyperplasia on nifedipine (N)-induced coronary vasodilation is unknown. It was the aim of this study to investigate N-induced epicardial and microvascular response in cases of normal endothelial function, endothelial dysfunction, normal coronary morphology and intimal hyperplasia.

Methods: The investigation was performed in 70 patients 5 ± 5 months after HTx. Coronary microvascular function (Doppler FloWire) was determined with i.c. acetylcholine (ACh; 150 μg/5 min; i.c.), adenosine (ADO;800 μg/5 min; i.c.) and N (0.2 mg/30 s). Proximal and distal epicardial diameter changes to ACh, ADO and N were investigated using QCA. IVUS was used to detect significant intimal hyperplasia (mean maximal intimal thickening > 0.6 mm). In a subgroup (n = 38) coronary sinus and aortic endothelin (ET) levels were determined.

Results: Epicardial dilation to N was more pronounced in distal compared to proximal segments (18 ± 15% versus 10 ± 11% diameter increase) and was inversly correlated to epicardial diameter change in response to ACh (r = −0.24; p = 0.04). In cases of intimal hyperplasia distal vasodilation was increased compared to normal segments (24 ± 8% versus 16 ± 6% diameter increase; p = 0.03). Coronary flow response to N was comparable to ADO- and ACh-mediated flow increase (2.1 ± 0.6 compared to 2.6 ± 1 and 2.5 ± 0.9, respectively). A trend was observed between high ET plasma levels in the coronary sinus and an improved microvasodilation to N (p = 0.04).

Conclusion: N is a potent epicardial and microvascular vasodilator, comparable to ADO. Epicardial dilation to N is augmented in cases of epicardial endothelial dysfunction and/or intimal thickening. The association between microvascular response to N and ET levels in the coronary sinus suggests that the mechanism of N-induced microvascular vasodilation is at least in part modulated by ET.

VASCULAR REMODELLING: BASIC MECHANISMS

2587 Apoptosis is significantly higher in arteries with enlargement versus constrictive remodelling after ballon angioplasty

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Background: Apoptosis has been previously described after balloon angioplasty but data regarding arterial remodeling and restenosis are missing and contradictory, respectively. This study was therefore designed to evaluate the relationship among apoptosis, arterial remodeling, and restenosis after balloon angioplasty in the atherosclerotic rabbit model.

Methods and Results: Atherosclerosis was induced in femoral arteries of 16 New Zealand white rabbits by air-desiccation and high cholesterol diet. One month later, angioplasty was performed. Apoptosis, arterial remodeling, and residual stenosis were evaluated by TUNEL and histomorphometry respectively. Apoptosis was significantly more important in arteries with enlargement remodeling than in those with constrictive remodeling (34 ± 7% vs 8 ± 7%, p = 0.03; 34 ± 4% vs 4 ± 2%, p = 0.01 respectively at day 14 and 21). Residual stenosis inversely correlated with apoptosis (r = −0.57, p = 0.02).

Conclusions: These findings suggest that apoptosis may play a role in arterial remodeling and restenosis after balloon angioplasty. Strategies aiming at enhancing apoptosis might participate to promote enlargement remodeling, and to prevent restenosis after balloon angioplasty.

2588 Increased collagen synthesis and content in stented versus balloon treated arteries

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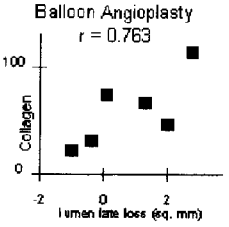
Although balloon angioplasty (BA) upregulates arterial wall collagen synthesis and collagen content, it is unclear which layers of the vessel wall are involved. Furthermore, the collagen response after arterial stenting has not been studied. We studied collagen synthesis and content in the various layers of the vessel wall after stenting and BA. In a double-injury model in normocholesterolemic rabbits, adjacent iliac arteries underwent BA (3.0 mm) or stent placement (Nir, 3.0 × 16 mm). Animals were sacrificed at 1 (n = 8) and 10 weeks (n = 16). The intima was separated from the medial-adventitial layer. These were incubated ex-vivo in ^{14}C-proline containing medium for 6 hrs. Collagen content (μg OHprol) and synthesis (cpm/segment) (mean ± SEM) were determined by assays for ^{14}C-OHproline and total hydroxyproline, respectively. Late lumen loss was calculated from intravascular ultrasound (IVUS) measurements done immediately after BA injury or stenting and at 10 weeks. We found stenting significantly increases collagen synthesis (2–3 fold) and total content (2 fold) at 1 and 10 weeks compared to balloon angioplasty. This effect is present in both the intima and media-adventitial layers (see Table). At 10 weeks lumen area by IVUS decreases from 3.4 ± 0.38 mm^2 to 2.7 ± 0.64 mm^2 and from 5.2 ± 0.18 to 4.6 ± 0.29 mm^2 respectively in BA and stented arteries. Late lumen loss was found to correlate best with intima collagen content in BA arteries (n = 6) (see figure) but not in stented arteries.

	Intima 1 wk	Med/adv 1 wk	Intima 10 wk	Med/adv 10 wk
Collagen synthesis				
BA	714 ± 391	797 ± 247*	154 ± 43*	376 ± 90*
Stent	1240 ± 331	2485 ± 699	450 ± 130	805 ± 115
Collagen content				
BA	27 ± 6	164 ± 25*	48 ± 7*	181 ± 21*
Stent	34 ± 4	252 ± 26	103 ± 9	385 ± 47

*p < 0.05 Stent versus BA.



Collagen response and mechanism of late lumen loss after injury might be different in stenting versus balloon angioplasty.

2589 Urokinase plasminogen activator in injured adventitia augments fibroblast differentiation to myofibroblasts, early proliferation and neoadventitia growth

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The activation of adventitial fibroblasts, their differentiation, proliferation, migration and involvement in neointima formation are important contributors to the failure of revascularization procedures such as coronary angioplasty and aortocoronary saphenos vein grafts. The mechanisms regulating the differentiation of the adventitial fibroblasts to myofibroblasts and their proliferation are not to be fully elucidated. Growth factors together with a variety of proteolytic enzymes are thought to be involved in the early proliferation and migration of fibroblasts after adventitial injury. This study was designed to investigate in vivo how elevations in urokinase plasminogen activator (uPA) and its proteolytic activity affect fibroblasts differentiation, proliferation and adventitia remodeling following following surgical injury of the rat carotid adventitia.

Methods: The left common carotid artery of the rats was subjected to surgical injury followed by perivascular application of uPA (ruPA) or a proteolytically inactive ruPA, in which glutamine has been substituted for histidine in position 204 (ruPA H/Q). The effects of these forms of ruPA on fibroblasts differentiation (the expression of alpha-actin), proliferation (the expression of proliferating cell nuclear antigen (PCNA)) and adventitia remodeling (the quantitative morphometry) were assessed 96 hours after injury.

Results: The frequency of alpha actin positive cells in adventitia increased in injured artery comparing to uninjured vessel (p < 0.05). Recombinant uPA increased the frequency of PCNA positive cells (p < 0.05) but ruPA H/Q was ineffective. At this time r-uPA also increased the size of the neoadventitia by 50% and ruPA H/Q did not induce such changes. Recombinant uPA also increased the frequency of PCNA positive cells in injured adventitia whereas ruPA H/Q did not affect such parameters.

In conclusion, the elevation in uPA following injury of the rat carotid artery adventitia augments fibroblast differentiation to myofibroblasts, their early proliferation and increase in the size of the neoadventitia. These effects are highly dependent on its proteolytic properties.

2590 Constrictive arterial remodelling after balloon angioplasty is not related with the absence of macrophages and endothelial cells

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Constrictive arterial remodeling is a major determinant of restenotic luminal narrowing following balloon angioplasty. Reports on the relation of local constrictive remodeling with inflammatory processes and the presence of endothelium are controversial.

Methods: Atherosclerosis was induced in the iliac arteries of 16 Yucatan micropigs by a combinaton of denudation and atherogenic diet. Balloon angioplasty was performed in 38 arteries, with serial intravascular ultrasound before and after intervention and at 1 (n = 6 vessels), 2 (n = 8), 4 (n = 5), 7 (n = 5), 14 (n = 8) or 42 (n = 6) days follow up. Remodeling was expressed as% change of vessel area on ultrasound at follow up compared with post angioplasty values. All segments were stained on the presence of macrophages (acid phosphatase) and endothelial cells (lectines). The area of staining for macrophages was measured in the intima and media using analySIS and expressed as% of the total vessel wall area. The staining for endothelial cells was expressed as percentage of the luminal circumference.

Results: Vessel area decreased over time among groups, indicating a time related remodeling response: from +39% at day 1, +13% at day 2, −1% at day 4, −2% at days 7 and 14 towards −11% at day 42 (+ = enlargement, − = shrinkage). Endothelial cell coverage increased slowly over time (day 1 49 ± 20% to 66 ± 25% at day 42). Macrophage content was highest at day 7 and 14 (3.4 ± 2.3 and 3.6 ± 2.0%, respectively) and lowest at day 1 (1.3 ± 1.5%). Regression analysis for the pooled data revealed no relation between the extent of remodeling and endothelial coverage nor macrophage content ($r = 0.08$ for macrophages and $r = -0.31$ for endothelial coverage, for both, $p > 0.1$). Also for the separate time points no relation between the extent of remodeling and macrophage content nor endothelial coverage could be demonstrated.

Conclusion: The mode of post angioplasty remodeling is not related with macrophage content nor with endothelial coverage.

2591 Matrix metalloprotease-2 and -9 activity is associated with luminal narrowing following balloon dilation in rabbits

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Luminal narrowing after balloon angioplasty, is the result of intimal hyperplasia and constrictive remodeling. The local arterial size decrease is probably a result of degradation and resynthesis of extracellular matrix surrounding the arterial cells. A major component of the extracellular matrix in arteries is collagen which is degraded by a family of matrix metalloproteinases (MMPs). The aim of the present study is to investigate the association between MMP activity and luminal narrowing after balloon dilition.

Methods: In 32 rabbits, we performed balloon dilation in the iliac artery. Animals were terminated at 2 days, 1, 2 or 4 weeks follow up. Quantitative angiography was performed at dilation and termination. Histomorphologic analysis and zymography was performed on the dilated and non-dilated (control) contralateral arteries.

Results: Two days after balloon dilation, MMP-9 activity increased 1.6 ± 0.2 times in the dilated arteries compared to the control arteries, and increased 1 week after intervention to 2.9 ± 0.4 times. At 2 and 4 weeks, MMP-9 activity returned to control levels. MMP-2 activity increased, only at two weeks, to 1.6 ± 0.2 times in the dilated artery compared to the control artery. Two weeks after balloon dilation, lumen diameter had decreased 0.58 ± 0.07 mm (0.46 ± 0.07 mm due to constrictive remodeling, 0.11 ± 0.04 mm by intimal hyperplasia). At 4 weeks, late lumen loss was 0.75 ± 0.05 mm and neointima thickness 0.16 ± 0.04 mm(21% of loss).

Conclusions: In response to balloon injury, the increase in MMP-9 activity preceeds the increase in MMP-2 activity. MMP-2 and -9 activity increases before and during the shrinkage of the ballooned segment which supports the hypothesis that MMPs play a role in constrictive arterial remodeling following balloon angioplasty

MINOR MYOCARDIAL INJURY: DOES IT MATTER?

2593 Angiographic findings in patients with refractory unstable angina according to the troponin T status

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The CAPTURE trial enrolling patients (pts) with unstable angina documented treatment benefit for abciximab which was particular evident in patients with elevated troponin T (TnT). As mechanism of TnT release remains unclear so far we related the angiographic data to the TnT status. In 853 patients angiograms at baseline and 24 hrs after allocated treatment were centrally assessed with respect to TIMI flow, lesion severity, and visibility of thrombus.

Results: TnT > 0.01 μg/L was found in 58% and > 0.1 μg/L in 31% of the pts. Thrombus was visible in 14.6% of pts with TnT > 0.1 μg/L versus 4.2% for TnT negative pts ($P = 0.004$). In 95.5% of patients with visible thrombus TnT release > 0.01 μg/L was detectable. Complex lesions (type > B2/C; 37.8 vs. 25%; $P < 0.001$) and TIMI flow < 2 (15.7 vs. 5.2%; $P < 0.001$) were more frequent in TnT positive pts. Abciximab was effective with respect to reduction of visible thrombus and increase of TIMI flow in TnT positive pts only. TnT status, but not angiographic findings, served as an independent predictor for both outcome and efficacy of treatment with abciximab.

Conclusions: Complex lesion characteristics and thrombus formation at baseline were significantly connected to the TnT release. However, TnT status was the more powerful predictor of increased cardiac risk. Accordingly, TnT can be considered as a more sensitive marker for the underlying pathology leading to the refractoriness of treatment in patients with unstable angina.

2594 Higher microinfarction rate by stenting and rotational atherectomy than by balloon angioplasty

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Background: Significant elevations of creatine kinase (CK), CK-MB, and troponin T (TnT) after successful coronary interventions have been recognized as markers of peri-interventional myocardial necrosis.

Methods: In order to answer the question if the interventional techniques have a different influence on the incidence of these myonecrotic events, 639 consecutive patients were subdived in those with balloon angioplasty (PTCA), stenting (STENT), and rotational atherectomy (ROTA). Blood samples were taken before the intervention as well as 6, 12, and 24 hours after the procedure. Enzyme activity assays were used for CK/CK-MB level quantification, rapid bedside test (Cardiac T™, Boehringer Mannheim) for the detection of a TnT release. Normal range values at baseline were obligatory for study inclusion.

Results:

	PTCA (n = 168)	Stent (n = 429)	ROTA (n = 42)
CK 1.5–3	4 (2.4%)*	38 (8.9%)*	2 (4.8%)
CK > 3	1 (0.8%)*	14 (3.3%)**	6 (14.3%)*/**
pos. TnT	7 (4.1%)*	92 (21.4%)*	16 (38.1%)*

(*/**$p < 0.001$, CK > 3: $p = 0.05$ for PTCA vs. Stent; CK 1.5–3: $p < 0.05$ for PTCA vs. ROTA, n.s. for STENT vs. ROTA)

Conclusion: Peri-interventional myocardial necrosis occurs more frequently after stenting and rotational atherectomy than after balloon angioplasty. Extensive squeezing of atherosclerotic plaques, ablation of particles, and distal microembolization are possible mechanisms, that can explain the higher incidence of myonecrotic events seen with stenting and rotational atherectomy than with balloon angioplasty.

2595 Influence of coronary stenting on the frequency of minor myocardial damage ("infarctlet") after percutaneous transluminal coronary angioplasty

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An elevation of cardiac enzymes after percutaneous transluminal coronary angioplasty (PTCA), indicating a minor myocardial damage ("infarctlet") is supposed to be of important prognostic value. Since most of the published data were recorded before the "era of stenting" little is known about the influence of coronary stenting on the frequency of these infarctlets.

Methods: Since October 1997, 560 patients (pts.) who underwent PTCA for stable or unstable angina were included in a prospective registry. An acute myocardial infarction in the past 48 hours was an exclusion criterion. Total-CK, CK-MB and troponin T were measured before intervention, 1 to 2 hours and 8 to 24 hours after intervention. Clinical and procedural data were documented.

Results: 271 pts. (48%) underwent the procedure for stable angina and 289 pts. (52%) had an unstable angina. An implantation of at least one coronary stent occurred in 270 pts. (48%). These pts. showed a significant higher rate of elevated cardiac enzymes:

Elevated enzyme	Stent implantation	Without Stent	p-value
Total-ck	16%	6%	<0.001
CK-MB	45%	30%	0.011
Troponin T	25%	11%	<0.001

Pts. with coronary stenting were not different in the demographic and clinical characteristics compared to pts. without stentimplantation. However, there was a 10-fold higher rate of documented reasons for enzymatic abnormalities in stented pts. such as side branch occlusion or major dissection (23% vs. 2%, p < 0.001)

Conclusion: Coronary stenting is associated with an increase in the frequency of elevated cardiac enzymes (total-CK 2.7-fold, troponin T 1.5-fold). The ongoing follow-up (6 and 12 months) has to reveal the prognostic relevance of the observed enzymatic abnormalities.

2596 Incidence of myocardial enzyme release following multivessel stenting in the ARTS trial

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Background: Rise in CK and CKMB following transcatheter treatment has been extensively scrutinized and the incidence of enzyme release following single lesion treatment ranges between 3 and 17%. The actual incidence of enzyme release following multivessel treatment has not been documented in larger trials.

Method: In the ARTS study, comparing conventional CABG to multivessel stenting, 600 patients (pts) were randomized to percutaneous treatment and received 2.9 ± 1.2 stents per patient, implanted at a maximum pressure of 13 ± 3 atm, resulting in a total length of 47.4 ± 21.6 mm of stented vessel. CK and CKMB were sampled at 6, 12 and 18 hours post-procedure. CK and/or CKMB were not available in 3% of the patients. Patient and lesion related parameters (n = 1027), pre-, peri and post procedural were itemized and analyzed in a multivariate logistic model.

Results: Overall enzyme release was observed in 30% of the patients.

Above normal	6 hours	12 hours	18 hours	Max value
CKMB 1–2x	16%	21%	23%	20%
CKMB 3–5x	4%	6%	6%	4%
CKMB > 5x	4%	7%	6%	6%

Among the 78 univariated significant variables related to the enzyme release 9 parameters were retained in the multivariate model: 1. CKMB pre-procedure (p = 8.E-07), 2. stenosis RCA pre-crux (p = 0.0004), 3. any side branch occlusion of LAD (p = 0.003), 4. side branch occlusion of proximal LAD (p = 0.01), 5. irregular contour LAD (p = 0.015), 6. urgent admission to hospital post-randomization) (p = 0.017), 7. total stent length (p = 0.032), 8. maximal post-stent dilatation pressure (p = 0.038), 9. EF% at screening (p = 0.048).

Conclusion: The observed incidence of enzyme release in this population appears to be higher than in pts with single lesion treatment and is related either to acute ischemic events occurring shortly before the procedure or related to lesional and procedural characteristics. The prevention (use of IIB/IIIA antagonist receptors) and the long-term significance of this enzyme release (MACE) remains to be elucidated.

2597 Cardioprotective effect of β-blocker therapy in reducing CK-MB release after coronary intervention

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It has been shown that patients on β-blocker therapy sustaining myocardial infarction (MI) have lower infarct size compared to those not on β-blockers most likely mediated by blunting the heightened adrenergic tone and decreasing myocardial oxygen demand. CK-MB enzyme elevation has been shown to occur in 10–33% of cases after successful coronary intervention. To evaluate whether β-blockers exert similar protective benefit after coronary intervention, we analyzed the incidence of post procedure CK-MB elevation in 1675 consecutive patients undergoing coronary interventions; of these 643 (38.4%) patients were taking β-blockers prior to their intervention and 1032 (61.6%) were not on β-blockers. Incidence of CK-MB release was 13.2% in patients on β-blockers as compared to 22.1% in the patients who were not on β-blocker therapy (p < 0.001). Among the various factors analyzed in a multiple linear regression model, no β-blocker use (p < 0.001), diffuse/multiple lesions (p < 0.01), peripheral vascular and aortic disease (p < 0.01), stent use (p < 0.02) and CCS angina class III-IV (p < 0.02) independently correlated with CK-MB elevation. During mid-term follow-up at 15 ± 3 months, there have been 5 deaths in the β-blocker group (0.78%) and 17 deaths in the no β-blocker group (1.74%); p = 0.045.

Conclusion: These non-randomized data suggest that prior β-blocker therapy has a beneficial effect in limiting the CK-MB release during coronary interventions. This intriguing observation needs to be verified in a prospective manner or by pooled data analysis of several previous interventional trials reporting CK-MB release in relation to β-blocker use.

2598 Importance of chest pain early after percutaneous coronary intervention: incidence and relation to ECG changes, cardiac enzymes and follow-up events

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Currently, the clinical relevance of chest pain (CP) and elevated cardiac enzymes after percutaneous coronary interventions (PCI) is controversial. Therefore, we studied the incidence of CP early after PCI and its correlation with ECG changes, cardiac enzymes, clinical and procedural variables and follow-up events.

Methods. The study population consisted of 199 consecutive patients (pts) (men 84%, mean age 60.1 ± 9.4 years) after primary successful PCI (21% PTCA, 79% stent). During the first 16 hours following PCI, the occurrence of CP was noted, ECG's were recorded at 0 and 16 hours and serial measurements of CPK, CK-MB, CK-MB mass (MB-M), myoglobin (myo) and troponin I (tro I) at 0, 4, 8 and 16 hours were performed. 76 pts (38%) with elevated enzyme levels at time 0 were excluded. A clinical follow-up was obtained at 6 months.

Results. 40 pts (32.8%) experienced CP, new ECG changes were detected in 3 (2.5%). Enzyme levels in pts with/without CP are shown below:

CP	CPK		CK-MB		MB-M		myo		tro I	
	+	−	+	−	+	−	+	−	+	−
0	70	78	17	17	2.0	2.0	26	25	0.2	0.2
4	87	78	16	16	5.1	2.6*	54	30*	0.5	0.1
8	121	81*	20	17*	10.6	4.3*	51	27*	1.3	0.6
16	163	82*	24	18*	17.8	5.4*	40	27*	2.4	0.4*

(*p < 0.05)

Significantly more pts with CP had MB-M and tro I levels higher than twice the upper normal limit 16 hours after PCI: 43.6 vs 11.1% (<.0001) and 45.0 vs 17.5% (<.003) respectively. CP and tro I showed no correlation with clinical and procedural variables. MB-M was associated with balloon size (<.03), stent diameter (<.02) and hypertension (<.05). We found no correlation of CP or enzymes with ECG changes. Elevated tro I (<.002) and MB-M (<.04) but not CP could be identified as risk factors for recurrent CP during follow-up.

Conclusion: CP early after PCI correlated with elevated cardiac enzymes but not with ECG changes indicating periinterventional myocardial necrosis. Elevated cardiac enzyme levels early after PCI are associated with recurrent CP during follow-up.

PAEDIATRIC CATHETER INTERVENTION

2618 Transcatheter closure of membranous ventricular septal defects with a new nitinol prosthesis in an animal model

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The purpose of the study was to evaluate a new device for closure of perimembranous VSD in a natural swine model.

Materials and Methods: Transcatheter closure of membranous VSD was attempted in 11 Yucatan minipigs with natural membranous VSDs. The device is constructed from 0.004 inch Nitinol wires with two retention buttons and a connecting waist filled with polyester fibers. Two different designs where used in this study: concentric retention buttons (n = 3) and eccentric design with a 2 mm small flange toward the aorta (n = 8). A 6 or 7 F introducing sheath was used to deliver the device.

Results: Successful implantation of the device was achieved in all animals. Complete closure rate was 54.5% (6/11) immediately after placement and 100% at one week. The aneurysm of membranous septum increased significantly in size in two of the three animals using the concentric device, but none of the cases using the eccentric device. Trace to moderate aortic regurgitation was presented in 2 of the 3 animals using the concentric device, and in 1 of 8 animals using the eccentric device. Three animals had a trace to moderate tricuspid regurgitation. Pathologic examination showed the devices to be covered by smooth, glistening neoendothelium at three months.

Conclusions: Effective occlusion of membranous ventricular septal defect is feasible and save with this new nitinol prosthesis. The eccentric device has advantages in a follow-up period of three months.

2619 Stent implantation in coarctation of the aorta: indermediate-term follow-up and technical considerations

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The purpose of this study was to present initial and intermediate-term results of stent implantation (SI) in children with coarctation of the aorta (CoA). A small number of previous studies, most of them preliminary, have reported use of stems for CoA with encouraging results.

Methods: Thirteen patients (pts), aged 5 months to 15 years (mean = 11 ± 4 years) with CoA underwent SI. Eight pts had significant re-CoA; 5 pts following previous surgical repair and 3 after balloon dilation. Three and two pts had local and long-segment CoA, respectively. SI was performed under antegrade angiographic guidance (transeptal placement of a Berman 6F to 8F diagnostic catheter into the left ventricle or the aorta).

Results: Immediate after SI the mean peak systolic gradient (MPSG) fell from 47 ± 28 mmHg to 4 ± 5 mmHg ($p < 0.05$). Proximal stent migration without adverse effects occurred in one pt during an attempt for further dilation. No any other complication was observed. At follow-up catheterization (9 pts, 1 to 5 years after SI) no significant change ($p > 0.05$) was noted in the MPSG (6 ± 5 mmHg) and the mean CoA diameter (14 ± 1 mm). At the latest follow-up (26 ± 18 months) the arm to leg blood pressure gradient is 11 ± 7 mmHg. Neither complications nor stent fracture was encountered.

Conclusions: SI may be a useful alternative to balloon dilation or surgery in selected children with CoA. AAG may improve the safety and the efficacy of the procedure.

2620 Interventional occlusion of big atrial septal defects larger than 20 mm diameter with the Amplatzer septal occluder

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Since the last 10 years (Y) various devices have been used for interventional occlusion of atrial septal defects (ASD). Most of these were limited for the use in defects up to 20 mm diameter. 1997 the Amplatzer Septal Occluder (ASO) was introduced and its use was extended for defects up to 34 mm diameter. We report about our clinical experience in the use of the ASO in big ASD larger than 20 mm diameter.

Method: Stretched diameter of the device was measured by inflating the sizing balloon within the defect up to originate a waist in the balloon. An ASO 1–2 mm larger than the waist of the balloon was choosen and implanted through 9–11 French sheathes. In opposite to the implantation into smaller defects pullback of the device onto the atrial septum was only performed when the connecting stent of the ASO was developed to achieve the maximal centering characteristics and have the maximal diameter of the retention skirt of the left atrial disc to find support on the edges of the defect. Thereafter the right atrial disc was deployed and actively configured by advancing the sheath and the delivery cable against the atrial septum. After placement the fixation of the device and the mechanical stability was proven by an extensive "Minnesota wiggle". The ASO was released only when TEE showed no or just a trivial residual colour flow through the connecting stent, otherwise repositioning was performed.

Results: Out of 225 patients (P) after successful occlusion of interatrial defects 30 P (3.9–77.7 y old) had defects larger than 20 mm diameter (median 22 mm diameter (20–32), 25/75% quartiles = 20/26 mm) Occlusion could be performed without any complications or embolization. Mean shunt size was Qp:Qs 2.3:1 (1.5–3.7:1), mean flouroscopy time 12.4 min (4.1–24.1). In 90% of the P complete closure after intervention could be shown by TEE with colour flow doppler 4 weeks after implantation, hospital stay was 3 days. 3 P showed insignificant residual shunt. Except the 1 P with persistent atrial fibrillation only 2 P showed transient atrial tachyarrhythmias within the first 3 months after implantation controllable by β-blocker treatment.

Conclusion: Transcatheter closure of large ASD with the ASO is feasible safe and effective. Embolization or complication risk seem not to be higher if one adheres to the different sizing- and implantation-procedure for large defects.

2621 One single centre and six-year experience with percutaneous occlusion of atrial septal defect: results with four different occluders

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Percutaneous closure of atrial septal defect (ASD) is available for many years. The aim of this study is to present and compare our 112 consecutive patients who underwent transcatheter occlusion of ASD.

From April 1992 to November 1998, 116 percutaneous closures were attempted in 112 patients. Occluders included Sideris device (1992–97, n = 71, group 1), ASDOS device (1996–97, n = 9, group 2), Amplatzer device (1997–98, n = 29, group 3) and Cardioseal device (1998, n = 3, group 4).

	n	SD	Fluor. time	Success		Residual Sht	
				n	%	n	%
Sideris	71	19.3 ± 4.7	23.8 ± 13.7	54	76	16	30
ASDOS	9	20.2 ± 2.8	48.5 ± 18.3	6	67	3	50
Amplatzer	29	20.3 ± 4.4	7.2 ± 8	27	93	0	0
Cardioseal	3	9.7 ± 6.0	24 ± 14.7	2	67	-	

SD = stretched diameter (mm); Fluoro. = fluoroscopy (min); Success = success of implantation; Sht = shunt at latest follow-up.

In group 1, implantation succeeded in 54 pts. During follow-up (up to 6 years), 38 pts had no residual shunt; but one of them had to be operated due to cardiac perforation. Sixteen pts had residual shunt (shunt ≤ 3 mm, n = 10), and 2 of them had to be operated for significant shunting. Silent fracture of one leg occurred in 2 pts and 2 other pts had to be recatheterised to retrieve embolised counter-occluder. In group 2, implantation succeeded in 6 pts and 3 of them had no residual shunt at follow-up (up to 21 months). In group 3, implantation succeeded in 27 pts. Another one had to be operated at day 1 because of embolization of the occluder to pulmonary artery. During follow-up (1 year), no pt had residual shunt. In group 4, implantation succeeded in 2 pts.

Conclusion: Our recent experience indicates that Amplatzer device is an efficient occluder for percutaneous closure of ASD. This devices produces higher occlusion rates of ASDs with shorter fluoroscopy time.

2622 Pre-seeding of atrial septal defect closure devices (STARFlex) with autologous cells improves short-term ingrowth

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Background: Interventional closure of suitable atrial septal defects (ASD) has become an attractive alternative in comparison to the surgical standard therapy. Rapid, complete and firm ingrowth of the closure device into the surrounding myocardial tissue is a major determinant in assessing the interventional procedure's quality since it reduces potential complications such as residual defects, thrombo-/embolism, friction lesions and arm fractures. The purpose of this study was to evaluate the influence on ingrowth of an ASD-occluder pre-seeded with autologous cells in an experimental animal model.

Methods: An ASD was created in anaesthetised sheep (35–40 kg, n = 6/group) by transseptal puncture under fluoroscopy and subsequent standardised balloon dilatation with increasing balloon diameters. Fibroblasts were isolated from a small skin biopsy and expanded in culture using routine techniques. After allowing for healing of the defect edges (2 weeks) the ASD's were closed using either autologous pre-seeded or conventional (acellular) devices. STARFlex®-devices, a self-centering modification of the CardioSEAL®-device, were employed percutaneously in all animals through the same 10F sheath. After a follow-up period of 10 days to 3 months animals were sacrificed and the device within the heart examined macroscopically and histologically.

Results: ASD-occluders pre-seeded with autologous cells showed a significantly improved ingrowth after only 10 days compared to both, our own control group after 3 months and data published previously in the literature. In particular, pre-seeded devices showed a several times thicker layer of connective tissue consisting of a network of fibroblasts, fibrocytes, capillaries and small vessels and newly synthesised collagen fibres on both atrial sides of the device. Compared to the thin layer of ingrown tissue in the periphery of conventional occluders the fibrous tissue on pre-seeded devices embedded not only the dacron fabric, but also completely covered the spring arms of the device underneath a layer of endothelium which was in continuity with the atrial endocardium.

Conclusion: In an experimental sheep model pre-seeding of septal occluders with autologous cells results in an improved short-term ingrowth. A thicker layer of connective tissue attaches the implant more rapidly, completely and firmly to the adjacent atrium.

2623 Advances in stent treatment for stenotic ductus arteriosus in newborns and infants with hypoplastic left heart syndrome

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Maintaining Ductus arteriosus (DA) patency in infants with hypoplastic left heart syndrome (HLHS) by Palmaz stents for bridging to heart transplantation (HTX) has been demonstrated. The objective of our study was to assess the feasibility of DA stenting in pts with HLHS with facilitated implantation techniques and advanced stent technology.

Methods: 30 stents were implanted in the DA of 26 pts with HLHS. 4 pts received 2 stents placed in series. Palmaz stents (n = 9) were delivered from the pulmonary artery (PA) route mostly using long sheath guidance (7–8F). Implantation of JO-stents (n = 21) was performed without long sheath protection..

Results: All patients survived the catheterization procedure. The final stent diameter varied from 5 to 10 mm. Five pts had stent placement to reach an outpatient status awaiting HTX, the others had progressive DA stenosis with hemodynamic and metabolic deterioration including cardiopulmonary resuscitation in 4 pts. DA patency was achieved for up to 52 days. Switching to more flexible stents allowed using 4 or 5F introducer sheaths, long sheath guidance could be avoided further decreasing morbidity.11 pts underwent HTX, and 3 palliative surgery according the Norwood I procedure, 1 patient reached Hemifontan by combined DA-stenting and PA-banding, 1 had corrective surgery, 2 are still waiting for a heart donor at home. 7 pts died in right heart failure awaiting further surgery.

Conclusion: Progress in stent technology facilitates implantation procedure. Effective widening in ductal stenosis offers rescue therapy in ductus dependent heart defects. Pts with HLHS can reach an outpatient status awaiting HTX. Combination with PA-banding offers the possibility of late palliative surgery as well as transplantation.

NEWER ASPECTS ON BETA-BLOCKADE IN CONGESTIVE HEART FAILURE

2628 Selective β-1 blockade improves left ventricular energy status, systolic and diastolic function in the rats with postinfarct heart failure

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Background: The results from recent clinical studies support the concept of beta-blockade therapy in congestive heart failure (CHF). However, the mechanisms for the beneficial effects of beta-blockade in CHF are incompletely understood. The aim of this study was to evaluate the effects of selective beta1-blockade on left ventricular (LV) energy status and function in rats during early postinfarct remodeling phase.

Methods: Male Sprague-Dawley rats body weight (BW) 200–250 were used. Myocardial infarction (MI) was induced by ligation of the left coronary artery. Two different groups of rats were studied: rats with MI treated with metoprolol (5 mg/kg/h; n = 8) during 4 weeks and rats with MI placebo treated (n = 6). All rats were investigated with 31P MRS and transthoracic echocardiography (ECHO) 3 days (3 d) and 3 weeks (3 w) after induction of MI. Infarct size was estimated by ECHO and only rats with large MI were selected. Volume-selective 31P MRS was performed on 20 cm bore, 2,35T Bruker Biospec BMT 24/30 magnet using cardiac gated ISIS (Image Selected in Vivo Spectroscopy) method.

Results: The results are summarized in the table. Treatment with metoprolol increased LV PCr/ATP ratio indicating improved myocardial energy reserve. At the same there was improvement in parameters reflecting LV systolic and diastolic function in the rats treated with metoprolol compared to the placebo group.

	PCr/ATP	EF%	DT ms	HR beats/min
Metoprolol	1.2 ± 0.09 *	3.4 ± 1.8 *	17 ± 3 *	−168 *
Placebo	0.04 ± 0.056	−9.66 ± 1.8	3 ± 3	−73

The values represent the means ± SEM of the difference before and after the treatment, * = $p < 0.05$ v.placebo. PCr/ATP = phosphocreatine/adenosine-3-phosphate ratio, EF = ejection fraction, DT = deceleration time of mitral E-wave, HR = heart rate

Conclusion: Metoprolol improves myocardial energy status in the rats during early postinfarct remodeling period. The beneficial effect on cardiac bioenergetics may be an important mechanism for the improvement in LV systolic and diastolic function after selective beta-1 blockade.

2629 Influence of long-term metoprolol treatment on the myocardial adrenergic nervous activity in patients with congestive heart failure as measured by MIBG uptake

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Background. Intensified myocardial adrenergic nervous stimulation resulting in down-regulation of the β-receptors has been demonstrated in patients with congestive heart failure (CHF). Myocardial ^{123}I-MIBG (analog of norepinephrine (NE)) uptake is reduced in cardiomyopathy resulting from both a reduced re-uptake 1 and increased release of NE from adrenergic nerve endings. We hypothesized that metoprolol has a favorable effect on MIBG uptake reflecting improvement of myocardial adrenergic nervous system integrity at the presynaptic level.

Methods. 59 consecutive patients (pts) with stable CHF class II or III and an EF < 35% entered the titration phase after measurement of baseline parameters. Starting dose was 25 mg metoprolol, maximal dose 150 mg. Pts who tolerated at least 50 mg were randomized to receive either placebo (n = 11) or one of 3 doses of metoprolol: 50 (n = 5), 100 (n = 11) or 150 (n = 27) mg depending on their maximal tolerated dose. ^{123}I-MIBG uptake was measured using SPECT imaging 4 hours after injection.

Results. Mean age of the randomized pts was 65 ± 10, 54% were in class II. Mean dose of metoprolol in the randomized pts was 126 ± 35 mg.

	Placebo			Metoprolol		
	baseline	6 months	Δ (%)	baseline	6 months	Δ (%)
MIBG	90 ± 44	82 ± 26	−8	87 ± 46	103 ± 56	+22*
NE	3.7 ± 1.7	4.2 ± 3.0	31	3.5 ± 2.1	3.8 ± 2.3	107
EF	27 ± 6	28 ± 9	9	26 ± 9	32 ± 9*	36
EDD	70 ± 4	71 ± 6	1	74 ± 10	67 ± 10*	−9.5

Results are expressed as mean ± SD. * = $p < 0.05$; MIBG = myocardial uptake (counts/voxel), NE = plasma NE (nmol/l). EF = ejection fraction (%), EDD = end diastolic diameter (mm).

Conclusion. Myocardial MIBG uptake increased significantly during treatment with metoprolol in CHF pts indicating a presynaptic effect of metoprolol in patients with congestive heart failure.

2630 Effect of metoprolol on QT, QT dispersion and left ventricular function in patients with heart failure

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The exact effects of metoprolol (meto) on cardiac de- and repolarisation in patients with depressed left ventricular function are unclear. QT, corrected QT (QTc), QT dispersion (disp.) and QTc dispersion were therefore assessed in a 12-lead rest ECG of 103 patients with moderately depressed left ventricular function before and 6 months after oral metoprolol (50 mg t.i.d, n = 50) or placebo (n = 53) therapy in a prospective, randomized, double blind study. Left ventricular ejection fraction (LVEF) was assessed by radionuclide angiography at baseline and 6 months later.

Results:

	Placebo		Meto	
	Baseline	6 months	Baseline	6 months
LVEF [%]	27 ± 7	28 ± 10	27 ± 7	35 ± 10*
Heart rate [/min]	83 ± 16	79 ± 14	77 ± 14	66 ± 15*
QT [ms]	416 ± 43	419 ± 43	424 ± 41	436 ± 47
QTc [$ms^{1/2}$] Bazett	482 ± 49	476 ± 48	475 ± 43	454 ± 47*#
QTc [$ms^{1/3}$] Fridericia	419 ± 77	407 ± 68	404 ± 63	361 ± 66*§
QT disp. [ms]	64 ± 25	63 ± 23	65 ± 21	67 ± 27
QTc disp. [ms]	78 ± 30	73 ± 31	73 ± 25	71 ± 31

*$p < 0.001$ vs. metoprolol baseline, #$p < 0.02$ vs. placebo 6 months, §$p < 0.001$ vs. placebo 6 months.

Conclusion: QTc decreased and LVEF increased significantly in patients treated with meto. Thus, the decrease in QTc duration may reflect stabilization of the action potential which may contribute to the antifibrillatory effect of metoprolol and to the improved prognosis in these patients.

2631 Different intrinsic activity of bucindolol, carvedilol and metoprolol in human left ventricular myocardium

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Objective: In clinical trials, beneficial effects of the β-adrenoceptor (AR) antagonists bucindolol (BUC), carvedilol (CARV) and metoprolol (METO) on left ventricular (LV) function in patients with chronic heart failure (CHF) have been observed. Nevertheless, the effects of these agents on the β-adrenergic system, i.e. receptor regulation, appear to be different. As these differences could be explained by different receptor interaction, this study investigates intrinsic activity as well as G-protein interaction of BUC, CARV and METO in human myocardium.

Methods: Radioligand binding studies using [^{125}I]-ICYP were performed in human LV myocardial preparations. Functional experiments were performed in intact LV myocardium from patients with CHF.

Results: BUC and CARV bind non-selectively to β_1- and β_2-ARs. BUC reveals agonist-like binding properties on β_1- and β_2-ARs, CARV predominantly on β_1-ARs, as the binding curves are shifted to the right by GppNHp. In contrast, METO is 35-fold β_1-selective, and the binding is not affected by GppNHp. At concentrations producing the same amount of β-AR occupation, METO antagonized isoprenaline-enhanced force of contraction (FOC) to a much higher degree than CARV and BUC ($p < 0.01$). In muscles that were prestimulated with forskolin, a diterpene that facilitates coupling of G-proteins with adenylate cyclase, BUC increased FOC in 38% of the experiments and decreased it in 62%. CARV decreased FOC by 27 ± 8%, METO by 89 ± 2% ($p < 0.001$ vs. CARV and BUC).

Conclusion: In human myocardium, METO possesses greater inverse agonist activity than CARV and BUC. BUC even exerts intrinsic sympathomimetic activity. This might lead to different negative inotropic effects upon initiation of β-blocker treatment in patients with CHF. Agonist-like binding of CARV and BUC, but not METO may have implications on the degree of phosphorylation of cardiac β-ARs and might be responsible for the different regulation of ventricular β-ARs in patients with CHF that were treated with these agents.

2632 Combination therapy with metoprolol and felodipine reduce benefit in resting and exercise haemodynamics as compaired with metoprolol alone in patients with severe chronic heart failure

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In addition to the standard therapy with diuretics, digitalis and ACE inhibitors, beta-adrenergic blockers have become a widely accepted strategy in the treatment of chronic heart failure (CHF). The role of calcium antagonists in CHF are controversial. Especially the hemodynamic effect of a combination of β-blocker therapy with long acting calcium antagonists has not been established yet.

To evaluate the hemodynamic changes induced by a combined therapy with β-blockers and calcium antagonists added to the standard therapy, patients with CHF (ejection fraction < 40%) were treated in a prospective, randomized, double-blind, placebo controled study with either metoprolol alone (titrated up to 100 mg/d, n = 13, MP) or combined metoprolol with felodipine (titrated up to 10 mg/d, n = 13, MF). At baseline and after 6 months, hemodynamic parameters were determined by right heart catheterization at rest and during exercise.

The heart rate at rest decreased significantly ($p < 0.05$) in both groups (MF: −10.3%; MP: −15.5%). Under maximal exercise, however, only metoprolol alone led to a significant reduction in heart rate (MF: −7.6% n.s.; MP: −19.2%, $p < 0.001$). Mean pulmonary arterial pressures were significantly decreased at rest and during maximal exercise only in the MP group (−30.4% and −23.4%), but not in the MF group, where only minor changes occurred. Furthermore the stroke volume index increased significantly at rest (MF: +13.5% n.s.; MP: +29.7%, $p < 0.05$) and during maximal exercise (MF: +17.7% n.s.; MP: +40.2%, $p < 0.01$) in the metoprolol group, but not under combination therapy.

In conclusion: Only β-blocker therapy as add on to the standard therapy lead to an improvement in resting and exercise hemodynamics in patients with severe CHF. In contrast, the combined therapy even mitigated the hemodynamic improvement seen on the β-blocker therapy alone suggesting the superior role of β-blockers in CHF.

2633 Effects of long-term β-blockade on the pattern of left ventricular diastolic filling in patients with dilated cardiomyopathy

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Recent clinical trials confirmed beneficial effects of beta-blockade in patients with dilated cardiomyopathy (DC). However, therapeutic benefits of beta-blocker therapy in patients with different patterns of left ventricular (LV) diastolic filling are less clear. This study was designed to evaluate clinical and cardiac effects of long-term therapy with metoprolol in patients with DC and restrictive LV filling, with the focus on the transmitral flow pattern.

Methods: 48 patients (aged 44 ± 9 years) were enrolled into the study. Patients were included if they were in sinus rhythm and had the restrictive pattern of LV diastolic filling at baseline. Twenty-four patients were randomised to standard therapy (ACE inhibitors, diuretics and digoxin), and 24 patients to metoprolol in addition to the standard therapy. Metoprolol was started at a dose of 10 mg daily and was progressively titrated up to the maximal doses of 100–150 mg daily. Patients underwent an assessment of functional status (NYHA classification and the 6-minute walk test). M-mode, B-mode echocardiography, and cardiac Doppler studies were performed to assess indices of LV systolic function and diastolic filling.

Results: patients were followed for 18 months. Mortality was not an end point in this study. The improvement in NYHA functional class and exercise capacity was significantly greater in the metoprolol group compared to the standard therapy group. Both therapies produced comparative effects on echocardiographic indices of LV systolic function. However, their effects on Doppler indices of LV diastolic filling were significantly different. After 18 months, the restrictive pattern of LV filling converted into a nonrestrictive pattern in 68% of patients on metoprolol compared to 28% patients on the standard therapy ($p < 0.05$).

In conclusion, long-term beta-blockade showed a strong potential in reversing the restrictive pattern of LV filling into a nonrestrictive pattern in patients with DC.

NEUROHORMONAL INHIBITION IN HEART FAILURE: EXPERIMENTAL AND CLINICAL ASPECTS

2643 Cardio- and nephroprotective effects of endothelin antagonists in uraemic cardiomyopathy of rats

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Increased endothelin-1 (ET-1) levels were found in patients with chronic renal failure These correlate with the severity of renal failure. Patients with elevated ET-1 concentrations have an increased cardiovascular mortality.

Methods: Male rats were subtotally nephrectomized and treated with an endothelin$_A$-receptor antagonist (30 mg/kg/d, LU302146) or an endothelin$_{AB}$-receptor antagonist (30 mg/kg/d, LU302872) for 12 weeks. One group was left untreated (SNX) and one was sham operated (sham). Determined were ET-1 serum-, ET-1 urin-concenetration, protein-excretion, heat weight and pulmonary β-adrenergic receptor density (β-AR), left ventricular contractility (LC) and relaxation (LR). The basal radical formation in aortas were measured

Results: ET-1 concentrations in the serum were increased with ET_A-(8.21 ± 0.96 fmol/ml) and ET_{AB}-antagonists (7.22 ± 0.7) compared to SNX (3.42 ± 0.61). ET-1 excretion was augmented in all groups. Myokardial hypertrophy was decreased by ET_A and ET_{AB} antagonists. Basal radical production decreased with both ET_A- or ET_{AB}-antagonists by 40%. The pulmonary β-AR increased from 733 ± 53 fmol/mg protein (sham) to 886.07 ± 41 in SNX but was not influenced by ET_A or ET_{AB}-antagonists. α-subunit of the stimulatory G-protein was increased in SNX by 53% and was not changed by ET antagonists. LC and LR were decreased in SNX by 40%. this was prevented by ET_{AB} antagonist treatment. Protein-excretion of SNX (174.4 ± 32 mg/d) was increased in comparison to the ET_A-group (72.9 ± 26.6) and the ETAB-group (116.0 ± 36.1, vs sham: 13.5 ± 3 mg/d).

Conclusion: Treatment with ET_A and ET_{AB} antagonists improve left ventricular function and inhibit ventricular hypertrophy as well as radical formation in rat aorta. These data show that in uremic cardiomyopathy ET-antagonists have cardio- and nephroprotective effects.

2644 Treatment with the endothelin-A receptor antagonist LU 135252 improves renal dysfunction in rats with chronic heart failure following myocardial infarction

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Renal dysfunction is a common phenomenon in rats with chronic heart failure following myocardial infarction.

Methods: We investigated the effect of treatment with an endothelin (ET) antagonist on renal function in rats with experimental heart failure (HF) 12 weeks following myocardial infarction and compared with sham-operated animals (SHAM). Rats were treated by gavage starting on the 7th postoperative day either with placebo (HF-P, SHAM-P) or with the selective ET_A-receptor antagonist LU 135252 (30 mg/kg/d; HF-L, SHAM-L). Only animals with extensive myocardial infarction (≥46% of left ventricle) were included in the study. Infarct size was matched between HF-P and HF-L. Endogenous creatinine clearance, urinary excretion of endothelin and fractional sodium excretion were determined 12 weeks following myocardial infarction.

Results: Endogenous creatinine clearance was significantly lower in HF-P compared to SHAM-P (HF-P: 0.64 ± 0.05 vs. SHAM-P: 0.81 ± 0.04 ml/min/100 g bw; p = 0.01). Treatment with LU 135252 significantly improved renal function in chronic HF (HF-L: 0.98 ± 0.21 vs. SHAM-L: 0.83 ± 0.10). Urinary endothelin excretion was significantly lower in HF-P compared to SHAM-P (HF-P: 180 ± 60 vs. SHAM-P: 303 ± 19 pg/24 h; p = 0.01). In the treatment group, no difference could be observed between HF and SHAM, although the ET_A-receptor antagonist markedly increased urinary endothelin excretion (HF-L: 536 ± 111 vs. SHAM-L: 462 ± 86). Fractional sodium excretion was similar in the four groups.

Conclusion: Our data demonstrate a restoration of impaired renal function in chronic ischemic heart failure by treatment with the selective ETA-receptor antagonist LU 135252. These results offer a promising therapeutical option for the treatment of renal insufficiency in patients with chronic heart failure.

2645 Effect of long-term therapy with trimetazidine in cardiomyopathic Syrian hamster BIO 14:6; effect on the defective cardiac Na,K-ATPase

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Effects of chronic therapy with the anti-ischemic agent, trimetazidine (T), on the progression of left ventricular failure on survival was assessed in the BIO 14:6 cardiomyopathic hamster (CMH). Abnormal calcium homeostasis and spasms of the microcirculation producing transcient focal ischemia, have been postulated to be at the origin of the cell death in the CMH. Active transport of Na^+ and K^+ across the cardiac cell membrane essential for excitability and contractility, was reported to be altered in CMH early.

Methods: T was administered in the drinking water at the dose of 18 mg/kg body wt/day from 30 to 350 days of age (n = 26). Aged-matched golden syrian hamsters served as healthy control (C). The cytosolic Ca^{++} concentration in cardiac myocytes was measured using the Ca-sensitive fluorescent dye Fura 2. The expression of the catalytic α-subunit isoform of Na,K-ATPase has been investigated in microsomal membranes by immunoblotting employing polyclonal anti rat fusion protein and enzymological assays.

Results: CMHs suffered reduced longevity and heart hypertrophy. At 220 days CMHs displayed a calcium overload. When compared to controls, there was a significant decrease ($p < 0.05$) in α1 subunit isoform of Na,K-ATPase. The membrane Na,K-ATPase activity was also significantly lower in CMH than Na,K-ATPase activity may be due to a decreased density of the expression of α1 polypeptides. T increased the median survival time of CMH by 57% and cardiac hypertrophy disappeared. The mean cytosolic Ca^{++} concentration in CMH myocytes (543 ± 28 nM) was reduced by 54% by T. The Na,K-ATPase activity and membrane protein expression were significantly improved by T ($p < 0.05$). In conclusion, a long term T treatment that improves the survival of CMH, would reduce cytosolic Na+ and Ca^{++} overloads in this animal model of human cardiomyopathy.

2646 The bradykinin receptor antagonist icatibant attenuates the effects on blood pressure of acute ACE inhibition in normal man

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The pharmacological effect of ACE inhibitors (ACEI) may be partly mediated via bradykinin (BK) accumulation.We investigated the effect of the specific BK2 receptor antagonist icatibant on the blood pressure and neuro-hormonal response to acute ACE inhibition in normal man.

Methods: We performed a four phase, double-blind, double-dummy, placebo controlled study in 12 male volunteers (22.9 ± 1.9 years) on a normal Na diet. Icatibant (10 mg iv) was coadministered over the first 15 minutes of a 2-hour infusion of the ACEI perindoprilat (1.5 mg i.v.). In each phase, volunteers received one of: perindoprilat (P)+ placebo (PI); icatibant (I) + placebo; perindoprilat + icatibant; placebo + placebo. Blood pressure, heart rate and neuro-hormonal (plasma ACE activity, active renin concentration (ARC) and Ang I and Ang II concentrations) were measured at intervals to 12 hours after the start of infusions. We prospectively decided to analyse the data from the first 3 hours from the start of drug infusion plus the full 12 hour observation period. Haemodynamic and laboratory data were compared between groups following baseline and placebo correction. A mixed model ANOVA was fitted to all data using BMDP. The maximum change in MAP and HR on each study day was calculated for each volunteer.

Results: Over the first 3 hours P reduced MAP (mean max reduction 8.1 mmHg, $p < 0.0005$ cf placebo). I alone raised MAP (mean max increase 6.1 mmHg, p = 0.001 cf placebo). The fall in MAP with P was attenuated by coadministration of I (mean max reduction 6.5 mmHg, p = 0.001 cf P alone). Over the same period, P was associated with an increase (mean max increase 2.8 bpm, $p < 0.0005$ cf placebo) and I with a reduction (6.5 bpm, $p < 0.0005$ cf placebo) in HR. Coadministration of I did not alter the HR response to P alone (p = 0.059). Similar patterns were observed for the full 12 hour period. Comparison of the area under the MAP/Time curve for each treatment arm supported the findings of the statistical model. P inhibited (95.4 ± 3.7%) ACE activity, increased ARC and lowered the [Ang II/Ang I + Ang II] ratio (Each $p < 0.0005$ cf placebo). Co- administration of I had no effect on neurohormonal responses to P.

Conclusions: BK2 antagonism attenuates the BP lowering effect of acute ACE inhibition in normal man. BK may be involved in the control of resting BP in man.

2647 Dose of angiotensin converting enzyme inhibitors in patients with heart failure: understanding the gap between clinical trials and clinical practice

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Background: High dose (clinical trial dose = CTD) angiotensin converting enzyme inhibitors (ACEI) are more efficacious than low dose in treating patients (Pts) with heart failure (CHF). However, the proportion of Pts with CHF who may be able to tolerate the CTD is unknown.

Methods: We undertook a prospective study of consecutive Pts with CHF seen at the CHF Clinics of 2 Canadian University Hospitals. The only inclusion criteria was that they were followed at one of the specialized clinics (by cardiologists with special interest and expertise in CHF) for at least 3 months. A careful history of their therapy with ACEI was obtained directly and confirmed by chart review. Suboptimal dose ACEI was defined as <7.5 mg bid for enalapril, <25 mg tid for captopril, or <15 mg od for lisinopril.

Results: We studied 200 consecutive Pts (138 males), mean (± SD) age of 69 ± 12 years and mean ejection fraction of 31 ± 12%. There were 28, 87, 71 & 14 Pts in NYHA functional class I, II, III & IV, respectively. Only 68 Pts (34%) were taking ACEI at CTD. In the remaining 132 Pts (66%), the reasons for the use of suboptimal dose or no ACEI were: symptomatic low blood pressure, renal dysfunction, and h/o ACEI-induced skin rash, cough or hyperkalemia, as noted in the Table. In only 22 of these 132 Pts (11% of the total) were we successful in increasing the dose of ACEI to the CTD levels, usually by decreasing the dose of diuretics. The majority of Pts who tolerated up titration of ACEI were in functional class I & II. At the end of the study, only 45% of Pts (34 + 11%) were able to tolerate the CTD.

Table

	Low BP	RD	Cough	Other	Total
Sub-Op Dose	51	15	2	19	87 (44%)
No ACEI	14	13	9	9	45 (22%)
Total	65 (32%)	28 (14%)	11(6%)	28 (14%)	132

ACEI = angiotensin converting enzyme inhibitor; BP = blood pressure; RD = renal dysfunction; Sub-Op = suboptimal. Percentage (%) is relative to the total study population.

Conclusion: Despite efforts to maximize the the dose of ACEI in a patient population with CHF followed at specialized CHF clinics, less than one half of Pts were able to tolerate the recommended CTD. The gap between clinical trials and clinical practice is more complex than just physician's failure to comply with practice guidelines.

2648 Renal, cardiac and endocrine effects of long-term vasopeptidase inhibition in chronic heart failure

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Combined inhibition of neutral endopeptidase(NEP) and angiotensin converting enzyme(ACE) is postulated to be advantageous in treatment of chronic heart failure(CHF). The purpose of this substudy was to evaluate the mechanisms of potential benefit in CHF(cardiac, renal, neurohumoral)in a subgroup of patients from the first study of chronic vasopeptidase inhibition with omapatrilat in CHF.

Methods: The study was a randomised, double blind, single-centre study in 41 patients with NYHA Class II-IV, LVEF < 40%. Patients were randomised to 2.5, 5, 10, 20 or 40 mg once daily. Clinical status assessment, echocardiography, and digital applanation tonometry were performed at baseline and after 3 months of chronic therapy. Data for all doses combined and also dose-dependent changes [2.5 mg, 5–10 mg, 20–40 mg] are shown.

Results: There was an improvement in patient clinical assessment of heart failure status at 3 months** [20–40 mg (improved moderately) vs. 2.5 mg (no change)**].

Table 1

	HR bpm	EF %	SBP mmHg	Uvol ml/24 hr	Una mmol/24 hr	ANP pmol/l	BNP pmol/l	EPI pmol/l
Baseline	71	24	131	1797	112	66.0	47.8	148
3 months	67*	28**	116**	2148**	135**	65.3	39.3**	101**
Change	from	Baseline	2.5 mg		5–10 mg		20–40 mg	
EF	%		−3.4		6.73**		7.41**	
Wallstress	g/cm^2		29.4		−33.5		−66.4*	
SBP	mmHg		−3.6		−16.8		−25**	
Una	mmol/24 hr		12.1		14.1		47.2	
ANP	pmol/l		−13.6		−4.0		12.5	

SBP = systolic blood pressure; Uvol = urinary volume; Una = urinary sodium; EPI = epinephrine; p < 0.05*, p < 0.01*.

Conclusion: Three month omapatrilat treatment in patients with CHF resulted in improved clinical status. There was a dose-dependent improvement in LVEF secondary to afterload reduction. The increased urine sodium and volume excretion at 3 months suggests a natriuretic and diuretic effect which may have a delayed onset. The increase in ANP at higher doses, despite the paradoxical fall in BNP and hemodynamic improvement, is consistent with NEP inhibition.

MEDICAL THERAPY IN ACUTE CORONARY SYNDROMES

2662 Heparin anticoagulation treatment during hyperfibrinogenaemia in acute coronary attacks

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Background: in patients with acute myocardial infarction (AMI) fibrinogen levels (F) after thrombolytic therapy correlate with heparin consumption and ischaemic events (Ies). A controlled trial was designed to ascertain whether: 1. hypercoagulation and thrombin generation was a common fact in the first month after AMI. 2. it would be possible to decrease thrombin activity and Ies with long-term heparin treatment.

Methods: patients with AMI treated with streptokinase were allocated at random to receive either heparin (H) i.v. for one week, followed by nadroparin (LMWH) for 14 days (Prolong H Group; n = 80) or 5.700 u/day of nadroparin 2 days (Control Group; n = 68). Assays of Trombin-Antithrombin Complex (TAC) and prothrombin fragments 1 + 2 (FRAGM) were performed on days 3 and 30 to assess thrombin activity (Thr Ac).

Results: the table shows Thr Ac for both groups:

	CTAT			FRAGM		
	Control G	Prolong G	P	Control G	Prolong G	P
Day 3	7.3 ± 6	5.9 ± 5	0.5	2.2 ± 1	1.2 ± 0.7	0.03
Day 30	5.8 ± 5	4.0 ± 2	0.05	1.9 ± 1	1.5 ± 0.7	0.07

In the acute phase Thr Ac was similar in patients with Ies and those without complications. On day 30, the mean values of Thr Ac were within the normal range in patients with a favorable course (CTAT = 4.5 ± 2; FRAGM 1.7 ± 1) but remained elevated in cases with Ies (CTAT = 7.0 ± 4; FRAGM 3.14 ± 2; p 0.03)

Conclusions: 1. Patients with AMI have high Thr Ac 72 h after STK treatment, when F levels begin to rise. 2. Thr Ac is higher in the control Group 3. There is a trend for F levels and Thr Ac to normalize one month later, but patients with major Ies show persistently elevated values of F, CTAT and FRAGM.

2663 High-dose hirulog enhances speed and stability of reperfusion compared to heparin in conjunction with thrombolytic therapy: continuous ST-segment recovery in the HERO-I study

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Adjunctive therapy may influence the speed and/or the stability of reperfusion following thrombolytic therapy for acute MI. Continuous digital 12-lead ST-segment recovery analysis provides quantitative measures of reperfusion. All pts with MI by ST elevation, <6 hr. of chest pain, given streptokinase and randomized to heparin, low-dose and high-dose Hirulog in the HERO-I study who underwent ST-monitoring were analyzed. From 210 pts, 180 studies were analyzable for: absolute PEAK ST levels (uV); >50% recovery at 90 minutes suggesting reperfusion (ST-90); time to >50% recovery lasting >4 hr. (STABLE ST (min.)); recurrent ischemia before STABLE ST (RE-ST); and LATE ST re-elevation after STABLE ST. Data were analyzed blinded to therapy. For results, given as median or percentage, see table.

Table

Variable	Heparin	Low dose	High dose	*p-value
No. patients	60	61	59	
Peak	528	498	400	0.070
ST-90	51%	63%	76%	0.006
Stable ST	128	118	118	0.116
Re-ST	63%	47%	36%	0.006
Late ST	24%	17%	9%	0.028

*p-value compares heparin vs. high dose Hirulog

Conclusions: Hirulog, especially high dose Hirulog, significantly enhances the speed and stability of reperfusion in combination with streptokinase in acute MI.

2664 The combined use of pravastatin and thrombolysis in acute myocardial infarction: effect on the patency of infarct-related artery

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The effect of cholesterol lowering drugs in acute myocardial infarction (AMI) is not well established. In this study pravastatin was administrated to pts with AMI, in combination with thrombolytic therapy. Effects on arterial stenosis and restenosis after PTCA were evaluated by coronary angiography. One hundred fifty consecutive pts with first MI were prospectively enrolled in the study and randomized into two groups. Group-I(n = 72), received pravastatin (40 mg/day) within the first hour of thrombolytic therapy irrespective of serum lipid levels. Group-II (n = 78) was given only thrombolytic therapy without any cholesterol lowering agent. All pts were within the first 6 hours of chest pain. In both groups tissue plasminogen activator and streptokinase administration rates were similar. Basal characteristics of the groups were also similar. Lipid levels were determined immediately after admission and after 1 and 6 months. Infarct related arterial (IRA) stenosis rates were compared between the two groups by quantitative coronary angiography one month after the infaction. A total of 71 pts (34 pts (47%) in pravastatin-group and 37 pts (48%) in control group) underwent invasive intervention. After the 6-month follow-up, pts were reevaluated with clinically and angiographically for restenosis. Groups were compared for restenosis rates of the infarct related arteries with respect to the serum lipid levels.

Results: see table.

Comparison of the groups

	Pravachol-group	Control-group	p
Clinical Reperfusion	56 (78%)	56 (73%)	ns
LDL (mg/dl) admission	145 ± 30	149 ± 40	ns
LDL (mg/dl) 6th month	98 ± 17	144 ± 27	0.00
IRA lesion% 1st month	86 ± 10	90 ± 66	ns
6th month	45 ± 22	67 ± 25	0.000
Restenosis rates	11(33%)	15(41%)	ns

Combined use of cholesterol lowering drug and thrombolytic therapy in AMI did not affect short-term arterial patency on the first month angiography; however, at 6-month control, arterial patency and restenosis rates were better for patients receiving pravastatin. Reduction in restenosis rates may be due to regulation of endothelial or platelet functions as well as lowering of blood cholesterol levels by pravastatin.

2665 Incomplete Infarction Trial of European Research Collaborators Evaluating Prognosis Post-Thrombolysis (INTERCEPT): a randomized comparison of diltiazem once daily and placebo following thrombolysis-treated myocardial infarction

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Diltiazem has been demonstrated to reduce cardfiac events following non-Q-wave infarction. We hypothesized that this agent would likewise reduce events following thrombolysis-treated myocardial infarction, both settings being associated with "incomplete infarction" occurrence.

We performed a double blind, multicenter, parallel group, sequential analyzed study in 874 patients treated with thrombolysis for acute myocardial infarction comparing the effects of treatment with diltiazem 300 mg once daily (D) and placebo (P) on subsequent cardiac event recurrences. Patients were randomized within 36–96 hours of pain onset and treated for up to 6 months All patients recieved ASA.

Main inclusion criteria were: age up to 75 years, prolonged chest pain with ECG signs of ischemia and enzyme proven myocardial necrosis, thrombolysis-treatment and ASA prior to 12 hours after pain onset and absence of congestive heart failure. Baseline patients characteristics were comparable.

For the primary endpoint, consisting of the cumulative first event rate of cardiac death (CD), non-fatal reinfarction (NFR) and medically refractory ischemia (RI), 97 events (22.6%) and 131 events (29.5%) occurred in, respectively D and P treated patients (HR 0.78; 95%CI 0.60–1.02; p = 0.07), a 23% relative reduction. Significant reductions favoring D were observed in non-fatal events and in the need for myocardial revascularisation (MR) for ischemia recurrences. NFR + RI decreased by 26% (HR 0.76; 95% CI 0.58–1.00; p = 0.05), NFR + MR decreased by 37% (HR 0.67; 95% CI 0.46–0.96; p = 0.03) and MR was reduced by 42% (HR 0.61; CI 0.39–0.96; p = 0.03). No major safety issues were encountered.

We conclude that diltiazem once daily can be safely administered as secondary prevention following thrombolysis-treated myocardial infarction and exerts important favorable effects in decreasing non-fatal events and myocardial revascularisation procedures.

2666 Are there differences in the treatment of acute myocardial infarction in West and East Germany after unification? The Myocardial Infarction Registry (MIR)

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After unification in 1989 differences in the treatment of acute myocardial infarction in West and East Germany may persist. We compared the therapy of acute myocardial infarction in West and East Germany.

Methods: The Myocardial Infarction Registry (MIR) is a prospective, multicenter registry of patients with acute myocardial infarction in West and East Germany from 01.04.1997 to 31.03.1998. 14608 patients were treated at 211 hospitals.

Results:

	West G.	East G.	p-value
Patients (n)	8990	5618	
Age (median, years)	68	69	NS
Female sex (%)	34.1	36.7	NS
Prehospital delay (median, min)	180	210	<0.001
Contraindication for thromholysis (%)	6.1	6.3	NS
Thrombolysis and/or PTCA (%)	51.3	37.7	<0.001
Thrombolysis (%)	40.8	28.9	<0.001
PTCA (%)	8.5	7.0	<0.001
Aspirin (%)	92.9	86.3	<0.001
β-blocker (%) 1	56.4	50.1	<0.001
ACE-inhibitor (%)	53.6	51.6	<0.001

G. = Germany

Conclusion: Even nearly 10 years after unification, significantly more patients in West Germany were treated with reperfusion therapy and adjunctive therapy, including aspirin, β-blockers and ACE inhibitors.

2667 An optimised therapy strategy in patients with ami is associated with a reduction in hospital mortality: results of the Myocardial Infarction Registry (MIR) in Germany 1998

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Daily practice of the treatment of patients with AMI in community hospitals may differ from recommendations of randomised trials. We sought to determine the use of reperfusion therapy and adjunctive drugs improving prognosis of AMI and their influence on hospital outcome.

Methods: The Myocardial Infarction Registry (MIR) is a multicenter and prospective observational registry with 217 participating hospitals in Germany. The primary aim of the study is to optimise therapy strategies in the treatment of AMI. All patients with q-wave AMI, admitted within 96 hours after the onset of pain were included from 12/96–5/98. Base line characteristics and the use of the combined therapies improving prognosis (reperfusion therapy, aspirin, betablocker and ACE-inhibitor) were registered. The treating physicians were obliged to document why a therapy was not given. A multiple logistic regression analysis was applied to calculate the influence of therapy on intrahospital mortality.

Results: In total 14598 patients with AMI were registered. Mean age was 67 years, 65% were male. 46% received a reperfusion therapy. Aspirin was given to 90%, betablocker to 54% and ACE-inhibitors to 53% of the patients.

Influence of reperfusion and adjunctive therapy on hospital mortality

	odds ratio	95% CI
Reperfusion therapy	0.7	0.6–0.8
Aspirin	0.6	0.4–0.7
Betablocker	0.6	0.5–0.7
ACE-inhibitor	0.5	0.4–0.6

Conclusions: In patients with AMI the combined treatment of reperfusion therapy, aspirin, betablocker and ACE-inhibitor is associated with a reduction in intrahospital mortality. Participation in a quality registry and the obligation to document why a therapy is not given may result in an increased use of reperfusion and adjunctive therapy.

ULTRASONIC EVALUATION OF CORONARY FLOW RESERVE

2668 Coronary flow reserve is supranormal in endurance athletes: a transthoracic echocardiographic study

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Background: Coronary flow reserve measurements offer a valuable assessment of microvascular coronary circulation. Invasive means of assessing coronary flow reserve do not allow investigation of states of health. Transthoracic echocardiography has recently been shown capable of assessment of coronary flow reserve. We therefore aimed to compare and contrast coronary flow reserve in endurance athletes and healthy sedentary controls.

Methods and Results: 29 male endurance athletes (age 27.3 ± 6.6 yrs, BMI 22.1 ± 1.9 kg/m^2) and 23 male controls (age 27.2 ± 6.1 yrs, BMI 23.9 ± 2.6 kg/m^2) with no coronary risk factors underwent transthoracic echocardiographic assessment of distal left anterior descending coronary artery diameter and flow both at rest and during intravenous adenosine infusion (140 mg/kg/min). Distal LAD diameter and flow were adequately assessed in 19 controls (83%) and 26 athletes (90%). Distal LAD diameter in athletes (2.04 ± 0.25 mm) was not significantly greater than that of sedentary controls (1.97 ± 0.27 mm; p = ns). Percent increase in LAD diameter following 400 microgrammes sublingual nitrate, however, was greater among athletes (14.1 ± 7.2%) than controls (8.8 ± 5.7%; p < 0.01). Left ventricular mass index in athletes (130 ± 19 g/m^2) exceeded that of controls (98 ± 14 g/m^2; p < 0.01). Resting flow among athletes (10.6 ± 3.1 ml/min, 8.2 ± 2.2 ml/min/100 g LVmass) was less than that of controls (14.3 ± 3.6 ml/min, 4.4 ± 1.2 ml/min/100 g LVmass); both p < 0.01). Hyperemic flow among athletes (61.9 ± 17.8 ml/min) exceeded that of controls (51.1 ± 14.6 ml/min; p = 0.02), but not when corrected for LV mass (25.9 ± 5.6 vs 28.5 ± 7.4 ml/min/100 g LVmass; p = ns) Coronary flow reserve was therefore substantially greater amongst athletes (5.9 ± 1.0) than controls (3.7 ± 0.7; p < 0.01)

Conclusions: Coronary flow reserve in endurance athletes is supranormal and endothelium-independent vasodilatation is enhanced. Hypertrophy of the myocardium per se does not necessarily impair coronary flow reserve. Adenosine transthoracic echocardiography is a promising technique for the investigation of coronary flow reserve.

2669 Increased chronotropic sensitivity and reduced coronary flow reserve are associated with inotropic incompetence during β-adrenergic stimulation in patients with mild hypertension

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Whether or not coronary function is impaired in pts with mild arterial hypertension (HBP) is still debated. Aim of this study was to assess coronary flow reserve (CFR) and the response of coronary flow to beta-adrenergically mediated increase in chronotropic and inotropic myocardial activity in pts with mild HBP.

Methods: in 10 normotensive subjets (N) and 10 age- and gender-matched pts with mild HBP, all without coronary artery disease, coronary flow velocity (CFV) in LAD was monitored by TEE-Doppler at baseline and during stepwise Dobutamine infusion (DOB: steps of 15, 30 and 60 μg/kg/3 min) under continuous BP and ECG monitoring. LV fractional shortening (FS) and septal systolic thickening (SST) were assessed simultaneously by transthoracic echo. CFR was estimated just before DOB by Adenosine infusion (ADO: 700 μg/kg/5 min).

Results: in pts vs controls, MBP was 104 ± 15 and 97 ± 13 mmHg, HR 84 ± 14 vs 81 ± 15 bpm and LV mass index 144 ± 56 vs 110 ± 15 g/sqm (p = n.s. for all). Basal FS and SST were also comparable. CFR was significantly lower in pts (2.5 ± 0.4 vs 3.7 ± 1.1, p < 0.01), due to higher baseline CFV (32 ± 11 vs 22 ± 5 cm/sec, p < 0.05) and comparable maximal CFV (78 ± 18 vs 79 ± 18 cm/sec). The higher basal CFV was related to higher rate-pressure product (RPP: 12321 ± 2166 vs 10845 ± 2884 mmHg*bpm, p < 0.05).

During DOB, chest pain, ST-shift or LV asynergy never occurred, and the ratio of maximal achieved to basal CFV was 1.9 ± 0.4 in pts and 1.7 ± 0.4 in N (n.s.). In both groups, significant direct relations between stepwise increase in CFV and the corresponding increments in HR, FS and SST were found (r value between 0.513 and 0.714); however, compared to N, pts had steeper increase (p < 0.05) in HR (14 ± 15 vs 6 ± 12 bpm) and CFV (15 ± 12 vs 8 ± 9 cm/sec), but lower increase in SST (7 ± 10% vs 16 ± 14%, p < 0.05).

Conclusion: in pts with mild HBP, increased resting CFV and chronotropic sensitivity to adrenergic stimulation may lead to encroach CFR even during submaximal stress, possibly resulting in an inadequate inotropic response despite the absence of significant structural abnormalities.

2670 Visualization of proximal left coronary artery blood flow and identification of proximal left coronary artery stenosis using transthoracic Doppler echocardiography

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This study evaluated the ability of transthoracic Doppler echocardiography to visualize proximal left coronary artery flow and assess coronary artery stenosis.

Subjects and method; We studied 78 healthy volunteers (22 males, 56 females, mean age 58.9 years) and 48 patients who were suspected of coronary artery disease without previous anterior myocardial infarction (40 males, 8 females, mean age 64.5 years). Transthoracic Doppler echocardiography was performed on all subjects using Sequoia (Acuson, Mountainview) with 2.5 ~ 7.0 MHz transducers and coronary angiography was then performed on all patients. Subjects were divided into the following 3 groups: 78 volunteers, Group I; 17 patients with stenosis (>50% stenosis in diameter) at proximal left coronary artery (PLCA) from main trunk to segment 7 according to AHA classification, Group II; 31 patients without PLCA stenosis, Group III.

Results; PLCA flow could be visualized during diastole by color Doppler in 84.6% of volunteers (66/78) and in 83.3% of patients (40/48). Aliasing signals were found in only 2 of 78 volunteers in the 39 cm/s Nyquist limit. In contrast, 18/40 patients (11 Group II, 7 Group III) showed aliasing signal under the same condition. The highest diastolic mean velocity (HDMV) measured by pulsed Doppler without angle correction at several points within PLCA was higher in Group II than in Group III (p < 0.001). On the other hand, the lowest diastolic mean velocity (LDMV) within PLCA was similar between Group II and Group III (p = N.S.). The flow velocity ratio (HDMV/LDMV) 2.0 within PLCA could distinguish between Group II and Group III with a sensitivity of 73.3% and specificity of 80%.

Conclusion; The present findings indicate that the combined use of color Doppler and pulsed Doppler echocardiography provides an effective means of visualizing proximal left coronary artery blood flow and thus provides a non-invasive method of identifying proximal left coronary stenosis.

2671 Non-invasive and direct diagnosis of restenotic lesion after coronary intervention on transthoracic Doppler echocardiography

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According to recent development of ultrasound instrument with high-sensitive Doppler, epicardial coronary artery flow has been visualized by transthoracic Doppler echocardiography (TTDE). The aim of this study was to estimate the accuracy of non-invasive and direct diagnosis of restenotic lesion after coronary intervention to proximal left anterior descending artery (LAD) by TTDE using new instrument.

Methods: TTDE studies were performed with a Acuson Sequoia C256 system. In consecutive 44 patients who were previously done coronary intervention to LAD lesion, TTDE and coronary arteriography (CAG) were examined, simultaneously. Coronary flow mapping in LAD by TTDE was performed by the color Doppler-guided pulsed Doppler. Diastolic mean velocity ratio (DMVR = HDMV/LDMV) in LAD was calculated from highest diastolic mean velocity (HDMV) and lowest diastolic mean velocity (LDMV). The correlation between DMVR from TTDE and percentage of diameter stenosis (%DS) from CAG was investigated.

Results: In 40 of 44 patients (91%), DMVR could be measured by TTDE. There was significant quadratic correlation; $y = 1.3 - 0.2x + 0.01x^2$, between DMVR (y) from TTDE and%DS (x) from CAG (r = 0.90, p < 0.0001). If DMVR was 2.0 or more which was regarded as an abnormally high value, restenotic lesion with 50 or more%DS was diagnosed with 91% sensitivity, 96% specificity, and 93% accuracy.

Conclusion: The ratio of lowest velocity to highest velocity in LAD by TTDE was a very useful parameter to evaluate the restenotic lesion in LAD after coronary intervention, non-invasively, directly, and accurately.

2672 Evaluation of left internal mammary artery flow reserve with dobutamine echocardiography: comparison to flow reserve by adenosine Doppler echocardiography and to the LAD territory ischaemic responce

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Transthoracic adenosine Doppler echocardiography (ADEN) may be used for the evaluation of left internal artery mammary grafted to left anterior descending artery (LIMA/LAD) flow reserve (CFR).

Aim of the study was to assess the respective CFR (CFRdob) during dobutamine stress echocardiography (DOB) and to interrogate its relationship with CFR by ADEN (CFRaden).

Moreover the estimated CFR was evaluated in comparison to the detection of ischemic response by DOB in the LAD territory.

Patients/Methods: Twenty consecutive pts with CABG and LIMA/LAD underwent DOB followed post 20 min by ADEN. CFR was estimated at the phase of 30 μg/kg/min of DOB (CFRdob) and post ADEN at140 μg/kg/min for 6 min (CFRaden). The peak velocities (Vpeak: cm/sec) and the respective time-velocity integrals (TVI: cm) of proximal LIMA were evaluated in systole (S) and diastole (D) at rest (R) and during both DOB and ADEN. Four/20 pts had an ischemic response by DOB in the LAD territory.

Results: Doppler flow profile of LIMA had similar S characteristics during DOB and ADEN. However CFR was greater by ADEN: (table)

	SVpeak	DVpeak	SVTI	DVTI	CFR
DOB	87 ± 31	40 ± 8	15 ± 7	10 ± 4	1.21 ± 0.5
ADEN	81 ± 22	48 ± 12	16 ± 6	13 ± 3	1.63 ± 0.5

p = 0.04.

The degree of underesimation of CFR by DOBwas related with CFR(aden): r = 0.51, p = 0.05. However in 3/20 pts CFR(dob) was greater than CFR(aden).

The 4/20 pts with ischemia detected in the LAD territory by DOB had decreased CFR compared to pts with normal DOB response in similar% both by ADEN (1.25 ± 0.1 vrs 1.61 ± 0.5: 29%) and DOB (0.95 ± 0.3 vrs1.24 ± 0.6: 30%).

In conclusion, CFR of the LIMA/LAD may be estimated during DOB but it usually underestimates respective CFR estimated by ADEN. Despite the greater values of CFR during its evaluation by ADEN, detection of ischemia by DOB in the LAD territory is related with a similar decrease of CFR by both means.

2673 Transthoracic Doppler evaluation of mammary artery grafts-flow reserve after minimal invasive bypass surgery: validation by intravascular Doppler flow wire measurements

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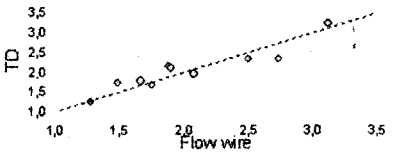
Background: Transthoracic doppler (= TD) of the left internal mammary artery (LIMA) during adenosine infusion is used to evaluate flow reserve after minimal invasive direct coronary artery bypass (MIDCAB)-surgery. The aim of the study was to validate the noninvasive doppler measurements by invasive flow wire (= FW) measurements.

Methods: 10 patients undergoing MIDCAB-surgery of the left anterior descending coronary artery (LAD) were examined 5–8 days after surgery. Parasternal TD-measurements were performed using a 10 MHZ linear array probe on a HDI 3000 (ATL, Bothell) at rest and during adenosine infusion (140 μg/kg/min) for assessment of flow reserve. FW- measurements of the LIMA were simultaneously performed using a 0.014-inch Doppler guide wire. Graft patency was proved by angiography in all patients but one, who showed a 71% stenosis of the graft.

Results: There is a high agreement between TD-data and intramammary FW-measurements of LIMA-flow reserve. Fig. compares adenosine induced increase in average peak velocity (= flow reserve) in TD and FW. Correlation coefficient r = 0.93; Regression equation: TD = 0.29 + 0.85 × FW ± 0.20;



Conclusions: Noninvasive doppler measurements of the LIMA flow reserve represent a reliable tool in the functional assessment of LIMA-grafts after MIDCAB surgery.

PROGNOSTIC VALUE OF STRESS ECHOCARDIOGRAPHY

2674 Ischaemia at dobutamine echo is an independent predictor of cardiac death

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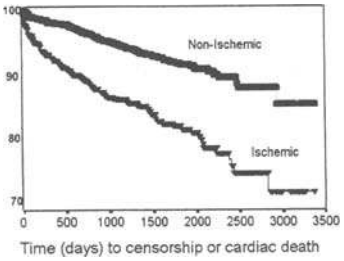
Dobutamine echo (DbE) has been shown to predict subsequent cardiac events, but insufficient pts have been studied to examine cardiac death rather than soft, composite endpoints. Moreover, prediction of events has been based on abnormal DbE, including scar segts which identify all risk rather than treatable risk. We sought whether ischemia at DbE could be used to predict cardiac death.

Methods: Standard DbE protocols were performed in 3156 pts (age 63 ± 12 y, 1801 men) with known or suspected CAD at two large US echo labs. Studies were interpreted using a 16-segment model by expert observers, and pts were classified as having normal findings, ischemia or scar. Survival curves were generated from follow-up over 9 years (mean 3.8 ± 1.9). A Cox proportional hazards model was developed to analyze the effect of ischemia, independent of other determinants of outcome. Significant CAD was identified in 746 of 1073 pts (70%) undergoing coronary angiography.

Results: Ischemia was identified in 2429 (77%). Cardiac death occurred in 259 patients and 41 (1.3%) were lost to follow-up. Ischemia was an independent predictor of cardiac death (RR 2.7, p < 0.001), even in models including angiographic disease extent (ischemia RR 1.8, p = 0.005; 3 vessel disease RR 2.1, p = 0.006; 1 and 2 vessel p = ns).



Conclusion: Ischemia at DbE is an independent predictor of cardiac death, even when angiographic anatomy is known.

2675 Prognostic significance of stress echo in women with high pretest probability of coronary artery disease

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Prevalence of significant CAD in women with typical angina is lower than in males. Non-Invasive imaging techniques are frequently used in this cohort of patients for further risk stratification. Prognostic significance of Stress Echo (SE) in women with high pre-test probability of CAD is not evaluated.

Aim of the study was to assess prognostic significance of SE in women with high – ≥80% – pre-test probability of CAD.

Methods: From the database of the Cardiology Department of the RFH 133 women (mean age 63 ± 9 y) with pre-test probability of CAD ≥ 80% who underwent SE (treadmill or dobutamine SE) between 1995 and 1998 were selected. The Bruce protocol was used during Treadmill SE. Dobutamine-atropine SE was performed according the conventional protocol. Events looked for were cardiac deaths, myocardial infarctions, unstable angina, revascularisation. Cox proportional hazard model was used to evaluate ability of clinical variables to predict an event.

Results: There were 93 negative SE (NSE) in this high risk population. Mean F/U was 20.1 ± 8.5 months. There were 9 events: 8 (2 cardiac deaths, I admission with unstable angina, 5 revascularisations) in positive stress echo (PSE) group and 1 in NSE group (angioplasty after worsening of angina at 20 months). Only two variables were identified as univariate predictors of cardiac events: positive SE (p = 0.0003) and age (p = 0.0188). With Cox step-wise analysis positive SE was found to be the only independent predictor of future cardiac events: Odds Ratio = 19.1. The event-free survival rate to 20 months post stress was 98% for patients with a negative SE and 79.6% for patients with a positive SE (p = 0.0001).

Conclusion: 1. Negative Stress Echocardiography predicts low risk of future cardiac events in women with high (≥80%) pre-test probability of CAD. 2. Positive Stress Echo in women with high pre-test probability of CAD identifies pts. likely to experience a cardiac event.

2676 Long-term prognostic significance of dobutamine stress echocardiography in patients with medically stabilized unstable angina

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We have previously reported the safety and usefulness for risk stratification of dobutamine-atropine stress echocardiography (DSE) in patients with medically stabilized unstable angina (UA) in a short follow-up period of three months. The aim of the present study was to assess if the prognostic value of DSE is maintained through time. One hundred twenty-two patients (pts) were studied (mean age 64 ± 12 years, 29 women). DSE was performed on third day after hospital admission in eligible pts. Endpoints were recurrent unstable angina, myocardial infarction (MI) or cardiac death. Patients undergoing coronary revascularization before hospital discharge were excluded.

Results: Mean follow-up was 24 ± 7 months (0.5, 34). Nine of the 21 pts (43%) with a positive DSE presented cardiac events during follow-up: 2 patient died, 1 had MI and 6 had recurrent class III-IV angina requiring hospital readmission. Among 81 pts with negative DSE, 1 (1%) died, 1 (1%) had MI and 12 pts (15%) had recurrent angina. Event-free survival of pts with a negative DSE for ischemia was 82% compared to 55% for those with a positive DSE (Log Rank 9.37; p = 0.002). Survival without MI was 94% in pts with a negative DSE compared to 84% for those with a positive DSE (Log Rank 6.60; p = 0.01). Predictors of cardiac events during follow-up were history of previous MI, ECG abnormalities on admission, left ventricular (LV) ejection fraction and a positive result of DSE for ischemia. Multivariate analysis selected LV dysfunction and a positive DSE as independent predictors of cardiac events.

Conclusions: DSE performed early in medically treated patients with UA allows their early discharge from hospital and shows a good prognostic capability at a long term follow-up.

2677 Prognostic significance of biphasic response to dobutamine stress echo following uncomplicated myocardial infarction

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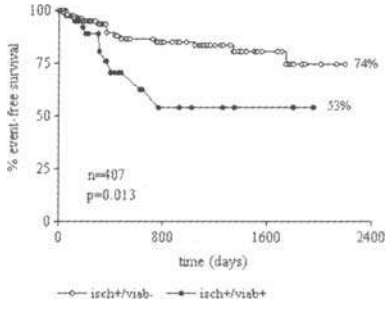
Aim: to evaluate the prognostic significance of biphasic (BR, low-dose improvement with high-dose deterioration) as compared to monophasic (MR, deterioration without improvement) response to dobutamine stress echo (DSE) in pts. with uncomplicated myocardial infarction (MI).

Methods: 407 pts. undergoing DSE within 10 days of MI were followed-up to 23 (range 1–78) months for reinfarction, death and unstable angina. Revascularized pts. were censored. Both low-dose (up to 10 mcg/kg/min) and high-dose response (up to 40 mcg/kg/min with additional atropine) were assessed.

Results: 194 pts. had positive DSE (46 with BR and 148 with MR). Sixty events occurred (20 MI, 11 death and 29 unstable angina). BR was associated to lower (p < 0.05) % event-free survival and shorter (p < 0.01) event-free time than MR. The event rate in BR and, respectively, in MR was: 4.3% vs. 3.3% for reinfarction, 4.3 vs. 1.35% for death and 13% vs. 6.7% for unstable angina.



Conclusions: the biphasic response is associated with increased risk of cardiac events in patients with positive DSE following uncomplicated MI.

2678 Prognostic value of pharmacological stress echocardiography in patients with left bundle-branch block

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Patients with left bundle branch block (LBBB) have an increased risk for cardiac death, especially when underlying coronary artery disease is present.

To evaluate the prognostic value of stress echocardiography in this setting, we interrogated the EPIC-EDIC multicenter stress echo trial data bank and selected 175 patients with LBBB (111 males, mean age 65+9 years; 55 with previous myocardial infarction) submitted to high dose dipyridamole (74 patients) or dobutamine (101 patients) stress echocardiography. All enrolling centers had been quality-controlled for stress echo reading. Peripheral reading directly entered the data bank. Stress echocardiography was positive for myocardial ischemia in 62 patients. During a follow-up period of 21+18 months, 47 cardiac events occurred (10 deaths, 9 acute myocardial infarctions, and 28 revascularization procedures). Cardiac events were significantly more frequent in the patients with positive when compared to the patients with negative test (30/62 vs 17/113, respectively; 48% vs 15%; p < 0.01). The three-year infarction-free survival was significantly lower for patients with positive when compared with those with negative stress echocardiography (68% vs 92%, respectively; p < 0.02).

In conclusion, pharmacological stress echocardiography is effective in prognostic stratification of patients with resting LBBB.

2679 Prognostic contribution of left ventricular inotropic reserve evaluated by dobutamine stress echocardiography in left bundle-branch block

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Aim of the study was to assess the contribution of left ventricular (LV) inotropic reserve estimated by dobutamine stress echocardiography (DOB) in order to evaluate prognosis in patients with LBBB.

Patients and Methods: 66 patients with LBBB underwent DOB. LV endsystolic (ES) and enddiastolic (ED) volumes (vol) were estimated at rest (R) and peak dobutamine (D). The ejection fraction at R and D and their difference dEF were calculated.

The 66 pts were followed up for 27 ± 21 months. None had an ischemic event; 4 pts died due to progressive severe heart failure and 13 more had an episode of acute or progressive decompensation (CHF events: group F). The other 49 pts had an uneventfull follow up (group N).

Results: Incidence of underlying coronary artery disease was similar between F/N (5/17 vrs 16/49). F and N groups had also at R similar: LVEDvol/diameter, EF, QRS duration, wall thickness/LVED diameter ratio (RelWth). However group N had greater increase of EF post Dob both in absolute values and% changes:

	LVEDdiam	LVEDvolR	%dEF	dEF	EFR	QRS	RelWth
F	6.6 ± 1	188 ± 47	−12 ± 18	−6 ± 8	42 ± 9	149 ± 12	0.26 ± 0.3
N	6.4 ± 1	207 ± 131	29 ± 34	11 ± 12	43 ± 18	143 ± 23	0.27 ± 0.05
			p = 0.03	p = 0.02			

The relative risk (RR) for CHF event when dEF > 0 was 6 (95% CI 1.4–24). In contrast ischemia detection by DOB had a RR of only 1.6 (95% CI 0.8–3).

Using logistic regression analysis for prediction of CHF event, both EFR and LVEDvolR had much lower contribution than the presence of a dEF > 0 (respective odds ratio: 0.6 and 1 vs 4.45)

Using the Kaplan Meier analysis, when the criterion of dEF>0 was considered, then a better outcome for CHF event was found for those pts who increased EF post Dob (long rank = 4.5, p = 0.032)

Conclusion: LV inotropic reserve evaluation by DOB in LBBB pts provides significant prognostic information for heart failure decompensation. This information is independent from LV resting function, degree of dilatation and detection of underlying ischemia by DOB.

PTCA IN ACUTE CORONARY SYNDROMES

P2698 Cost-effectiveness of direct coronary stenting

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Direct stent implantation (DSI), without any prior dilatation tecnique, is progressively used, in selected lesions, with a good feasibility in previous reports. In order to assess its cost-effectiveness, we analyzed two groups of 50 consecutive isolated single lesion PTCA performed during 1st and 2nd quarter of 1998 using DSI or conventional stenting technique. Baseline patient-related and lesion related data were similar in both groups except age and calcification grade, higher in case of predilatation. Count of disposable PTCA items, PTCA duration and angiographic frame numbers recorded on the DICOM CD were assessed:

	DSI+	DSI−	p
N of guiding catheters	1.2 ± 0.6	1.22 ± 0.5	NS
N of wires	1.04 ± 0.2	1.18 ± 0.5	NS
N of balloons	1.27 ± 0.4	1.31 ± 0.7	NS
N of stents	1.04 ± 0.2	1.22 ± 0.6	<0.05
PTCA duration (min)	30 ± 9	42 ± 12	<0.001
N of frames	871 ± 400	1194 ± 410	<0.001

Thus, despite its use in less calcified lesion, DSI is not associated with a major reduction of disposable items consumption, except for stent/lesion ratio. Radiation exposure and cathlab occupancy are dramatically reduced in case of DSI.

P2699 Is primary coronary stenting a feasible and safe strategy?

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Primary stenting – i.e., stenting of lesions with no prior balloon dilatation is a new technique which offers a less expensive and faster alternative to the currently accepted technique.

From April until August 1998, an open registry (5 centers) evaluated the safety and performance of the Tenax coated coronary stent (Biotronik) in a "real world" population of patients with coronary artery disease.

266 consecutive implantations were collected in 241 patients (pts). In this group, direct stenting was performed in 48 pts (64.5 ± 12.7 years – 18.8% females) and 50 procedures. The clinical indication for intervention was stable angina (12.5%), unstable angina (40%), acute myocardial infarction (MI) (10.4%), recent MI (35.4%), and silent ischemia (2.1%). Target lesion was LAD in 40%, L Cx in 12% and RCA in 44%, saphenous vein graft in 2% and left main in 2%. 56% of pts had complex characteristic lesions (B2-C). Two stent lengths were used (15 mm in 82% of the cases, 20 mm in 18%). The stent was used as a system, premounted in a balloon delivery system. The three balloon diameters used were 3 mm (48%); 3.5 mm (44%) and 4 mm (8%). High pressure balloons were used for stent deployment with a mean inflation pressure of 12.5 bars. 48% of the pts underwent individual inflation deployment, while 52% required one secondary dilatation. All 50 procedures were successful. No stents were lost during the procedure and no stenosis was found after stenting.

Clinical follow-up was obtained in 44/48 pts at 5.8 months. No deaths, MI or CABG occurred during this period. Target lesion revascularization was required in 2.3% (1/44 pts) and 2.27% (5/220 pts) in the other group of stenting with prior balloon dilatation

Conclusions: Primary stenting using the Tenax stent is a new and very encouraging technique. The clinical and angiographic outcomes of our preliminary experience suggest it is a promising design that needs further evaluation in larger randomized clinical trials.

P2700 Direct coronary stenting without balloon predilatation in selected lesions: short and mid-term results

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In order to simplify the procedure and to limit vessel injury, we prospectively studied the safety and efficiency of direct stent implantation without balloon predilatation in selected coronary lesions, using the balloon expandable ACS Multi-Link™ stent (15 to 28 mm length). Bifurcations with a significant side-branch and calcified lesions were excluded.

Methods: From November '95 to September '98, 395 patients (83% male) with 453 lesions were treated by this technique. Mean age was 63.8 ± 11.9 years. Clinical indications for stenting were unstable angina in 226 pts (57%), acute or recent MI in 98 (25%), symptomatic restenosis in 43 (11%) and silent ischemia in 28 (7%). Lesions were eccentric in 47%, angulated in 15%, ostial in 7%, with a mean length of 12.2 ± 6.5 mm (7–25) and a mean reference vessel diameter of 3.2 ± 0.7 mm. Procedure was mainly performed with 6F guiding catheters (96%).

Results: Primary stent crossing through the stenosis was successful in 440 lesions (97.1%); in the last 13 lesions, stenting was successfully performed after balloon predilatation. Complete stent deployment (mean inflation pressure = 14.3 ± 2.7 atm) was attained in 423/440 (96.8%); in the 17 others lesions, high pressure adjunctive PTCA with short balloon was required to achieve optimal stent expansion. Five threatening dissections occurred distally to the stent and were treated by a secondary stent. No major in-hospital complications were noted. Two symptomatic sub-acute coronary occlusions (0.5%) occurred during the first month. At 6 months follow-up, target lesion revascularization (TLR) concerning the 278 first patients was 5.9% (19/321 lésions).

Conclusion: Direct coronary stent implantation without balloon predilatation seems safe and efficient in selected lesions. The excellent initial and mid-term results must be validated by randomized studies.

P2701 Single-centre experience of direct stent implantation in 1,000 patients

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De novo coronary stenting has been validated in some coronary lesions by several randomized studies. In this setting, we used, from 10/95 to 12/98, direct stent implantation (DSI) without prior dilatation technique in 1000 pts excluding age > 70, onset of (related to the target artery) angina or MI > 3 months, TIMI 0 occlusion. Clinical indication were almost exclusively acute syndromes: unstable angina 52%, recent MI 26%, acute MI 13% and stable angina in 9%. Lesions were simple in 61% and complex in 39%. Clinical success was 98.2%, MACE rate was 1.4% and stent thrombosis was 0.5%. Additional balloon inflation was used in 23% and additional stenting in 4%. Technical success (defined as a successful deployment of the stent on the target lesion) was correlated with DSI/total stenting ratio in our practice and depends on the stent/delivery device system:

	Technical success	DSI ratio
Multilink™	94%	16%
RXMultilink™	86%	5%
NIRPrimo™	96%	25%
Multilink Duet™	97%	36%

All direct stenting failures were successfully treated with conventional technique. Stent loss rate was 0.3%. There were 3 cases of partial failure to deploy the stent with residual stenosis from 31% to 39%.

Thus, DSI is feasible in selected coronary lesions and its use is dependent on delivery device quality.

P2702 A randomized comparison of direct coronary stenting without angioplasty predilation and conventional stent implantation for acute coronary syndromes

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Background: Direct coronary stenting without balloon predilation has been shown to be an alternative strategy for treatment of highly selected coronary lesions in which stent implantation is planned. However no randomized study has been performed to assess the immediate and long term results of this new strategy of direct coronary stenting by comparison to conventional stent implantation after balloon predilation.

Methods: In the SWAP (Stenting Without Angioplasty Predilation) study, 120 patients with acute coronary syndromes eligible for coronary dilation were randomized to direct coronary stenting without balloon predilation (Group A) or to stent implantation after conventional balloon predilation (Group B). Highly calcified lesions, lesions in a tortuous vessel and persistent total occlusions after angioplasty guide wire placement were excluded. Only tubular premounted Nir® stents were used with high pressure stent deployement.

Results: Baseline clinical and angiographic characteristics of the study patients were similar in the two groups. No difference was observed in procedural success rates and the occurrence of no-reflow was indentical in both groups. Acute gain measured by quantitative coronary angiography was similar in the 2 groups. Duration of the procedure and radiation exposure time were shorter in group A ($p < 0.001$). The cost of the procedure was reduced in group A ($p < 0.01$). In-hospital and one month outcome (including death, acute myocardial infarction, target lesion redilation and bypass surgery) were not different between the two groups.

Conclusion: The present randomized study demonstrates the safety of direct coronary stenting without angioplasty predilation in selected acute coronary syndromes-related lesions. This new strategy of stent implantation reduces the cost of the procedure. One month clinical outcome is excellent and long-term follow-up is ongoing.

P2703 Comparison of three coronary stenting techniques in acute myocardial infarction angioplasty

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In order to define the best way to treat patients with acute myocardial infarction (AMI) using coronary stenting, we retrospectively studied in the last 15 months, all consecutive pts treated, in a single center, with angioplasty and coronary stenting in an occluded vessel (TIMI 0 or I) which was related to AMI (= 65% of all AMI PTCA). Pts were selected within 24 hours after the onset of symptoms. Rescue angioplasty after lytics failure and cardiogenic shocks were excluded from the study. Three groups were analyzed: A – AMI pts (N = 161) treated with direct angioplasty and conventional stenting after balloon dilatation, B – AMI pts (N = 64) treated with direct angioplasty using direct stent implantation without any prior dilatation technique (in this group, initial TIMI flow 0 or I became at least II after crossing of the wire through the occlusion), C – AMI pts (N = 23) receiving prehopsital (in intensive mobile care unit) infusion of abciximab 20 minutes before the angioplasty and treated with conventional stenting (using predilatation). Final flow was independently assessed in the three groups using TIMI classification and TIMI frame count measured with the distal landmark method. The rate of final TIMI III flow was identical in A and C groups (87%) and signficantly higher in B group (97%) compared to group A ($p < 0.05$). Mortality rate was lower in group B (0% versus 8% in group A, $p < 0.05$).

Thus, direct stent implantation without prior balloon inflation is associated with a higher rate of TIMI III flow and lower mortality than conventional stenting technique. If this benefit is a translation of a bias selection of pts with flow improvement after wire crossing or a real benefit due to thrombus and/or atheroma entrapment by direct stent deployment may be discussed. Additional benefit of abciximab infusion to direct stenting needs further studies.

P2704 Improvement of global and regional left ventricular function by rapid thrombectomy catheter angiojet after acute myocardial infarction

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Backgrounds: Late reperfusion has been reported to be useful for the prevention of left ventricular remodeling post acute myocardial infarction (AMI). However, adequate reperfusion of the infarct bed may be difficult to obtain in late reperfusion, because of a large amount of intracoronary thrombus. Thrombectomy catheter, AngioJet (POSSIS Medical, Inc. MN), may be useful for adequate restoration of infarct artery and myocardial salvage.

Methods: The goal of our study is to evaluate the effect of thrombus removal on LV myocardial salvage in late reperfused AMI patients. A total of 48 AMI patients presenting TIMI 0 flow and undergoing late reperfusion (elapsed time more than 12 hours) were enrolled in this study. Subjects were divided into 2 groups according to the reperfusion strategy. Group P consists of 25 patients underwent primary angioplasty, and group A consists of 23 patients underwent AngioJet followed by adjunctive angioplasty. Left ventriculogram was performed on admission and at 3 months follow up and ejection fraction (EF) and regional wall motion (RWM) by means of centerline method were calculated.

Results: There was no difference in elapsed time (group P: 14 ± 17 hours, group A: 19 ± 19 hours) and LV remodeling. Improvement of EF was significantly greater in group A more than that in group P (see table).

Serial changes in LV function

	Pre LVEF	Pre RWM	Change LVEF	Change RWM	Change EDVI	Change ESVI
Group A	46.1±12.9	−2.7±0.7	10.9±6.6	0.86±0.52	12.8±20.1	−6.7±11.6
Group P	55.1±13.1	−1.8±0.8	3.4±9.7	0.54±0.61	0.0±32.7	−1.0±17.8
P-value	0.06	NS	<0.02	0.10	NS	NS

Conclusions: These preliminary data may suggest that thrombus removal by AngioJet is an effective strategy for the recovery of left ventricular function in late reperfused AMI patients.

P2705 Coronary angioplasty with liberal use of stents in patients with unstable angina: clinical and electrocardiographic predictors of in-hospital outcome

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The clinical and electrocardiographic (ECG) presentation is a strong prognostic factor in patients (pts) with unstable angina (UA); its importance, however, is debated in patients treated with PTCA and liberal use of stents.

Methods: from 04/97 to 04/98 patients submitted to coronary arteriography due to UA in the participating centers were included in a prospective registry to monitor both the use of revascularization procedures and the acute outcome.

Results: of 987 pts included in the registry 571 (58%) were treated with PTCA: age was 62 ± 12 y, 123 were female, LVEF was 0.55 ± 0.1, 328 (57%) had multivessel disease. UA type IIIB or IIIC was present in 281/571 pts (49%). Refractory UA, prolonged (>10 min) chest pain, and both were present in 133, 217 and 85 pts, respectively. Stenting was performed in 486/571 pts (85%), and it was elective in 335; abciximab was used in 42 pts, and ticlopidine and/or aspirin in all. In-hospital major adverse cardiac events (MACE) (death, AMI, urgent CABG/re-PTCA) occurred in 29/571 pts (5.1%). Among clinical and ECG variables those shown in the table were significantly associated with a worse outcome. Pain-related ST-segment depression ≥ 1 mm, and ST-segment elevation/T-wave pseudo-normalization (present in 42% and 41.5% of pts, respectively) were not predictive of outcome after PTCA, although ST elevation was significantly associated with refractory + prolonged UA ($p = 0.001$) and UA classes IIIB or IIIC ($p = 0.0001$).

	Yes	MACE%	No	MACE%	χ^2	p
Prolonged UA	217	8.3	354	3.7	3.82	0.041
Prol. + refr. UA	85	11.7	486	3.9	9.26	0.006
IIIB or IIIC UA	279	7.2	292	3.1	4.94	0.02
Recent AMI	108	9.2	463	4.1	4.82	0.031
LVEF < 0.4	38	13.2	533	4.5	5.51	0.036

In *multivariate analysis* only prolonged + refractory UA ($p = 0.0056$) and LVEF < 0.4 ($p = 0.042$) were associated with MACE after PTCA.

In conclusion: prolonged + refractory UA and a low LVEF remain predictors of MACE before discharge in pts with PTCA and liberal use of stents.

P2706 Stenting of a total coronary occlusion in the course of an acute ischaemic syndrome carries a high rate of chronic restenosis

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In a population of 235 consecutive patients (182 M – 53 F) with acute ischemic syndromes, treated with stenting in the acute phase, we were able to repeat angiography in 221 pts (94%); patients who were not re-studied at 6 months refused the procedure; there were no deaths or re-hospitalization in these patients.

Two groups were analysed according to the anatomy at the initial presentation before the procedure:

– Group A: acute total occlusion of the culprit vessel before stenting (28 pts)
– Group B: patent culprit vessel before stenting (193 pts)

Fifteen patients were re-studied early (within 30 days) because of symptoms. The remaining population had control angiography at 6 months. Results were analysed using Fisher Exact Test.

Results: In the 15 patients studied at 30 days stent thrombosis or severely impaired flow within the stent was found in 3 out of 28 patients in Group A and in 12 out of 193 patients in Group B. In the remaining 206 patients re-studied at 6 months no stent thrombosis was found. Re-stenosis rate within the stent was however found in 9/25 (Group A) and in 33/181 (Group B):

	Thrombosis at 30 days	Restenosis at 6 months
Group A	3/28 (10.7%)	9/25 (36%)
Group B	12/193 (6.1%)	33/181 (18.2%)

Study Limitations: no GP IIb/IIIa antagonist were employed in this study.

Conclusions: 1. A high stent thrombosis rate was found at 30 days in both groups, with no statistically significant difference ($p = 0.29$ NS).

2. A higher chronic re-stenosis rate was evident in the group who presented initially with an occluded culprit vessel (36%; $p = 0.041$) while, in the group with initially patent vessel, the restenosis rate was comparable to that reported for elective procedures (18.2%).

P2707 Efficacy of heparin coated stent in the early setting of acute myocardial infarction

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Primary stenting for acute myocardial infarction(AMI) is being increased with improved late outcome compared to PTCA. However potent antiplatelets, anticoagulants and antithrombotic agent have been used, due to the risk of stent thrombosis. Heparin coated (HC) stent has been tested to decrease platelet deposition and thrombotic events compared to uncoated (UC) stent

The purpose of this study was to evaluate the effects of HC stent on the major cardiovasclular complications and safety in the early setting of AMI. Included patients arrived at the Cardiac Cath. lab. no later than 6 hrs from the onset of chest pain. Ninety nine patients were implanted with 108 HC stents (Corline Heparin Surface, Jomed. Sweden). 23 patients (23%) showed a large thrombus burden angiographically before stenting. No patients received postprocedural heparin or GpIIb/IIIa receptor antagonist (Abciximab) even in patients with a large thrombus burden. All patients were given aspirin indefinitely and ticlopidine for 4 weeks. Patency of infarct related artery was tested by CAG at 2 wks and 6 months, respectively.

The angiographic and procedural success rate were 100% and 98%, respectively.

	30 days	6 months
Major Adverse Cardiac Events		
Death (%)	2 (2/99)	4.8 (4/84)
Recurrent MI (%)	0	0
TLR (%)	0	6.0 (5/84)
Angiographic		
Reocclusion (%)	0 (0/82)	1.8 (1/55)
Restenosis (%)		12.7 (7/55)

Conclusion: HC stenting in AMI eliminated the need of postprocedural anticoagulation without significant increase in MACE and reocclusion, and with the acceptable restenosis rate. In addition, HC stent was safe and feasible even in the large thrombus burden.

P2708 Percutaneous transluminal ultrasound thrombolysis in native coronaries in the setting of acute coronary syndromes

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Percutaneous coronary ultrasound thrombolysis (CUT) in AMI induced effective reperfusion and myocardial salvage. The purpose of the Acolysis Registry was to investigate ultrasound thrombolysis in multiple clinical settings of intra-coronary thrombosis.

Methods: Patients (pts) with acute coronary syndromes and angiographically suggested thrombus were treated by CUT.

Results: Pts (n = 126) were mostly male (80%) and aged 55 ± 12 years. The vessels were occluded (TIMI grade 0–1) in 84%. The clot median age was 3 days (range 0–60 days). The pts presented with unstable angina (42%), myocardial infarction (29%), and post infarction angina (29%). CUT (41 kHz, 18 w) was attempted in the RCA (52%); LAD (38%); and LCX (10%). Successful recanalization (TIMI2–3) was achieved in 89% of the pts with residual stenosis of 69 ± 20%. Final angiogram revealed successful recanalization in 98% of pts (TIMI flow 3 in 94%) and residual stenosis of 6 ± 10%. Device-related adverse events were recorded in 1 pt with non-Q wave MI and 4 pts with angiographically-evident embolization. There were no deaths, emergent coronary artery bypass graft surgery, Q wave MI. Adjunct PTCA and/or stent was used in 97%. Reopro and thrombolytic agents were used in 16% and 2% (respectively) of the cases.

In conclusion: coronary ultrasound thrombolysis is a very safe and effective device solution for the treatment of high-risk, thrombus-rich lesions in the native coronary arteries.

P2709 30-day mortality after early invasive approach in unstable coronary artery disease

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Background: There is an ongoing debate whether patients with unstable coronary artery disease (UCAD) should be treated conservatively or with an early revascularisation. The TIMI III B and the VANQWISH studies did not show any reduction of death/MI by an invasive strategy. In the latter there was an unexpectedly high mortality rate (11.6%) in patients treated with CABG. We report the 30 days mortality in the invasive group in the FRISC II trial and relate the mortality to patient characteristics.

Method: In the FRISC II-trial 2456 patients with UCAD were randomised to a direct invasive strategy (n = 1223) with coronary angiograms and, if appropriate, early revascularisation within the first 7 days or to a noninvasive approach. Patients with previous CABG were excluded. All patients were treated with s.c. lmwh (dalteparin) b.i.d. until revascularisation.

Results: 1223 patients were randomised to invasive strategy. Angiography was performed in 98.1%, CABG in 35.2%, PTCA in 42.7%. Median time from admission to PTCA and CABG was 3 and 7 days respectively. 15 patients (1.2%) died within 30 days from randomisation/revascularisation – 9 after CABG, 1 after PTCA and 5 after angiography before revascularisation. The 30 days mortality after CABG was 2.1%, PTCA 0.2%.

Pt characteristics	Alive 30 days	Dead 30 days	
n	1208	15	
Age (mean ± SD)	64.7 ± 9.3	73.2 ± 5.7	p < 0.001
Female sex	28.3%	60%	p < 0.02
Diabetes	12.2%	53.3%	p < 0.001
Previous MI	22.4%	53.3%	p < 0.01
ST-depression at entry	45.1%	71.4%	p < 0.05
3 VD or main stem stenos	29.8%	79.6%	p < 0.001

Conclusion: In UCAD early revascularisation can be performed with a low mortality. However, the risk is increased at high age, female sex, diabetes, previous MI, ST-depression at entry and advanced coronary artery disease.

P2710 Comparison of outcome of recurrent and first acute myocardial infarction patients in Israel in 1992–1996

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Patients (pts) with recurrent myocardial infarction (MI) are at increased risk for complications and death. However, the impact of therapeutic interventions on their outcome has not been assessed.

Methods: We compared 1093 recurrent MI pts (26%) with 3202 first MI pts (74%) included in the National Israeli Thrombolytic Survey conducted during 1–2/92, 1–2/94 and 1–5/96 in the 25 coronary care units operating in Israel.

Results: 7-day, 30-day and 1-year mortality was 10, 16, and 26% in pts with recurrent MI vs. 6, 9 and 14% among first MI pts, respectively. The relative risks of mortality ± 95% confidence interval, adjusted for age, gender, hypertension, diabetes, prior angina, anterior MI, Killip class, thrombolysis, or revascularization-(PTCA/CABG), were as follows:

	7-day	30-day	1-year
Thrombolysis treated pts			
Recurrent MI	1.69 (1.09–2.65)	1.51 (1.03–2.23)	1.18 (0.90–1.55)
First MI	0.94 (0.68–1.30)	0.84 (0.64–1.18)	0.79 (0.64–0.97)
Early CABG or PTCA treated pts			
Recurrent MI	0.36 (0.16–0.73)	0.45 (0.23–0.77)	0.66 (0.46–0.96)
First MI	0.37 (0.19–0.64)	0.55 (0.36–0.83)	0.66 (0.48–0.90)

Conclusions: This study suggests that thrombolytic therapy is not beneficial in pts with recurrent MI and that they should probably undergo early revascularization. The data of this study need confirmation in prospective, randomized trials.

P2711 Improved survival rate for stented lesions after a strategy of provisional stenting for acute coronary syndromes and myocardial infarction

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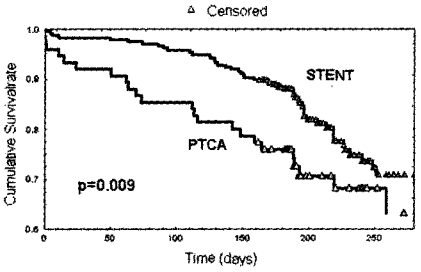
Treatment of myocardial infarction and acute coronary syndromes by means of immediate coronary angioplasty is still a matter of debate. We investigated retrospectively the clinical outcome of patients treated with coronary angioplasty within 24 hours after onset of symptoms. Stents were deployed if an optimal PTCA result could not be achieved (visual estimation of residual stenosis < 20%). We investigated 2 groups: pts receiving a Stent 237/312 (77%) or not (POBA) 75/312 (23%). 243 pts with 312 lesions were included in this cohort. Follow up was completed for 6 month, mean follow up time 208 days (213 and 193 days respectively).

Patients: Age 61 ± 11 years, 77% male, 50% former MI, Angioplasty was successful (residual stenosis < 50%, no MACE) in 71% of the PTCA group and 99% of the Stent group. When pts were admitted to the cathlab 29% (POBA) and 32% (STENT) had an occluded vessel. Procedure was successful in 80% (POBA) and 99% (STENT). 1 Death and 1 CABG occurred in the POBA group, 1 MI in the STENT group. Major cardiac events during follow up are listed below:

% (n)	Death	MI	CABG	Re-PTCA
POBA	8% (4)	2% (1)	13% (6)*	27% (13)
Stent	4% (7)	2% (5)	4% (7)	22% (42)

* p = 0.015, MI = Myocardial Infarction

The lesion specific MACE survival rate is shown in the figure.



Conclusion: In a strategy of provisional stenting in patients with acute MI or coronary syndromes, stenting improves significantly late outcome, despite a sufficient angiographic result after acute PTCA.

RESTENOSIS

P2712 Predictors of recurrent restenosis after rotational atherectomy of diffuse in-stent restenosis at 6-month angiographic follow-up: a serial intravascular ultrasound study

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Treatment of long and diffuse in-stent restenosis (ISR) remains challenging. Rotational atherectomy (RA) with adjunct PTCA is an alternative therapeutic approach in this clinical setting based on the concept of "tissue debulking". This study was intended to determine clinical, procedural, angiographic and intravascular ultrasound (IVUS) predictors of recurrent ISR at 6-month angiographic follow-up.

Methods: RA with adjunct low-pressure PTCA was performed in 40 patients with diffuse ISR (lesion length: 22 ± 20 mm). Serial IVUS measurements were performed before intervention, post RA and after adjunct PTCA. Follow-up angiography was available for all patients 6 ± 1 month after RA.

Results: Procedural success was achieved in all patients. Recurrent restenosis (>50% diameter stenosis [DS] by quantitative angiography) was observed in 18/40 patients (45%). Predictors of recurrent restenosis are given in the table. Target lesion revascularisation rate (TLR) at 6 month was 38% (15/40 patients).

	Restenosis	No Restenosis	p-value
Baseline DS (%)	83 ± 22	72 ± 17	<0.01
Stent Length (mm)	40.5 ± 21.3	21.5 ± 14.1	<0.001
Lesion Length (mm)	35.1 ± 20.2	15.2 ± 14.1	<0.001
Neointimal Recoil (%)	23.2 ± 13.6	8.9 ± 8.3	<0.001

Conclusions: RA with adjunct PTCA is an effective treatment strategy for diffuse ISR and results in a recurrent restenosis rate of 45% at 6-month angiographic follow-up. Diameter stenosis before intervention, total stent length, total lesion length and amount of acute neointimal recoil after RA were identified as predictors of recurrent restenosis.

P2713 A higher average shear stress is paradoxically predictive of restenosis and/or mace after balloon angioplasty in human coronary arteries

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Background: Vascular wall shear stress (WSS) is the frictional force exerted by the flowing blood at the vessel wall of the artery. In animal models, a higher WSS after balloon angioplasty (BA) has been associated with reduced intimal hyperplasia. Up to now, direct measurements of WSS and its impact on the outcome of balloon angioplasty – major adverse cardiac events (MACE) and/or restenosis (R) – have not been investigated in human coronary arteries.

Methods: For the patients (p) included in the DEBATE I trial where the predictive value of intracoronary Doppler flow velocity measurements for clinical outcome has been investigated, we have computed WSS following the Hagen-Poiseuille formula: WSS = 4 mu Q/pi r^3, with mu being blood viscosity (0.003 Ns/m^2), Q blood flow (m^3/s), r radius (m) of the coronary vessel, measured by quantitative angiography. After BA, Doppler data where available in 202 p distally to the lesion, in 56 p in the treated lesion and in 183 p proximally. We compared WSS between patients with and without MACE and/or R.

Results are summarized in the table. A multivariate logistic regression analysis demonstrated that with the measurements available at the site of angioplasty (minimal lumen diameter (MLD) and in-lesion average peak velocity), WSS in the lesion was the only predictor of MACE or restenosis (r = 0.22, p = 0.02). MLD, diameter stenosis and coronary flow reserve were excluded as statistically significant independent predictors of the clinical outcome.

Results

Mean (sd) [N m^{-}]	MACE or R (n = 72)	No events (n = 130)	p (Wilcoxon)
WSS prox	1.29 (0.62)	1.07 (0.54)	0.013
WSS in-lesion	4.51 (2.41)	2.97 (1.57)	0.016
WSS distal	0.76 (0.46)	0.84 (0.40)	0.028

Conclusion: The results of our study show that acute high shear stress in a treated lesion after balloon angioplasty might not be as beneficiary as previously assumed. Possibly, a higher shear stress at the post-PTCA site, presenting arterial wall injury, might enhance mural thrombus formation, with increased restenosis induction.

P2714 Repeated percutaneous interventional procedures for coronary in-stent restenosis: a quantitative angiographic study

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Several studies suggest that repeated percutaneous balloon angioplasties at the same coronary lesion are associated with a progressively increased risk of restenosis and that short time intervals between successive procedures are predictive of subsequent restenosis. We assessed the probability of angiographic restenosis when repeated percutaneous transluminal coronary interventions (repeated stent or repeat PTCA) were performed for lesions with restenosis after previous coronary stent placement.

Methods: Follow-up angiography was routinely advised after all procedures. Restenosis was defined as recurrence of ≥50% diameter stenosis determined by quantitative coronary angiography. Subject of the study were 1824 consecutive patients with successful coronary stent placement in 2307 lesions.

Results:

	Primary Intervention (2307 lesions)	First Reintervention (389 lesions)	Second Reintervention (78 lesions)
Incidence of restenosis, %	30	39	49
Target lesion revascularization rate, %	17	20	26

In multivariate analysis diabetes, small vessel size, long and complex lesions were predictive of recurrent restenosis. In addition, the number of previous interventions and a shorter time interval up to the reintervention were also predictive of restenosis.

Conclusions: Repeated interventions at the coronary lesion previously treated with stent placement are associated with a progressive increase in the restenosis rate. Factors known as predictors for the first occurrence of restenosis continue to play this role also for recurrences. The number of reinterventions is an independent risk factor for restenosis. Other forms of therapy should be sought for patients with recurrent restenosis.

P2715 Quantitative coronary angiography and myocardial fractional flow reserve for evaluation of in-stent restenosis

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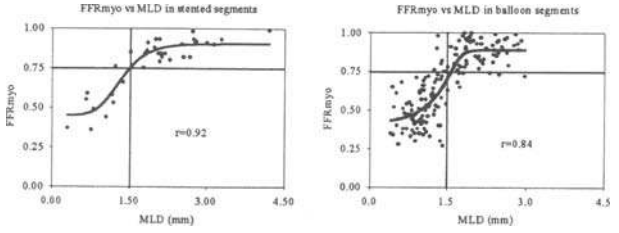
Background: Due to the angiographic limitations of assessing the severity of instent restenosis (R), we evaluated myocardial fractional flow reserve (FFRmyo), derived from the transstenotic pressure gradient. We hypothesized that the benefit of stenting (S) is not only due to the larger minimal luminal diameter (MLD, mm) but also the circular anatomy.

Methods: Quantitative angiographic analysis (QCA) and FFRmyo were measured in 38 stents (36 pts, mean age 59 y; 27 male) at 253 ± 139 days after S (fig. left) and compared to 110 'de novo' stenotic segments, treated by balloon angioplasty (fig right).

Results: The mean angiographic diameter stenosis (DS, %) was 33 ± 21. The R rate (DS ≥ 47, cut-off value for lesion significance according to Gould) was 32%. The mean MLD at follow up was 2 ± 0.85 with a reference vessel diameter of 2.88 ± 0.55. The measured mean FFRmyo at follow-up was 0.78 ± 0.17. As illustrated, there is a better relationship between FFRmyo and MLD in stented arteries than in balloon arteries.



Conclusions: (1) QCA correlates significantly with FFRmyo in chronically stented arteries and (2) the relation between QCA and FFRmyo is tighter in stented versus balloon segments. Thus, at seemingly identical MLD, the better FFRmyo after S may be due to a better luminal symmetry, resulting in a larger cross sectional area.

P2716 A novel quantitative parameter for evaluating diffuse in-stent narrowing at follow-up angiography

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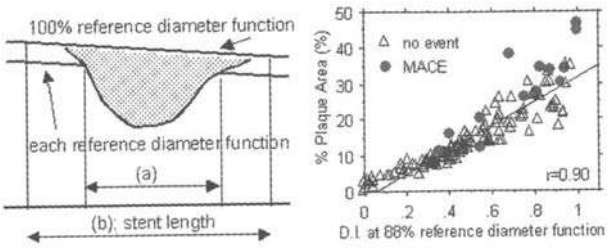
It is important to know whether in-stent restenosis is of a diffuse or focal nature, since diffuse stenosis may more easily lead to myocardial ischemia physiologically. The plaque volume in the stent is also important because plaque-rich stenosis may need subsequent therapy to reduce the incidence of restenosis after re-intervention. The purpose of this study, therefore, is to establish a new parameter for the objective description of the degree of diffuse or focal disease within the stent and to evaluate its relation with clinical events.

Methods: A total of 105 patients (134 lesions) with Wiktor-GX® Stents were evaluated at follow-up angiography. According to the QCA-CMS® definition, lesion length is derived from the 100% reference diameter function. By moving the reference diameter function downwards in the diameter function, the lesion length at each percentage of the diameter function can be calculated. Dividing this length (a) by the stent length (b) provides a Diffuse Index (D.I. = a/b), a value between 0 and 1, indicating little or diffuse plaque throughout the entire stent, respectively. The percentage plaque area (%PA) was calculated by dividing the plaque area by the sum of the plaque and luminal area within the stent. Major Adverse Cardiac Event (MACE) was defined as death, myocardial infarction, or Target Lesion Revascularization (TLR).

Results: There was a good correlation between the D.I. at 88% reference diameter function and the%PA (r = 0.90). The combination of D.I.> 0.75 and %PA > 25% resulted in a high incidence of subsequent MACE (9/20).



Diffuse Index.

Conclusions: The combination of percentage plaque area (%PA) and the new parameter Diffuse Index (D.I.) is valuable in the clinical decision making process of TLR.

P2717 Comparison of different strategies to detect restenoses after intracoronary stenting

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After intracoronary stenting the restenosis rate is reported to be in the range of 20%–30%. Still the optimal strategy for detection of patients with relevant restenoses is still a matter of debate. Thus, we compared 4 different strategies for the indication for controll angiography in 200 consecutive patients (pat.) with single-vessel-disease.

Method: All pat. presented with single-vessel-disease which was treated with at least 1 intracoronary stent. All pat. reported of angina pectoris (AP) and all pat. had angiographic controll between 4 and 12 months after stenting. Before angiographic controll pat. were asked for recurrent AP and a stress-ECG was performed. Restenosis was defined as diameter stenosis of at least 50% within the stented segment. We compared the sensitivity and specifity of 4 different noninvasive strategies to detect restenosis: 1. all pat. with recurrent AP (AP) have controll angiography 2. all pat. with recurrent AP and abnormal S-ECG (AP and S-ECG) have controll angiography 3. all pat. with recurrent AP and/or abnormal S-ECG (AP and/or S-ECG) have controll angiography 4. all pat. with abnormal S-ECG (S-ECG) have controll angiography.

Results: Restenosis rate was 28%. The table shows specifity and sensitivity.

Strategy	Sensitivity	Specificity
AP	73%	77%
AP and S-ECG	48%	68%
AP and/or S-ECG	38%	89%
S-ECG	84%	56%

Conclusion: The sensitivity and specificity were high for recurrent AP. Sensitivity by selecting pat. with recurrent AP and abnormal S-ECG. Nevertheless 16% of patients with restenosis will not be detected with noninvasive strategies.

P2718 In-stent restenosis: predictors of target lesions revascularization after repeat intervention

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Background: In-stent restenosis (ISR) can be safely treated by repeat percutaneous procedure (rePTCA). Reported subsequent target lesion revascularization (TLR) have varied from 20% to 80% and seem related to the type of restenotic lesion.

Methods: 262 rePTCA for ISR performed in 239 pts between May 1995 and January 1998 were retrospectively analyzed to identify any possible predictors of subsequent TLR. RePTCA was performed using balloon only (89%) or non-elective additional stenting (11%). Unstable angina was reported in 53.8%, stable angina in 42.7% and recent MI in 3.3%. Mean ISR-lesion length measured by Quantitative Coronary Arteriography was 16.7 ± 8.6 mm. Lesion characteristics were defined as FOCAL (≤10 mm), DIFFUSE (>10 mm within the body of the stent), PROLIFERATIVE (>10 mm beyond the stent margins) or total occlusion, and were present in 37%, 30%, 29% and 4% respectively. Reference Diameter was 3.08 ± 0.36 mm and post-rePTCA MLD was 3.07 ± 0.35 mm.

Results: The long-term clinical follow up (394 ± 232 days) was obtained in 229 pts (96%) and showed 1.7% total mortality and 19.1% TLR. The 6-month event free survival rate was 0.83 ± 0.02 (95% CI 0.78–0.87). The multivariate predictors of TLR after rePTCA are shown in Table:

Variables	Hazard ratio	95% CI	P Value
Time to ISR < 90 days	4.46	2.08–10.47	<0.0001
ISR pattern	1.59	0.93–2.71	0.088
Reference Diameter	0.34	0.13–0.91	0.030

Conclusion: Smaller post-rePTCA MLD and early intimal proliferation are independent predictors of TLR.

P2719 Six-month clinical and angiographic results of rotational atherectomy for in-stent restenosis

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Background: Long-term results of balloon angioplasty for the treatment of intrastent restenosis (IR) have been disappointing with a rate of recurrence approaching 80%. The few reported studies on rotational atherectomy (RA) have not explored long-term angiographic restenosis.

Objectives: To study efficacy and safety of RA for the treatment of IR.

Methods: We analyzed the acute clinical and angiographic results of 114 consecutive cases and clinical and angiographic six-month follow-up. 128 stents (30% P-Schatz, 23% Wiktor, 7% Wallstent, 11% AVE, 9% Multilink, 20% others) with IR (60% diffuse) were treated with RA.

Results: Lesions were located in LAD (48%), RCA (37%), LCX (14%) and SVG (1%). Procedural success (<50% residual stenosis without major complications) was 97%. There were three cases of non-Q wave myocardial infarction (MI). No death, emergency surgery or Q-wave MI were observed. 195 burrs were used; mean burr/artery ratio was 0.79 ± 0.16. Balloon PTCA at a mean deployment pressure of 8.8 ± 3.18 atm was performed in 108 cases. IR was reduced from a mean of 67.05 ± 13.9% to 24.8 ± 11.1%. IVUS was performed in 22 cases, showing an acute gain of 1.51 ± 1.0 to 4.8 ± 0.98 mm^2 after the procedure. 96 patients (p) completed 6-month follow-up. None died during follow up. One p suffered MI and 2 p were referred for elective surgery. Clinical restenosis occurred in 14 (19%). In 73 p (70%) angiographic evaluation was performed showing restenosis in 28 (39%). A burr size < 2.15 mm was the only predictive factor of recurrence of restenosis (p < 0.005).

Conclusions: RA for the treatment of IR can be performed with a high rate of procedural success. RA can be considered the most effective device to treat IR.

P2720 Treatment of diffuse in-stent restenosis: short and long-term results of excimer laser angioplasty versus rotational coronary atherectomy

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Background: Debulking with either excimer laser angioplasty (ELCA) or rotational atherectomy (RA) each appear to improve late recurrence in diffuse in-stent restenosis (ISR) lesions compared to balloon angioplasty alone, but there have been no comparative studies of these debulking strategies.

Methods and Results: We compared 250 diffuse ISR lesions in 182 patients treated with ELCA (n = 124) or RA (n = 126). Baseline patient characteristics, total occlusions (8%), stent use (27%), and angiographic success (100%) were similar in the two groups. Quantitative coronary angiography was performed and patients were followed-up clinically (table).

	ELCA	RA	p
SVG lesions (%)	43.4	5.6	<0.001
Lesion length (mm)	16 ± 2	18 ± 2	NS
Ref. Diam (mm)	2.98 ± 0.57	2.85 ± 0.41	0.02
Final Diam. Stenosis (%)	18.1 ± 5	18.7 ± 4	NS
In-hosp. Non-Q-MI (%)	9.8	7.9	NS
In-hosp. MACE* (%)	3.4	0	0.06
One-year TLR** (%)	31.4	21.6	0.05

*MACE = death/MI/urgent intervention; **TLR = target lesion revascularization

Conclusions: (1) Similar procedural results are achieved with both ELCA and RA; (2) There is a trend towards reduced in-hospital MACE with RA, possibly due to fewer SVG lesions; (3) Despite smaller vessel size, RA use was associated with lower TLR, suggesting that higher ablation efficiency may impact late clinical outcomes. A prospective, randomized clinical trial should compare these two athero-ablative strategies as an adjunct to balloon angioplasty for the treatment of diffuse in-stent restenosis is indicated.

P2721 In-stent restenosis patterns predict subsequent target lesion revascularization after treatment with balloon angioplasty

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Background: In-stent restenosis (ISR) can be safely treated by repeat percutaneous procedure (rePTCA). Reported subsequent target lesion revascularization (TLR) have varied from 20% to 80% and seem related to the type of restenotic lesion.

Methods: Different angiographic patterns of ISR and their role in predicting the need of subsequent TLR at 6 months and at 12 months follow-up were retrospectively analyzed in 262 ISR lesions treated with rePTCA (balloon only 89%; non-elective additional stents 11%) for ISR performed in 239 pts between May 1995 and January 1998.

Results: Patterns of ISR were: 37% FOCAL (length ≤ 10 mm), 30% DIFFUSE (length > 10 mm within the body of the stent), 29% PROLIFERATIVE (PROLIF) (length > 10 mm beyond the margins of the stent) and total occlusion (TO) 4%.

At long-term follow-up (381 ± 230 days) the likelihood of TLR for proliferative and diffuse patterns versus focal ISR, was 2.69 (95% CI = 1.18–6.10; p = 0.02) and 1.94 (95% CI = 0.82–4.59; p = 0.12) respectively. The TLR rate at 6 and at 12 months for different patterns is as follows:

TLR	FOCAL	DIFFUSE	PROLIF	TO	P value
6 months	6/64 (9.4%)	12/62 (19.4%)	14/62 (22.5%)	2/9 (22%)	0.05*
12 months	7/46 (15.2%)	14/44 (31.8%)	18/48 (37.5%)	2/8 (25%)	<0.05*

P value for linear trend Focal < Diffuse < Proliferative < Total.

Conclusion: After the treatment of ISR with balloon or additional stenting, increasing severity of restenosis pattern correlates with increasing TLR.

P2722 The interaction of lesion length and vessel size on incidence of angiographic restenosis rate after stenting

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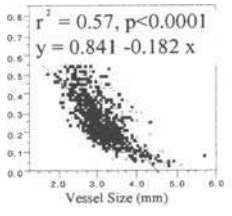
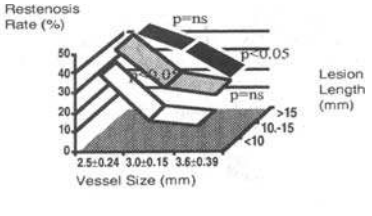
Aim of this study is to investigate the risk factor of angiographical restenosis after percutaneous coronary stenting.

Method: We analyzed the restenosis rate after coronary stenting in 1670 consecutive patients treated using high balloon pressure with IVUS guide. The logisitic regression (LR) on 42 variables found the lesion length (LL) and vessel size (VS) the most important predictors of restenosis. The left figure show high linear correlation Fit of LR probability of VS for restenosis. On the right is the interaction of LL and VS on restenosis analyzed at level of three typical vessel sizes.





Conclusions: Restenosis rate after coronary stenting ranged 13%–45% and was influenced by LL and VS. A decrease in reference vessel size bellow 3.0 mm and an increase in lesion length significantly increased the restenosis rate. An increase above 3.0 mm in vessel size lowered the restenosis rate only in lesion with the length of >15 mm. These finding may help to guide stent implantation.

P2723 A study of autopsy vessels after stenting

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Alterations of the vessel wall immediately after implantation of stents are analyzed in experimental studies but human vessel data immediately after stenting are rare. We analyzed vessels of 18 patients who died after coronary interventions. The formaline fixed arteries were cut serially and evaluated semiquantitative. The average age of the patients was 58 years and all showed multiple vessel disease, 50% with severe impairment of cardiac ejection fraction. 90% had unstable angina before the intervention. The reasons for fatal events were as follows: 10 patients died due to sudden cardiac events, 7 had relevant concommitant diseases and two patient were transplanted. All patients had balloon angioplasty before stent implantation was performed.

All explanted vascular segments had significant plaque burden leading to lumen reduction even if the angiographic lumen was not impaired and showed variation of plaque burden, calcification, tissue hyperplasia and foam cell clusters. The interventional treated vessel segments showed longitudinal and circumferential dissections. Three vessels had dissections not covered with stents leading to total lumen occlusion. Additional thrombotic occlusions were seen in five vessels, all segments had thrombotic appositions. Immediately after angioplasty the treated vessel segments revealed massive infiltration with neutrophile granulocytes close to the dissection. Later than two days the leukocytes were mainly located at the stent struts (30–50% of all present struts). At sites of neutrophile infiltration, the fraction of synthetic myocytes with abundant endoplasmatic reticulum, reduction of contractile filaments was increased, and an increased proliferation ratio (3.5% vs. 0.3%) was found in areas without dissection

Immediately after interventional treatment an intense cellular infiltration was found triggered by mechanical trauma. This intensive infiltration of neutrophils was followed by myocyte proliferation.

P2724 A new method for external heat delivery in arterial stents in vivo: a promising tool to stimulate cell apoptosis and prevent restenosis?

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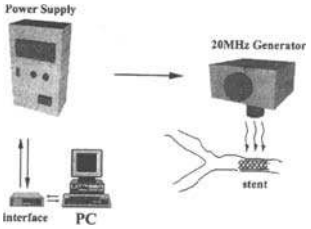
Background: Cell apoptosis is an important mechanism involved in the process of restenosis after coronary interventions. It has been suggested that heating of tissues may induce cell apoptosis.

Methods and Results: To induce heating of arteries in vivo we have developed a new method that uses electromagnetic energy to heat metals from a distance. Electromagnetic energy of a high-power 20 MHz generator is driven to a specially designed inductor to create an alternating magnetic field. Voltage and current drain are fully controlled by a personal computer (PC). As the magnetizing force on the metallic target (i.e. stent) periodically changes, additional energy is drained from the generator (to compensate for the lagging of the magnetizing flux) and appears on the metallic target as heat. This type of energy heats only metals leaving other materials or tissues unaffected. Thus, stents within the body can be heated from the outside and subsequently transmit heat to their surrounding tissues.

By regulating the generator's output power we achieved in in-vitro and in-vivo studies (femoral arteries, 5 pigs) effective heating of metallic stents of different compositions up to 100°C from a distance of 15 cm. Moreover, the nitinol stents were expanded remotely in a controlled fashion.



Conclusions: This new method that uses electromagnetic energy to heat metallic stents from a distance may be used for thermotherapy of coronary arteries after coronary stenting with the aim to reduce restenosis or for remote re-expansion of nitinol stents.

P2725 Fucoidan inhibits vascular smooth muscle cell proliferation and migration and is suitable for coating of stents

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Proliferation of vascular smooth muscle cells (SMC), a major pathomechanism of restenosis after PTCA, is stimulated by growth factors released from activated platelets. Fucoidan is a polysaccharide with subfractions of different molecular weight: FF7/1 (150 kD), FF7/2 (100 kD) and FF7/3 (50 kD). We investigated the effects of these fractions on SMC proliferation, platelet activation and aggregation.

Proliferation of cultured human vascular SMC incubated with different fucoidan fractions was analysed by growth assays. Platelet rich plasma of healthy volunteers was incubated with FF7/1, FF7/2 and FF7/3 at concentrations of 1.10 and 50 μg/ml. Platelet activation dependent expression of p-selectin and glycoprotein 53 was quantified by flow cytometry with antibodies CD62p and CD63. Platelet aggregation (PA) was measured by turbidimetry.

Proliferation of SMC was inhibited dose-dependently by FF7/1 and FF7/3 (FF 7/1: 39 ± 4%, FF7/3: 51 ± 3% vs control, $p < 0.05$). Platelets were activated by FF7/1 (+9.5 ± 2.3% and +7.0 ± 2.5% CD62p and CD 63 signals vs control, $p < 0.05$) whereas FF7/3 did not activate platelets significantly. PA was dependent on the fucoidan concentration and on the molecular weight. PA was stimulated by the high molecular weight fraction FF7/1, whereas the low molecular weight fraction FF7/3 did not induce a significant change of PA compared to control (FF7/1 vs FF7/3: 26.7 ± 14.2% vs 7.8 ± 3.5% increase in light transmission, $p < 0.02$).

Conclusions: Fucoidans inhibit proliferation of human SMC. The low molecular weight fraction, which does not activate platelets, may be useful for the prevention of restenosis and for coating of stents.

P2726 Separate and combined effects of continuous intravenous administration and local delivery of β-cyclodextrin sulfate (CDT) on intimal hyperplasia after angioplasty in swine

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Beta-cyclodextrin-sulfate (CDT) binds basic fibroblast growth factors, is anticoagulative, and reduces intimal hyperplasia after continuous IV infusion or perivascular placement in rats. We assessed the separate and combined effects of continuous IV administration and local delivery of CDT on neointimal formation in the porcine coronary arteries following balloon injury, using a 2 × 2 factorial design.

Pigs were randomized into 4 groups: 1) control, 2) continuous IV of 100 mg CDT/kd/d, 3) intramural delivery of 1250 mg CDT, 4) continuous IV of 100 mg CDT/kg/d and intramural delivery of 1250 mg CDT. Intramural delivery was performed using a Cordis Crescendo Catheter. Vessels were harvested at 14 days and evaluated for the maximal intimal thickness (MIT) and intimal area (IA) which was normalized to the injury index (II). Damage related to the local delivery was assessed by the II and combined histological criteria including adventitial rupture, retromedial hematoma, aneurysm and dissection.

	Control (n = 22)	Local (n = 22)	IV (n = 22)	IV + Local (n = 22)
MIT (mm)	0.45 ± 0.1	0.38 ± 0.1†	0.29 ± 0.6*	0.27 ± 0.1*
II	0.21 ± 0.1	0.25 ± 0.2	0.26 ± 0.1	0.22 ± 0.1
IA/II (mm^2)	2.82 ± 0.6	3.03 ± 4†	1.67 ± 0.7*	1.95 ± 0.8*
Damage (%)	6 (27%)	5 (23%)	7 (32%)	7 (32%)

Mean ± SD: *$p < 0.005$ vs control: †$p < 0.05$ vs IV and IV + local.

Conclusion: Intravenous administration of CDT had substantial effect on intimal hyperplasia while intramural delivery had no effect. No additional arterial injury is observed after delivery with a medication with anti-coagulation properties.

P2727 Local delivery of paclitaxel before stent implantation in a porcine restenosis model

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Paclitaxel is a new microtubule stabilizing drug with potent antitumor activity. It influences the cytoskeleton equlibrium by increasing the assembly of stable microtubules and thereby interacts with many cellular functions. The aim of this study was to evaluate the potential of paclitaxel to prevent restenosis in vivo after intracoronary stent implantation.

Methods: After local intracoronary delivery of 10 ml paclitaxel (10 μmol/l) with the double balloon perfusion catheter tantalum stents were placed in the application area of the left anterior descending artery in 10 pigs (balloon vessel ratio 1.1–1.3). Fourteen pigs served as control with stent implantation only. Vessels were excised 4 weeks following intervention. All pigs received 5,000 units of heparin at the beginning of the procedure and were treated with 100 mg aspirin daily starting three days before. Histopathology was performed on all vessels. Morphometric parameters of restenosis and vascular remodeling namely neointimal area (NA), percent area stenosis (PAS) and vessel area (EEL) were measured.

Results: No significant difference was observed in both groups in regard to NA (2.36 $\pm$ 1.03 mm^2 vs 4.09 $\pm$ 2.06 mm^2), PAS (46.9 $\pm$ 17.0% vs 66 $\pm$ 20.7%) and EEL (4.95 $\pm$ 0.95 mm^2 vs 6.24 $\pm$ 2.12 mm^2).

Conclusion: Local paclitaxel delivery had no beneficial effect on restenosis after stent-implantation. The lack of efficacy is most probably due to the strong and continous proliferative action of the metal stent.

P2728 Catheter-based delivery of ribozymes targeting PCNA mRNA after stenting reduces neointimal hyperplasia in a porcine model

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Background: In-stent stenosis caused by neointimal hyperplasia may potentially be inhibited by cytostatic therapy based on molecular biology techniques.

Methods: We synthesized chimeric DNA:RNA hammerhead ribozymes (Rz) directed against mRNA coding for the key cell cycle regulatory protein PCNA (proliferating cell nuclear antigen). The ribozymes combined with a lipid vehicle were delivered intramurally using a microporous catheter (Crescendo®, Cordis, Miami, FL.) after placement of a nitinol stent in nonlipemic porcine coronary arteries. Control arteries were stented without ribozyme. Angiographic follow-up and histomorphometry were performed at the 30-day timepoint.

Results: Angiographic minimal lumen diameter (MLD) at follow-up was improved in Rz-treated vessels compared to controls, and final percentage diameter stenosis was reduced (see Table). Histomorphometric data will also be presented.

QCA results

	N	Ref. Vessel (mm)	MLD (mm)	Diam. Stenosis (%)
Control	9	3.0 $\pm$ 0.4	1.2 $\pm$ 0.4	60 $\pm$ 12
Rz	8	2.8 $\pm$ 0.3	1.7 $\pm$ 0.5*	40 $\pm$ 17*

*P < 0.05 vs. control

Conclusion: Anti-PCNA ribozymes delivered locally after coronary stenting reduce in-stent stenosis in the porcine model. Plans for clinical evaluation are underway.

P2729 Statin therapy substantially reduces restenosis after coronary stent implantation in patients with the PI^{A2} glycoprotein IIb/IIIa receptor polymorphism

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Background: The platelet GPIIb/IIIa PI^{A2} polymorphism has been associated with the occurrence of acute coronary syndroms and higher risk of coronary stent thrombosis. Platelets also play a central role in restenosis development by inducing neointimal proliferation after coronary interventions. Besides lipid lowering effects, statins exhibit antiproliferative, antiinflammatory and antithrombotic properties, thereby potentially interfering with the major processes of in-stent restenosis.

Methods: Therefore, we investigated the effect of statin therapy on clinical and angiographic outcome in the presence or absence of the PI^{A2} allele in 506 patients following successful coronary stent implantation.

Results: (6 month follow-up)

Stent-Restenosis ≥50%	No Statin N = 250	Statin N = 256	p-value
PI A1/A1-Genotype	68/197 (34.5%)	55/200 (27.5%)	0.1
PI A1/A2-Genotype	25/53 (47.2%)	15/56 (26.8%)	0.02

The occurrence of major adverse coronary events (myocardial infarction, death, need for target vessel revascularisation) during 6 month follow up was substantially reduced among patients with the PI^{A2} allele receiving statin therapy (49.1% vs. 28.6%, p = 0.02).

Conclusion: Statin therapy dramatically abrogates stent restenosis and improves clinical outcome in patients bearing the PI^{A2} allele, suggesting that statins preferentially reduce neointimal proliferation after stent implantation in those patients.

IMAGING IN ONE EMERGENCY DEPARTMENT

P2730 Is myocardial perfusion by echocardiography useful in the management of patients with chest pain in the emergency department?

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Background: We previously showed that myocardial perfusion is accurately assessed by myocardial contrast echocardiography (MCE) 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 MCE to identify the perfusion patterns in these pts.

Methods: 49 pts (35 male, 59 $\pm$ 14 years, 28–90) 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: 21 pts; and C-non-suggestive of angina: 17 pts. MCE with triggered (1:1) 2nd harmonic imaging, was visually assessed (2 independent investigators), at rest and after IV injection of adenosine (ADN), using PESDA (sonicated solution of 1 ml 20% albumin, 12 ml 5% dextrose and 8 ml decafluorobutane gas), continuously infused at 1–2 ml/min. A marked and homogeneous contrast enhancement after ADN was defined as normal perfusion, and absence or heterogeneous enhancement in the walls was considered a perfusion defect. Coronary angiography (ANG) was obtained in 26 pts (in 11/11, 12/20 and 3/16 pts from groups A, B, and C respectively) within 48 hours from MCE. For each patient 3 LV territories (related to right coronary, circumflex and left anterior descending arteries) were considered.

Results: 78 territories were analyzed in pts with ANG with 33 related to coronary artery with obstruction ≥ 75% (all but one with abnormal perfusion); and 45 territories supplied by normal or no flow limiting (<75%) coronary artery (43 with normal perfusion). The sensitivity was 97%, the specificity was 95.5% and the global accuracy was 96.2%.

Conclusion: MCE with ADN is an accurate method to study myocardial perfusion in pts admitted to a CPC to elucidate the etiology of a chest pain.

P2731 Role of two-dimensional echocardiogram to improve diagnostic accuracy of acute coronary insufficiency in patients with chest pain and no ST-segment elevation

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Patients who present to the emergency room with chest pain and no ST segment elevation in the ECG constitute a clinical decision problem as many may have acute coronary insufficiency (AMI/UA). Serial determinations of plasma markers of myocardial injury are usually necessary, thus prolonging hospital stay.

Methods: We have developed an algorithm to evaluate these patients using chest pain type, serial ECG and plasma CKMB measurements, and 2-D Echo on admission. From a series of 1003 consecutive patients with chest pain 354 had neither ST segment elevation nor left bundle branch block (LBBB) in the first ECG, had performed Echo on admission and could have a final diagnosis made after appropriate work-up. Chest pain was prospectively classified either as typical/suggestive of angina (positive) or non-suggestive/not angina (negative). First ECG was designated as positive (ST depression/T inversion) or negative (normal/non-specific). Echo was designated as positive (segmental/global dysfunction in non-Q wave areas) or negative (normal contraction). Final diagnosis were AMI/UA (n = 215) or non-AMI/UA (n = 139).

Results: Positive predictive value of Echo was slightly better than first ECG and chest pain (90% vs 87% vs 80%, respectively) but negative predictive value was worse (49% vs 51% vs 80%). Adding Echo to chest pain and ECG improved the predictive value of any series of results of these tests except when both negatives.

Conclusion: In patients with chest pain and no ST elevation or LBBB, Echo is mostly informative when positive. A negative Echo does not rule out AMI/UA in any setting. Echo does not help for diagnosis when chest pain and ECG are both negative.

P2732 Acute tissue harmonic echocardiography is superior to biochemical variables in early risk stratification of patients presenting with non-ST-segment elevation acute coronary syndrome

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Recent studies have shown that the early measurement of the biochemical markers Troponin T (TnT) and Troponin I (TnI) as well as the inflammatory markers CRP, Interleukin-6 (IL-6) and Tissue necrosis factor alpha (TNF) appear useful as predictors of an adverse cardiac outcome in patients admitted with non ST segment elevation acute coronary syndromes (ACS). The purpose of the study was to examine the role of systolic wall thickening (SWT) abnormalities assessed by acute tissue harmonic echocardiography (TH Echo) in risk stratifying this patient group.

Methods: Patients admitted within 6 hours of chest pain with ACS were studied. Venous samples were taken on admission and batch assayed for CRP, IL-6, TNF, TnT and TnI which were scored as positive if they exceeded their upper reference range. Patients underwent TH Echo at presentation and the SWT was scored as normal or abnormal. The other variables were scored as positive if they exceeded their upper reference range.

Results: 80 patients were studied a mean of 175 mins from chest pain and were followed up for a median period of 227 days during which there were 28 cardiac events (4 deaths, 4 AMI and 20 revascularisation). Univariate analysis using clinical data, biochemical variables, ECG changes and TH Echo data showed that significant predictors of cardiac event were: abnormal SWT (p = 0.003), previous AMI (p = 0.02) and an abnormal ECG at presentation (p = 0.03). In the stepwise multivariate Cox's regression model only abnormal SWT achieved significance (p = 0.006; relative risk 3.9; 95% CI 1.5–10.3).

Conclusion: Abnormal SWT assessed by acute TH Echo was superior to the other variables measured in the early risk stratification of chest pain.

P2733 Comparison between two-dimensional echocardiography and myocardial perfusion imaging in the emergency department in patients with possible myocardial ischaemia

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Background. Accurate identification of patients (pts) at high risk for acute coronary syndromes among those seen in the emergency department (ED) with possible myocardial ischemia (MI) and nonischemic electrocardiograms (ECG) is problematic. Both 2-dimensional echocardiography (ECHO) and myocardial perfusion imaging with technetium-99m-sestamibi (T99mS) can identify pts at low and high risk; however, comparative studies are lacking.

Methods and Results. Pts initially considered at low or moderate risk for myocardial ischemia on the basis of the presenting history, physical examination, and ECG underwent both ECHO and T99mS within 4 hours of ED presentation. Positive ECHO was defined as at presence of segmental wall motion abnormalities or moderate to severe global systolic dysfunction; positive perfusion imaging was defined as a perfusion defect in association with abnormal wall motion, thickening, or both. End points included MI, percutaneous transluminal coronary angioplasty, and positive stress perfusion imaging. Both imaging procedures were performed in the ED on 205 pts. Ten pts had MI, and an additional 5 pts underwent percutaneous transluminal coronary angioplasty. ECHO and T99mS were positive in all 15. Overall agreement between the 2 tecniques was high (concordance 89%, with a κ coefficient 0.76) in the 37 who had MI or underwent coronary angiography. For all pts, concordance was 89%, with a κ coefficient of 0.68.

Conclusions. Agreement between ECHO and T99mS is high when used in pts in the ED with possible MI. Both techniques identified pts at high risk who required admission and those who could be safely discharged directly from ED.

NEW MARKERS IN ACUTE MYOCARDIAL INFARCTION

P2734 Ultrafast diagnosis of acute myocardial infarction by analysis of myoglobin kinetics

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Background. Early biochemical diagnosis of AMI is usually based upon detection of serum myoglobin beyond the normal range. We hypothesized that by analyzing myoglobin kinetics rather than looking at absolute values an even earlier diagnosis could be made.

Methods. We studied consecutive patients admitted to emergency ward within 4 hours from the onset of chest pain. Serial blood samples were obtained on admission, at 30 and 60 min; myoglobin percent (δ%) increase between admission and 30 min (0–30′) and between admission and 60 min (0–60′) were calculated. Serum myoglobin concentration was determined by the Beckman Kit on an Access Analyzer. The final diagnosis of AMI was based on serial sampling of specific biochemical markers of myocardial necrosis, ECG and 2D-echocardiogram.

Results. We enrolled 105 patients (pts, 65 male, mean age 61 yr., range 34–83); 46 (44%) had 'definite' AMI; the remaining were found to have no evidence of infarction. The efficacy of the proposed method, the interplay between sensitivity and specificity at different thresholds (T) of myoglobin δ% were assessed by the receiver operator curves (ROC).

	T	Sensitivity	Specificity	W	p
δ% 0–30′	11/21	97/90	73/93	0.956	<.0001
δ% 0–60′	11/21	100/100	79/84	0.973	<.0001

Conclusion. In this study population, the analysis of myoglobin kinetics yielded excellent diagnostic performance. An increase of myoglobin at 30 min exceeding the above thresholds (11/21%) allows very early identification of nearly all patients with acute myocardial infarction.

P2735 The role of out-of-hospital ECG recording in patients with an acute coronary syndrome

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Symptoms and ECG are the cornerstones of differential diagnosis and therapy of pts with an acute coronary syndrome (ACS). The aim of this prospective study was to determine how an out-of-hospital 12-channel ECG (O-ECG) together with the first in-hospital ECG (H-ECG) adds to the diagnosis and acceleration of therapeutic decisions in ACS patients.

Results: 227 consecutive pts with nitro-refractory angina pectoris (age 68 ± 14 years, 60% males, median duration of symptoms 56 min) were investigated. 20% (n = 45) of the pts showed major differences in the comparison of O-ECG's and H-ECG's (registered with a median time difference of 39 min).

73 (32%) pts had signs of an acute myocardial infarction (MI) (ST elevation in ≥2 leads) which was not present in the O-ECG of 4 pts. Of 43 pts (19%) with a subacute MI (Q waves and ST elevation or negative T waves) in the H-ECG, 12 had signs of an acute MI in the O-ECG, 3 signs of an old MI, and 28 pts had an identical O-ECG and H-ECG. Of 44 pts (19%) with signs of an old MI in the H-ECG (Q waves or QS complexes without ST elevation), 5 pts had signs of an acute MI in the O-ECG, 1 a subacute MI, 3 ST depressions and in 35 pts both ECG's were identical. In the remaining 67 pts (30%), 31 had only a ST depression in the H-ECG, a negative T wave (n = 6) bundle branch block (n = 12) or were normal (n = 18). In the O-ECG's of these 67 pts, 5 had the signs of an acute MI. Of the 69 pts with an acute MI in O-ECG, 54 (78%) received immediate prehospital thrombolysis by the emergency physician, and 13 (18%) were referred to acute PTCA/Stenting.

Conclusion: An ECG recorded at the scene in pts with an ACS not only allows immediate causal therapy (i.e. early prehospital thrombolysis) but is also a key and time-saving tool for evaluation of the patient and decision-making after hospital admission.

P2736 Non-invasive prediction at 60 minutes of failed reperfusion

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The early restoration of TIMI-3 flow following thrombolytic therapy for acute myocardial infarction (AMI) results in improved survival. To attempt to non-invasively predict lack of reperfusion (TIMI 0–2 flow) at 90 min, continuous ST segment monitoring, 60 min ECG's, and blood levels of myoglobin, CKMB (mass) and troponins T and I were obtained, in 60 patients undergoing angiography 90 minutes following streptokinase (1.5×10^6 MU over 30–60 min) for AMI. Using ratios of protein levels at 60 min to baseline (prior to streptokinase), we determined an index which predicted failure to achieve TIMI-3 flow at 90 minutes. At 90 min, the 29 patients (48%) with TIMI 3 flow had higher levels of myoglobin, CKMB (mass), troponins T and I at 60 and 90 min compared to patients with TIMI 0–2 flow. A ratio of ≤5 of any of these 4 proteins at 60 min detected TIMI flow 0–2 with 90% to 97% sensitivity, 37% to 53% specificity, 61% to 81% positive and 66% to 92% negative predictive accuracy. ST segment resolution ≤ 70% on 60 min ECGs was 75% sensitive and had 61% negative PA in determining TIMI flow 0–2 at 90 min. Steady state 50% ST recovery (sustained >4 hours) by 60 min was 96% sensitive and had 88% negative predictive accuracy. Multivariate predictors of failure to achieve TIMI 3 flow were: a troponin T ratio £5 at 60 min, and steady state 50% ST segment recovery (both $p < 0.02$).

Conclusion: Failure of TIMI-3 reperfusion can be predicted by troponin T levels and ST segment resolution by 60 min, facilitating triage of patients who may benefit from further reperfusion therapies.

P2737 Evaluation of myocardial reperfusion with serial assessment of electrocardiographic ST-segment after primary percutaneous transluminal coronary angioplasty

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Impaired myocardial reperfusion after primary coronary angioplasty(PTCA) implicates ongoing structural and/or functional problem of distal microcirculation and poor functional outcome. To evaluate the relation between ST change and impaired myocardial reperfusion immediately after angiographically successful (TIMI 3 grade flow) primary PTCA, we studied 51 pts with first acute Q wave myocardial infarction(MI)(ant:27, inf:24, mean age:64) with angiographically successful PTCA. Methods. The lead showing the greatest ST elevation in the 12-lead ECG was investigated before and immediately after PTCA and the resolution of ST elevation (dST = before-after PTCA) was calculated. A successful myocardial reperfusion was determined by quantitative tetrofosmin perfusion scintigraphy and defined as change(before-after PTCA)of 4 and more in the total defect score(DS)[the sum of defect score in each 13 segments: from 3(complete defect) to 0 (normal perfusion)]. Results. Twenty-four pts had impaired myocardial reperfusion (<4 change in DS: G1) and 27 pts had successful myocardial reperfusion (4 and more in DS: G2). The two groups did not differ significantly in age, site of MI, time from admission to PTCA, elapsed time and collateral grade. There was no significant difference in the degree of ST elevation before PTCA between G1 (1.9 ± 1.9 mm) and G2 (2.2 ± 1.4 mm). Pts in G2 showed a reduction in ST elevation after PTCA, but pts in G1 showed no significant change in ST elevation (dST = 1.7 ± 0.3 mm vs. −0.2 ± 1.5 mm: $p = 0.02$). Of 14 pts with ST re-elevation (dST>0) immediately after PTCA, 10 pts(71%) were in G1 and 4 pts in G2. Among 37 pts with no ST re-elevation (dST is 0 and less), 14 pts(38%) were in G1 and 23 pts in G2. The sensitivity and specificity of ST re-elevation in predicting impaired myocardial reperfusion were 42% and 85%, respectively. Conclusions. ST re-elevation is a specific ECG manifestation of impaired myocardial reperfusion after angiographically successful primary PTCA.

P27387 Serial change in fatty acid metabolism during acute phase of anterior myocardial infarction assessed by 123I BMIPP imaging

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Iodine-123-labeled-15-iodophenyl-3-methyl-pentadecanoic acid (BMIPP) has been proposed as a potential myocardial fatty acid(FA) probe. However, little is known about serial changes in FA utilization in myocardium that has been exposed to acute ischemia in patients with myocardial infarction(MI). We examined 28 consecutive patients with acute anteroseptal MI whose infarct related artery was successfully recanalized. Fourteen patients were spontaneously recanalized(SR), and the rest of 14 patients had occluded LAD which was successfully revascularized by primary PTCA(PTCA). Serial BMIPP studies were obtained within 72 hours(BMIPP1), 5–8 days(BMIPP2), and about 30 days after onset(BMIPP3). Tc-99m tetrofosmin imaging to determine area at risk(AAR) and infarct size(IS) was performed on admission and about 30 days after onset. Defect severity in BMIPP and TF was quantitatively assessed using polar map display as the severity index.

Results: Serial change in FA utilization in relation to AAR are shown in the table. BMIPP defect within 72 hours after onset(BMIPP1) were significantly smaller than AAR and larger than IS in both the SR and PTCA groups, and the severity improved during the very early phase of acute MI[AAR (mean 140SD67) > BMIPP1 (mean114 SD63) > BMIPP2 (mean97SD63) > BMIPP3 (mean89 SD62) > IS (mean67SD55)]. In addition, greater improvement during the superacute phase(BMIPP1 to BMIPP2) was observed in patients with SR which resulted in less myocardial damage compared with that of patients with totally occluded vessel subsequently undergone PTCA.

The severity of abnormal FA utilization

	BM1/AAR	BM2/AAR	BM3/AAR	IS/AAR
PCTA	86.1 ± 7.5	74.7 ± 12.5	69.6 ± 14.5	59.1 ± 21.1
SR	68.8 ± 19.3	50.7 ± 22.7	43.6 ± 30.8	43.6 ± 30.8
	P < 0.01	P < 0.01	P < 0.01	P < 0.01

Conclusion: FA utilization assessed by BMIPP showed dynamic changes during the acute phase of MI, and the degree of this improvement depend on the severity of ischemia.

P2739 Soluble vascular cell adhesion molecule as a marker of vessel patency after thrombolysis

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Soluble Vascular Cell Adhesion Molecule as a marker of vessel patency after thrombolysis.

Introduction: Soluble Cell Adhesion Molecules (sCAMs) have been shown to be elevated in Acute Myocardial Infarction (AMI).They have also been implicated in reperfusion injury and may be involved in leucocyte binding and extravasation to the reperfused myocardium.We set out to characterise the pattern of sCAM expression in the first 24 hours following AMI treated with thrombolysis and to assess its relationship with vessel patency.

Methods: Patients presenting with AMI, eligible for

thrombolysis, had serum drawn prior to thrombolysis and 60 minutes, 4, 12, and 24 hours post thrombolysis. A group of age and sex matched controls were used for comparison; they had serum drawn at 0 and 24 hours. All patients underwent coronary angiography within 5 days of presentation. Soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1), soluble Intercellular Adhesion Molecule-1 (sICAM-1) and sE-Selectin were measured using an ELISA technique (R+D).

Results: 27 patients have entered the study to date (male/female = 23/4, mean age 59 ± 8 years). The levels of sVCAM-1, but not sICAM-1 or sE-Selectin, increased significantly in the first 24 hours post thrombolysis (474 to 676 ng/ml, $p < 0.001$). sVCAM-1 levels in patients with patent infarct related vessels and TIMI 3 flow rose significantly (434 to 676 ng/nl, $p < 0.002$). Conversely, sVCAM-1 levels in those patients with an occluded vessel or TIMI 1 flow, did not increase significantly (614 to 718 ng/nl,$p = 0.42$).

Conclusion: sVCAM-1 levels rise after successful thrombolysis in AMI and may be a marker of vessel patency.

P2740 The role of cytokines (IL-6, IL-8) and their soluble receptors (sIL-6R) in acute myocardial infarction

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Interleukin 6 (IL6) plays a primary role in the synthesis of human acute phase proteins. Interleukin 8 (IL8) has a regulatory role in ischemic myocardium Moreover, it is well known that during AMI several acute phase responses take place. The objective of this study was to investigate the value of the cytokines as early diagnostic markers.

Methods: The serum levels of IL6, IL8 and sIL6R were examined in 30 patients with AMI, after admission (0 h) and at 24, 48 and 72 h later. The results from the patients group (24 male, 6 female, mean age 67.3 years) were compared with the respective ones of 100 blood donors (control group, 70 male, 30 female, mean age 36.5 years). Cytokines were measured by an Elisa assay.

Results are shown in tables 1 and 2.

Table 1. Patients with AMI

Cytokines	0 h	24 h	48 h	72 h	p
IL 6 pg/ml	18.3 ± 5.7	25.0 ± 8.2	35.6 ± 11.2	54.8 ± 16.5	<0.001
IL 8 ≫	16.7 ± 5.6	22.7 ± 6.0	41.7 ± 11.2	22.2 ± 8.1	<0.001
sIL6R ≫	7.5 ± 5.5	5.1 ± 3.5	3.1 ± 2.3	2.2 ± 2.5	<0.001

Table 2

Groups	No	IL6	IL8	sIL6R
Patients	30	18.3 ± 5.7	16.7 ± 5.6	7.5 ± 5.5
Blood donors	100	8.8 ± 3.6	7.3 ± 4.8	4.1 ± 2.6
p		<0.001	<0.001	<0.001

In conclusion, the serum levels of cytokines in patients with AMI were increased at all sampling points from admission to discharge, compared with levels in control subjects. The serum IL6 level reached its peak approximately 72 h (54.8), while IL8 level 48 h (41.7) after admission. The complex of IL6 and SIL6R acts agonistically. There was a significant positive linear correlation ($r = 0.8$) between levels of IL6 and IL8. IL6 may be the main mediator of acute phase response in patients with AMI.

P2741 Plasma cyclic-GMP: a marker of infarct-related artery patency?

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Plasma cyclic-GMP (cGMP) increases during the first hours of acute myocardial infarction (AMI), declining 24 h later. The aim of this study was to correlate plasma cGMP levels with angiographic data in AMI patients (pts).

Methods: 23 AMI pts admitted within 3 h of the onset of symptoms, were included in this study. Circulating plasma cGMP levels were measured 3, 6, 12 and 24 h after the onset of pain. Immediately after the last blood sample was taken, all pts underwent coronary angiography and were grouped according to the infarct-related coronary artery (IRA), the number of diseased vessels (NDV) and the patency (PAT) of the IRA. IRA was considered patent if there was a type 2 or 3 TIMI flow.

Results:

	(in pmol/ml)	3 h	6 h	12 h	24 h
NDV	1 (N = 10)	21.4 ± 3.1	13.2 ± 2.1	11.1 ± 2.0	12.6 ± 2.8
	2 (N = 10)	21.7 ± 3.5	11.4 ± 1.9	12.9 ± 2.2	10.5 ± 0.9
	3 (N = 3)	26.2 ± 6.9	14.8 ± 5.8	10.6 ± 6.0	4.7 ± 1.6
IRA	LAD (N = 14)	21.5 ± 2.4	11.6 ± 2.1	12.9 ± 2.2	10.4 ± 2.1
	LCX (N = 4)	27.2 ± 8.2	15.3 ± 2.0	9.9 ± 1.3	8.3 ± 2.6
	RCA (N = 5)	20.2 ± 4.1	13.3 ± 3.4	10.3 ± 3.8	13.3 ± 3.5
PAT	YES (N = 15)	19.4 ± 2.1√	11.0 ± 1.8	10.5 ± 1.8	7.0 ± 0.9*√
	NO (N = 8)	27.3 ± 4.3#	15.7 ± 1.9	14.3 ± 2.0	17.4 ± 2.2*#

NDV: P = NS between 1, 2 or 3 vessels. IRA: P = NS between coronary arteries (LAD, LCX, RCA). IRA PAT: (YES vs NO); 24 h, $P < 0.001$* PAT YES: (3 h vs 24 h) $P < 0.001$√, PAT NO: (3 h vs 24 h) P:NS#

Conclusions: In AMI pts, cGMP plasma levels are not related to the NDV and the IRA, but to the PAT; cGMP plasma levels are higher in pts with non patent IRA. In the case of non patent IRA, cGMP levels do not decline from baseline readings, as observed with the patent group.

P2742 Significance of reciprocal anterior ST-segment depression in inferior acute myocardial infarction: a clue for multivessel disease

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Although reciprocal ST-segment depression in patients (pts) with acute inferior myocardial infarction (AMI) is a common ECG finding, its significance is not yet established. In this prospective study we investigated the relationship of relative ST-segment elevation (STE) and reciprocal ST-segment depression (STD) with the extent of coronary artery disease.

Methods: Eighty-seven patients (pts) with inferior AMI, receiving thrombolytic therapy and undergoing coronary angiography within one month after AMI were enrolled in this study. The electrocardiographic maximum STE (STEmax) in leads II–III and maximums STD (STDmax) in precordial leads were measured. Pts were divided into 3 groups according the STDmax and STEmax. In Group I. there were 29 pts (mean age: 55 ± 4, male: 62%) who had STDmax > STEmax, Group II. Consisted of 20 pts (mean age: 57 ± 5, male: 64%) with STDmax < STEmax. In Group III. 38 pts (mean age: 54 ± 6, male: 70%) had no reciprocal ST-segment depression in ECG's. Vessel lumen narrowing >50% in angiography was accepted as significant.

Results: Demographic and clinical variables were similar in all groups. Significant left anterior descending artery lesion was present in the majority of Group I. patients. A Dominant right coronary artery was the most frequently involved infarct vessel with severe reciprocal changes during inferior myocardial infarction.

Group (n = 87)	SVD % (n = 48)	MVD % (n = 39)	P	IRA %		P
				RCA	Cx	
I (n = 29)	35	65	0.04	82	18	<0.001
II (n = 20)	70	30	0.02	70	30	0.02
III (n = 38)	63	37	0.04	58	42	0.2

(SVD: Single vessel disease, MVD: Multi vessel disease, IRA: Infarct related artery, RCA: Right coronary artery, Cx: Circumflex artery)

Conclusion: 1) The presence of reciprocal anterior STD in greater magnitude than STE during inferior myocardial infarction increases the likelihood of multi-vessel disease, namely left anterior descending artery involvement. This simple ECG finding may be used to differentiate high risk patients for a more aggressive approach.

2) A dominant RCA is more frequently involved with inferior myocardial infarction in the presence of severe reciprocal anterior ST depression.

P2743 PTX3, a prototypic long pentraxin, is a sensitive marker of acute myocardial infarction in humans

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Inflammation is an important component of ischemic heart disease,as reflected by raised serum levels of the "short" pentraxin C reactive protein (CRP).PTX3 is a prototypic long pentraxin whose expression is induced by cytokines. To test the hypothesis that PTX3 increases in acute myocardial infarction (AMI)in humans we studied the amount of PTX3 in the blood in 37 patients admitted to Coronary Care Unit (CCU)3.2 ± 3.2 hours after onset of AMI symptoms. Patients with history of inflammatory disorders were excluded. The majority of the patients received within the first 24 hours thrombolytics and oral aspirin. Plasma concentrations of PTX3 and CRP were measured up to hospital discharge by sandwich ELISA. To confirm that increased plasma concentration of PTX3 is the result of myocardial damage fragments of human hearts collected from 8 patients who died in heart failure within 48 hours after AMI, or from causes different from cardiovascular diseases (n = 4) and from one normal donor were used either frozen or fixed in formalin. In each case several sections were stained with MNB4 and MNB6 rat monoclonal anti PTX3 antibodies. PTX3 plasma concentrations were higher than the mean + 2SD of age- and sex-matched controls (2.01 ng/ml) in 27 out of 36 AMI patients. PTX3 peaked in plasma a median of 7.5 h(3 to 48 h)after CCU admission and mean peak concentration was 6.94 ± 11.26 ng/ml. At hospital discharge (12 ± 4 days), plasma concentrations of PTX3 were lower than the normal cutoff value in all but 3 patients. In contrast, CRP peaked in plasma a median of 24 h (3 to 72 h) after CCU admission, much later than PTX3 ($p < 0.001$). Plasma concentrations of PTX3 were unrelated to age, AMI site or extension and Killip class at entry. Patients aged more than 64 years and females had significantly higher PTX3 concentrations at 24 h ($p < 0.05$). CRP at 24 h was higher in patients with Killip 2–3 and in those not receiving aspirin maintenance therapy ($p < 0.05$). Immunohistochemically, PTX3 was detected in cardiomyocytes and endothelial cells from normal hearts, while fibroblast staining was very weak or absent. In infarcted myocardium PTX3 did not stain the damaged cells with empty cytoplasm whereas myocyte labeling was still present in the border zone. In conclusion, PTX3 is present in cardiomyocytes and endothelial cells of normal human myocardium and is absent in necrotic cardiomyocytes. Plasma concentration of PTX3 increases after the onset of symptoms of AMI much earlier than pentraxin CRP. Thus PTX3 appears to be released by the damaged myocytes and may be used as a sensitive initial marker for AMI.

P2744 Early cardiac marker testing predicts myocardial infarction by 90 minutes

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Background: Early and accurate evaluation of patients with chest pain is critically important for their appropriate triage and management.

Aim: We asked whether frequent serial testing of a panel of cardiac markers that utilized myoglobin, troponin I, and CK-MB (Triage®, Biosite Diag.) could accurately diagnose patients within 90 minutes of arriving in the emergency room.

Methods: In patients presenting to the emergency room with chest pain, quantitative cardiac markers were drawn at the point-of-care at 0, 30, 60, and 90 minutes. Cardiac markers were also drawn at 3 and 6 hours to substantiate final diagnosis of myocardial infarction. Troponin I was positive for myocardial infarction if >1.0 ng/ml. CK-MB was positive if >8.9 ng/ml. Myoglobin was considered positive if increasing >25% over 90 minutes and final value was >150 ng/ml.

Results: Of 918 patients presenting with chest pain, 45 had the final diagnosis of myocardial infarction. Of this group, troponin I was elevated in 84% by 90 minutes. With the addition of elevated CK-MB and increasing or elevated myoglobin, all 45 MI's were accurately diagnosed by 90 minutes (sensitivity 100%). In patients presenting less than 6 hours after symptom onset, myoglobin alone (absence of increased troponin I or CK-MB) detected 4 MI's by 90 minutes. The specificity of troponin I was 100%, while that of myoglobin in all patients without renal failure was 98.4%. Myoglobin specificity in patients presenting <6 hours after symptom onset was 96.5%.

Conclusion: Patients presenting with chest pain can be accurately diagnosed by 90 minutes when serial testing of a combination of cardiac markers are utilized.

P2745 Fatty acid-binding protein, a new marker useful in the early triage of chest pain patients presenting with equivocal ECGs

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More than 80% of all patients suspected of AMI and more than 40% of patients with later confirmed AMI present with equivocal ECG-findings. Thus, other diagnostic tools for early triage are needed.

Purpose: To evaluate a new marker, fatty acid-binding protein (FABP), which has been proposed as a very early and cardiospecific marker.

Methods: One hundred thirty consecutive patients admitted to the CCU for suspected AMI < 6 h from onset of symptoms with equivocal ECG-findings were enrolled. A blood sample was drawn on admission and – in 66% of the cases – repeated after 1–2 hours. Analysis was made for FABP, myoglobin, CK-MB mass, and troponin I. Sensitivity, specificity, and predictive values for AMI-diagnosis < 6 h from onset were calculated at prespecified cut-off values.

Results:

	FABP (10 μg/l)	Myoglobin (90 μg/l)	CK-MB (6.5 μg/l)	Tn I (2 μg/l)
Sensitivity	89 (68–98)	78 (56–92)	44 (24–66)	33 (16–56)
Specificity	87 (80–91)	90 (84–94)	97 (93–99)	98 (94–100)
PVpos	52 (33–70)	56 (35–76)	73 (38–93)	75 (35–97)
PVneg	98 (95–100)	96 (95–100)	92 (86–96)	90 (85–95)

AMI-prevalence 13.8%. 95% CI in brackets.

ROC-curve analysis revealed no sign. differences in the performance of FABP compared to myoglobin ($p = 0.52$) or CK-MB mass ($p = 0.22$), while both FABP and myoglobin performed sign. better than Tn I ($p = 0.03$ and 0.01, resp.).

Conclusion: FABP as well as myoglobin possess high sensitivities and very high negative predictive values. The two markers seem equally useful in the early triage of AMI-suspicious patients with equivocal ECG-findings, in particular in the early rule-out of AMI.

P2746 Increased endothelin-1 cardiac production in the acute phase of myocardial infarction

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Increased plasma concentration of endothelin-1 (ET-1) in the acute phase of myocardial infarction was reported. Experimental studies showed that chronic ET-1 receptor antagonist administration may improve ventricular remodelling and survival in myocardial infarction.

In the present study cardiac production of ET-1 was investigated in 9 patients with anterior acute myocardial infarction (AMI), with preserved hemodynamic status, who did not undergo thrombolysis. Serial blood samples for ET-1 assay were withdrawn during cardiac catheterization from peripheral vein (V), artery (A) and coronary sinus (CS) on the first day of AMI and repeated on the 2nd, 3rd, 7th, and 14th day. Blood samples from V, A and CS were also withdrawn from 11 patients with atypical chest pain who underwent coronary angiography and served as reference control values. ET-1 plasma concentration was measured by radioimmunoassay using a specific polyclonal rabbit antibody after chromatographic extraction.

In control subjects ET-1 A-CS gradient was 0.04 ± 0.05 pg/ml. During the first 3 days following AMI plasma concentration of ET-1 was significantly increased both in arterial and peripheral venous blood ($p < 0.05$), without any significant increase in the peripheral A-V gradient. Conversely, cardiac production of ET-1 was increased, as indicated by the elevated A-CS gradient (0.81 ± 0.34 pg/ml, on the first day, $p < 0.01$ vs controls), which remained high up to the 3rd day. Thereafter, A-CS gradient decreased and on the 7th and 14th day was similar to controls.

In conclusion, cardiac ET-1 production sharply increases during the first week following myocardial infarction.

P2747 Cardiac adrenergic system in acute myocardial infarction

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An activation of the systemic adrenergic system is known to occurr in patients with acute myocardial infarction (AMI), but no information is available on the role of the cardiac adrenergic system. This study was aimed to investigate cardiac adrenergic system in AMI.

In 27 patients (all males, aged 56 ± 7 yrs) with anterior AMI norepinephrine (NA) concentration was assayed in aortic, coronary sinus and peripheral venous blood at the 5th and at 20th day from AMI. Left ventricular end-systolic volume (LVESV), end-diastolic volume (LVEDV) and ejection fraction (EF) were measured by echocardiography on the 5th and 20th day and 6 months after AMI. Twelve patients who performed coronary angiography for atypical chest pain formed the control group.

AMI patients had peripheral venous NA concentration in the range of controls (171 ± 67 pg/ml) throughout the study. Conversely, at the 5th day all patients had a positive transcardiac NA gradient, significantly different from controls ($p < 0.01$). At the 20th day NA transcardiac gradient remained positive only in 10/27 patients. After 6 months the 10 patients with persistent activation of cardiac adrenergic system showed higher LVESV and LVEDV and lower EF than the 17 patients without cardiac adrenergic activation ($p < 0.05$).

A persistent cardiac adrenergic activation may be indicative of the development of left ventricular dysfunction in patients with AMI.

P2748 Evaluation of a rapid bedside test for streptokinase resistance applied in acute myocardial infarction

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Streptokinase (SK) remains a widely used thrombolytic agent in the treatment of acute myocardial infarction (AMI). Its lytic activity is variably hampered in the presence of specific neutralizing antibodies formed due to previous SK administration or streptococcal infaction, thus inducing streptokinase resistance (SKR). A rapid bedside test, introduced with the thrombolytic assessment system (TAS™), based on autologous clot lysis onset time (LOT) as a quantitative measurement of the lytic response to 100 U/ml SK in vitro for detection of SKR (resistant when LOT > 50 sec). To evaluate this test, 93 AMI patients were screened before the initiation of a standard dose of SK, ST segment elevation and lytic activity intensity were monitored during and up to 3 hours from the start of SK, and coronary angiography was done within 48 hours.

Results:

Clinical assessment % patients	LOT ≤ 50 sec (responder)	LOT > 50 sec (resistant)	P value
Efficient lytic activity	79%	38%	0.002
≥50% ST resolution on			
– continuous monitoring	80%	48%	0.012
– 3 hrs 12-lead ECG	88%	26%	<0.0001
TIMI grade 3 flow	81%	21%	<0.0001

Conclusion: 1) Clinical outcome was significantly less favorable in those with prolonged LOT in response to the in vitro SK challenge. 2) This bedside test can be a useful tool for rapid identification of streptokinase resistance and therefore could contribute to prompt selection of an alternative therapy before SK initiation.

THROMBOLYTIC THERAPY

P2749 Effects of thrombolytic therapy on erythrocyte antioxidant activity in post-infarction period

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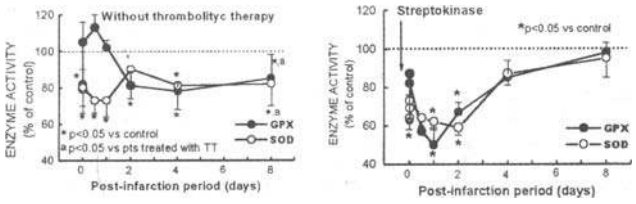
The deleterious effects of free radicals in acute myocardial ischemia/reperfusion are rather well known. However, the potential later effects of thrombolytic therapy (TT) on endogenous antioxidative status in post-infarction period are less well investigated.

Methods: We followed the time course of erythrocyte antioxidant activity in 25 patients (pts) with first acute myocardial infarction (MI). 12 pts were administered i.v. Streptokinase and 13 pts were treated without thrombolysis. Control group consisted of 24 healthy subjects. Glutathione peroxidase (GPX) and superoxide dismutase (SOD) were determined immediately after admittance to the hospital and subsequent TT, during first post-infarction day (1/2, 6, 12, 24 hrs) and 2, 4, and 8 days after MI.



Results: In pts without TT, time course of erythrocyte antioxidant level revealed an unbalanced GPX and SOD activities during first two days after MI. By the end of the study enzyme activities remained significantly lower than control levels in these pts. On the other hand, patients treated with TT demonstrated a pronounced rise in the activities of both GPX and SOD immediately after treatment, followed by concerted decrease until third post-infarction day. During further post-infarction period in pts treated with Streptokinase, erythrocyte antioxidant activity gradually recovered and finally reached control levels (day 8).

Conclusions: It can be concluded, that thrombolysis in pts with acute MI has later beneficial effects on their antioxidant status, which may contribute to the better overall prognosis in these pts.

P2750 Monocyte chaemotactic protein-1 rises after thrombolysis for acute myocardial infarction

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Introduction: Reperfusion injury after thrombolysis may be mediated by leucocyte infiltration and an inflammatory cascade. Animal models of reperfusion have demonstrated that neutrophil and monocyte chaemotaxis is largely mediated by Monocyte Chaemotactic Protein-1 (MCP-1). We set out to characterise the changes in MCP-1 levels in patients with Acute Myocardial Infarction (AMI) treated with thrombolysis.

Methods: Patients presenting with AMI, eligible for thrombolysis,had serum drawn at presentation, and at 60 minutes, 4, 12, and 24 hours post thrombolysis. Serum was centrifuged and stored at -70°C. MCP-1 levels were measured using an ELISA technique (R+D).

Results: 25 patients have entered the study to date (male/female = 21/4, mean age 56+/7). The average time from onset of pain to lysis was 210 ± 83 minutes. Levels of MCP-1 were significantly elevated at all time points post lysis compared to levels pretreatment.

Time (hours)	0	1	4	12	24
MCP-1 (pg/ml)	194	338	362	367	332
	–	$p < 0.01$	$p < 0.04$	$p < 0.02$	$p < 0.04$

P value = compared with MCP-1 at 0 hours.

There was a correlation of MCP-1 levels at 24 hours with peak creatine kinase levels ($r = 0.521$, $p = 0.05$).

Conclusion: Levels of MCP-1 increase post thrombolysis in AMI, reflecting leucocyte chaemotaxis during reperfusion and providing a potential mechanism for reperfusion injury.

P2751 The effect of tissue plasminogen activator on cerebral artery vasoreactivity

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The risks associated with thrombolytic therapy, whether for treatment of acute myocardial or cerebral infarction, include intracerebral hemorrhage and edema. One possible mechanism of damage from thrombolysis is a direct effect of tissue plasminogen activator (tPA) on the cerebral vessels themselves. This study investigated the direct effect of tPA on cerebral artery function, including myogenic responses and vasoreactivity.

Methods: Posterior cerebral arteries, isolated from male SD rats, were mounted in a special arteriograph system that allowed control of transmural pressure (TMP) and measurement of lumen diameter. Arteries were perfused with either physiologic saline solution (PSS, n = 6) or PSS + 100 μg/mL tPA (tPA, n = 6). After a 1 hour equilibration at TMP = 25 mmHg, TMP was increased stepwise to 200 mmHg and back to 75 mmHg and diameter recorded. Reactivity to serotonin (5HT, 0.01–10 μM) and vasodilation to acetylcholine (ACh, 10 μM) were also compared.

Results: The amount of pressure-dependent tone that arteries developed was significantly less in the presence of tPA:%tone = 21 ± 3% in tPA vs. 31 ± 3% in PSS ($p < 0.05$). tPA arteries also could not withstand pressure as well and underwent forced dilatation (loss of tone) at significantly lower TMP: 142 ± 10 vs. 179 ± 4 mmHg ($p < 0.01$). In addition, tPA arteries recovered less tone than PSS arteries following forced dilatation when TMP was returned to 75 mmHg: 17 ± 2% vs. 28 ± 3% ($p < 0.01$). Reactivity to 5HT was diminished in tPA vs. PSS arteries (EC50 = 88 ± 11 nM vs. 58 ± 4 nM; $p < 0.05$), as was the response to ACh which dilated arteries 10 ± 2% in tPA vs. 20 ± 4% in PSS ($p < 0.05$).

Conclusion: tPA perfusion has significant effects on cerebral artery reactivity and myogenic responses. Since the control of arterial diameter, both pressure- and agonist-induced, is crucial for cerebrovascular resistance and autoregulation of cerebral blood flow, any disturbance of these mechanisms may have damaging effects during or after tPA perfusion.

P2752 Accelerated streptokinase (0.75 MU in 10 minutes) and enoxaparin in the prehospital management of acute myocardial infarction

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Background: 1. We previously reported the safety and superiority of the inhospital administration of accelerated Streptokinase (1.5 MU infused in 20 min. or 0.75 M.U. over 10 min.) in the management of acute myocardial infarction (AMI) as compared to the standard regimen (SSK-1.5 M.U. in 60 min.). 2. Enoxaparin (ENOX) is a low molecular weight heparin which also have a fibrinolytic activity.

Objective: The safety and efficacy of the prehospital bolus of 0.75 MU SK in 10 min. in association with i.v. 40 mg. ENOX and 250 mg. of aspirin has been evaluated.

Methods: In 52 patients (pts.), age 58 ± 9, with well defined AMI, a combination of 0.75 M.U. of SK infused in 10 min. and followed by i.v. 40 mg. Enoxaparin plus 250 mg. Aspirin was administrated at the patient's home. After admision every patient received i.v. 40 mg. ENOX twice a day for the next 48 hours and aspirin 250 mg. daily. Three bedside criteria were used as revealing the coronary reperfusion (CR): 1. The rapid resolution of the chest pain. 2. The rapid decreasing of the ST segment elevation by more than 50% from the initial value. 3. The rapid increasing of the enzymes revealing necrosis. We evaluated the rates of CR, 21 day mortality, symptomatic hypotension, and of the haemorrhagic events.

Results: The CR was performed in 42 pts. (80.7%). No major haemorhagical events or other significant complications of the SK administration were registered. Three pts. without signs of CR died (5.7%). Symptomatic hypotension appeared in 17 pts. (32.7%) This side effect proved to be transient and well controlled with routine therapy in all pts.

Conclusion: The combination accelerated 0.75 M.U. SK-ENOX-aspirin is a safe and very efficient regimen in the prehospital management of AMI.

P2753 Rapid detection of streptokinase resistance

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The development of neutralising antibodies to streptokinase (SK) preclude its repeated use. Neutralising antibodies have been detected up to four years after initial treatment with SK. The effect of these antibodies, resistance to the fibrinolytic action of SK, is measured using the SK neutralising activity assay (SNA). The aim of this study was to assess SK resistance using a new rapid latex bead agglutination assay and to correlate this with the SNA measurement of SK resistance.

Methods: Patients presenting with acute myocardial infarction had serum samples taken prior to thrombolysis and then one and six months after discharge. Resistance to SK was measured using the SNA (in vitro clot lysis test). We also measured SK resistance using the latex bead assay: if significant neutralising antibodies are present in patients serum then agglutination occurs with in 5 minutes. Resistance to SK is scored 0–6 depending on the degree of agglutination.

Results: 14 patients have been studied to date (10 M/4 F, mean age 62 ± 10 yrs). Data is expressed as mean ± SEM. SNA increased significantly after treatment with SK (120 ± 17 U/ml before SK, 2230 ± 952 U/ml at 1 month, $p < 0.01$ and 1075 ± 208 U/ml at 6 months, $p < 0.05$). Similarly the latex agglutination score increased after SK (0/6 pre SK, 5/6 at 1 month, $p < 0.01$ and 4/6 at 6 months, $p < 0.03$). There was a strong correlation between SNA and the latex score ($r = 0.67$, $p < 0.01$ at 1 month and $r = 0.61$, $p < 0.03$ at 6 months).

Conclusion: Estimation of SK resistance using the latex bead assay correlates well with SNA. The latex agglutination assay has the potential to rapidly patients who will not respond to SK before administration of this thrombolytic agent.

P2754 Gender and geographic variations in thrombolytic treatment for acute myocardial infarction

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Case fatality of acute myocardial infarction (AMI) in women is higher than in men in some countries but not in others. Explanations for gender differences in case fatality are controversial. Furthermore, gender biases in diagnosis and treatment of AMI have been described. Aim of this paper is to study gender and cross-cultural differences in thrombolytic treatment for hospitalized cases of definite AMI for the ages 35 to 64,when thrombolytic treatment was still not widely adopted.

Methods: All (n = 3,412) hospitalized definite AMI events occurred in 1989–90 in five European regions of Finland, U.K. France and Spain taken from population based registres following the WHO-MONICA protocol were examined, 22% were AMI in women. Multiple logistic models were used to identify factors associated with treatment with fibrinolytics.

Results: Compared to men, women were on average significantly older, less often smokers, arrived later at hospital, had more atipycal pain, were less likely to be admitted to a coronary care unit (82% vs 89%) and of having had a previous AMI, more likely to have had an anterior MI, had less often an ST elevation, more often hypertensive, and less likely to receive thrombolytics (35 versus 40%). On multiple logistic analysis after adjusting for risk factors, care and clinical variables, women still received less thrombolytics (OR = 0.83, 95%CI = 0.66–1.02). There were no significant interactions of gender with other variables. All centres were less likely than U.K. centers to give thrombolytics. The clinical characteristics of patients on arrival at hospital, mainly the ST-segment elevation (OR = 3.9) and presence of typical chest pain (OR = 2.4) as well as being admitted to a coronary care unit (OR = 9.4) were the strongest determinants of the use of thrombolytic treatment.

Conclusions: Women tended to receive less thrombolytic treatment than men for definite hospitalized AMI in Europe, independent of geographical and clinical characteristics.

P2755 The use of reperfusion therapy in acute myocardial infarction

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The use of reperfusion therapy in acute myocardial infarction (AMI) was investigated in a stratified random sample of all patients aged 35–84 years, hospitalised in Belgium in 1995. A 2-step sampling method as applied: from all acute hospitals of the country a random sample was selected, stratified by region and by hospital size. In each selected hospital a random sample of patients with a discharge diagnosis for AMI was selected, stratified by age and by gender. The refusal rate was less than 5%. Results are based on a total of 965 patients from 44 hospitals. Thrombolysis was equally used in large or small hospitals in both regions. In premature cases in men (<55 years) thrombolysis was used in 61% as compared to 50% in those aged ≥ 55 years; thrombolysis was used in 59 and 39% of women aged respectively <65 and ≥65 years. Patients with a definite AMI entering within 12 hours of onset of symptoms and with ST-elevation (49% of total) received thrombolysis in 75% with the only difference by prematurity: 82% in premature cases and 67% in the older groups. "Door to needle times" were respectively <20 minutes and <60 minutes in 26 and 82% of premature men, 21 and 82% in men aged ≥ 55 years, 19 and 76% in premature women and 32 and 82% in women aged ≥ 65 years.

In-hospital PTCA was used in 189 patients but in only 40 (4%) on the day of admission.

These results observed in a representative sample of the patients entering with an AMI, show a widely use of reperfusion therapy. More attention should go to the elderly, particularly in women.

P2756 Increased risk of cardiac rupture in women who received thrombolytic therapy in acute myocardial infarction

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Background: Thrombolytic therapy (TLX) in AMI is associated with more complications in women than in men.

Methods: We reviewed the charts of all patients (pts) who received TLX for AMI hospitalized in all CCU's operating in Israel (n = 26) during a national survey lasting 5 months during 1996. We focused on cardiac rupture (free wal rupture and ventricular septal defect).

Results: Out of 2,377 AMI pts, 1,162 (49%) received TLX therapy. Characteristics and outcome of these pts according to gender were as follows:

	Total (%)	Female (%)	Male (%)
Number	1162	263 (23)	899 (77)
Age	60.6 ± 12	68.0 ± 11.4	58.5 ± 11.7*
Hypertension	405 (35)	145 (55)	260 (29)*
Diabetes Mellitus	271 (23)	84 (32)	187 (21)*
Prior AMI	186 (16)	39 (15)	147 (16)
Killip > 1	187 (16)	66 (26)	121 (14)*
CK	1884 ± 1662	1644 ± 1510	1955 ± 1698**
Cardiac rupture	32 (2.7)	16 (6.1)	16 (1.8)*
Hemorrhagic complic.	54 (4.6)	16 (6.1)	38 (4.2)
24 hr mortality	35 (3)	13 (4.9)	22 (2.4)***
7-day mortality	64 (5.5)	28 (10.6)	36 (4.0)*
30-day mortality	89 (7.7)	39 (14.8)	50 (5.6)*

*$p < 0.001$; **$p = 0.004$; ***$p = 0.04$

In a step-wise logistic regression analysis the most important independent predictors of cardiac rupture are age (OR 1.77; CI 1.24–2.60), female gender (OR 1.94; CI 0.88–4.30) and Killip > 1 on admission (OR 3.08; CI 1.43–6.62).

Conclusion: Alternative types of reperfusion should be considered for the management of AMI in women with increased admission risk.

P2757 Two accelerated streptokinase regimens are equivalent and more efficient than the standard 1.5 MU in 60 minutes regimen in patients with acute myocardial infarction

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Background: Since 1995 our cardiologists have the liberty to choose among three Streptokinase regimens for the management of patients (pts.) with acute myocardial infarction (AMI): Two accelerated (ASK) regimens (ASK1: 1.5 MU infused in 20 min. and ASK2: 0.75 MU in 10 min. followed after 60 min. by a new bolus of 0.75 MU in 10 min. if the signs of coronary reperfusion (CR) do not appear) and the standard (SSK) 1.5 MU over 60 min. one.

Objective: The results obtained within the last 4 years with the two ASK regimens as compared with the SSK one are presented.

Patients and Methods: Between January 1st, 1995 and December 31st, 1998, 618 pts. admitted within the first 6 hours after the onset of AMI received SK. In 312 pts. cardiologists chose the ASK regimens (ASK1-165 pts., ASK2-147 pts.) In 306 pts. the SSK regimen was administrated. All pts. received heparin and aspirin. Three bedside criteria of CR were used: 1. The rapid resolution of the chest pain. 2. The rapid decreasing (within 3 hours) of the ST segment elevation by more than 50% from the initial value. 3. The rapid increasing of the enzymes revealing necrosis. We evaluated the safety, the ratio of CR and the 30-day mortality.

Results: The rations of CR were similar in the two ASK subgroups: ASK1: 79.3%; ASK2-80.2% and significantly higher that the one of 61.7% registered in the SSK group ($p < 0.001$). The 30 day mortality was 6.7% in the ASK group and 11.11% in the SSK group ($p = 0.07$). No major haemorhagical complications were registered. Symptomatic hypotension was more frequent in the ASK group (34.9%) than in SSK group (22%). This side effect proved to be transitory and well controlled in all pts. using a rapid infusion of natrium chloride solution.

Conclusions. 1. The two ASK regimens are equivalent. 2. The ASK regimens are safe and followed by a higher rate of CR as compared to the SSK regimen. 3. The short-term mortality seems to be lower in pts. treated with ASK regimens.

P2758 Platelet reactivity and streptokinase resistance following antecedent streptokinase therapy for myocardial infarction

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Aims: First time thrombolysis with streptokinase (SK) in MI is established but efficacy of subsequent SK is unknown. We aimed to assess the efficacy of second administration of SK.

Methods: Platelet reactivity to shear stress, spontaneous and SK-induced thrombolysis, and SK-antibody titres were measured *in vitro* in 28 patients who had received SK for MI and compared to 15 controls. Non-anticoagulated venous blood was tested using an overall *in vitro* technique to assess thrombotic and thrombolytic activities. Blood is drawn in pulses through a capillary tube where haemodynamic forces induce platelet aggregation culminating in occlusion. Dislodgement/disintegration of the stabilised thrombus under pressure reflects thrombolysis. The time for (1) occlusive thrombus formation under high shear stress (platelet reactivity), and for (2) dislodgement of the thrombus (thrombolysis) is measured. This was repeated adding 12.5, 25 and 50 U/ml SK in *vitro*.

Results: SK-antibody titres were inversely related to time from MI. Platelet reactivity was greatly enhanced in patients ($p < 0.0001$). Spontaneous thrombolysis in patients was poor and in 17 failed to occur. In contrast, thrombolysis occurred in all but one control. In patients platelet reactivity was strongly related to thrombolytic activity ($r = -0.516$; $p = 0.0029$). The dose-response relationship of *in vitro* SK to thrombolytic effect was poor in patients compared to the steep dose-response curve of controls. SK *in vitro* was at least 4 times more effective in controls than in patients.

Conclusion: Chances of achieving patency with second administration of SK are poor. SK-antibody titre is not a reliable index of resistance and second time treatment with higher doses of SK cannot be tailored to the patient.

P2759 Clinical presentation of reocclusion of the infarct-related artery after successful thrombolytic therapy: impact of collateral filling

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Background: Reocclusion of the infant related artery (IRA) after successful thrombolytic therapy (TT) is associated with unfavorable outcome on both short- and long-term. This study describes the impact of collateral circulation on clinical presentation of patients with a reoccluded IRA.

Methods: Patients studied received TT for suspected acute myocardial infarction, had an angiographically confirmed open IRA < 48 hrs after TT, and underwent follow-up angiography at three months (APRICOT-trial). Cardiac events were scored between both angiographies.

Results: Reocclusion was observed in 29% of patients (71/248), with information on collateral development available in 66: 37 had collaterals of good quality compared to 29 who showed poor (n = 22) or no (n = 7) collateral circulation.

	Reocclusion (n = 66)		p-value
	Good Collaterals n = 37	Poor/no Collaterals n = 29	
Asymptomatic	15 (40%)	11 (38%)	0.83
Angina	18 (49%)	4 (14%)	<0.001
Angioplasty	1 (3%)	3 (10%)	<0.001
Reinfarction	3 (8%)	11 (38%)	<0.001

Conclusion: Reocclusion of the IRA was clinically silent in about 40% of patients, irrespective of the quality of collateral circulation. In case of symptomatic reocclusion patients with good collaterals more often presented with angina, whereas reinfarction was more frequent when collateral filling was inadequate.

P2760 One versus 4.5-year prognosis in patients with first acute myocardial infarction: the impact of thrombolysis

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Purpose: To define possible predictors for early (30 days^{-1} year) and late (1–4.5 years) mortality in patients <65 years old with first acute myocardial infarction (FAMI). Design: Prospective longitudinal study. Setting: Eight major centrally located Israeli hospitals provided data during one year.

Methods: The cohort included 1214 patients, 83% men, 37% hypertensives, 23% diabetics and 14% with previous anginal syndrome.

Results: Multivariate analysis showed that Killip class and thrombolysis were the only significant predictors for 1 year survival (odd ratio [OR] = 2.89; 95% confidence interval [CI] = 0.94 to 4.03, p = 0.03 and OR = 2.4; CI = 1.08 to 5.64, p = 0.03, respectively). Thrombolysis no longer affected the 4.5 year survival, while Killip class (OR = 1.57; CI = 1.03 to 2.39, p = 0.03), female gender (OR = 2.28; CI = 1.30 to 3.99, p = 0.004), diabetes mellitus (OR = 1.87; CI = 1.08 to 2.32, p = 0.02) and peripheral vascular disease (OR = 2.49; CI = 1.03 to 6.02, p = 0.04) entered the multivariate model. Hypertension and past history of ischemic heart disease had a significance of 0.09 and 0.05, respectively.

Conclusions: Thrombolysis appears to be an independent predictor for early but not for late survival in young patients with FAMI. Female gender and diabetes mellitus are important predictors for late mortality in this population.

P2761 Geographic variation among hospitals participating in a world-wide thrombolytic trial: an Intime-II substudy

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Background: Large international megatrials in acute myocardial infarction (MI) typically involve a heterogeneous mix of hospitals and countries. The magnitude and importance of this heterogeneity has not been well studied.

Methods: We surveyed all 855 hospitals participating in InTIME-II (nPA vs tPA for AMI) regarding location, size, teaching status, and practice patterns. Hospitals were divided into 4 geographic categories: Western Europe (WE), Eastern Europe (EE), Latin America (LA), North America (NA).

Results: Hospital characteristics (100% response) varied widely by region (see table). 30-day outcomes (death, re-MI, stroke) by region and hospital characteristics will be available after unblinding in March 1999 and will be presented.

Hospital characteristics by geographic region

	WE	EE	LA	NA	chi-sq p
No. hospitals, n	503	91	54	207	–
City/Referral hospital, %	65	97	96	57	<0.0001
No. hospital beds < 300 beds, %	24	13	54	57	<0.0001
300–699 beds, %	50	35	33	37	
>700 beds, %	26	51	13	6	
No. ICU beds < 10 ICU beds, %	26	11	17	21	<0.0001
10–29 ICU beds, %	58	42	48	49	
>30 ICU beds, %	16	47	35	30	
Teaching hospital, %	61	87	78	51	<0.0001
Lytic decision by cardiologist, %	62	92	87	42	<0.0001
Cardiologist manages inpatient, %	67	91	94	82	<0.0001
On-site PTCA available, %	38	60	76	42	<0.0001
%AMI treated w/ primary PTCA	8	13	21	15	<0.0001
On-site CABG available, %	17	53	83	37	<0.0001

(Data represent column percentages)

Conclusions: Hospitals participating in this worldwide AMI megatrial from EE and LA tended to be large, city, teaching, cardiology-dominant, tertiary centers; while hospitals in WE and NA included many smaller, local, non-teaching, general hospitals. These differences may be important considerations when comparing clinical outcomes among geographic regions in international MI megatrials.

P2762 Prediction of early reperfusion after streptokinase in acute myocardial infarction by a new test for functionally neutralising streptokinase antibodies

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Object: Approximately 25% of patients with acute myocardial infarction (AMI) do not obtain reperfusion after treatment with streptokinase (SK). We investigated, whether the occurrence of functionally neutralising SK antibodies as assessed by a new bedside test was related to the time to reperfusion.

Methods: Thirty-one patients with significant ST-elevation in the ECG, admitted to the CCU with a symptom delay of max. 6 hours, and treated with 1.5 MIU SK were included. Continuous vectorcardiography (VCG) was performed and the time to a 50% decrease in ST-VM from maximum was defined as reperfusion time. Citrated plasma was collected on admission and the level of functionally neutralizing SK antibodies was estimated by "TAS Streptokinase Test Panel", Nyco Med, measuring the lysis time of clotted fibrin in the sample (prolonged lysis time indicates presence of antibodies).

Results: Median age was 61.5 years. 74.2% were male. 20 (64.5%) had successful reperfusion within 90 minutes, assessed by VCG. The correlation between time to reperfusion and the estimated amount of functionally neutralizing SK antibodies was rS = 0.34 (Spearman's test, p = 0.07). The diagnostic performance (sensitivity, specificity, predictive value of positive (pV(+)) and negative (pV(−)) test) predicting unsuccessful reperfusion within 90 minutes from start of SK is listed in the table below.

	Sensitivity	Specificity	pV(+)	pV(−)	Diagn. accuracy
>120 sec.	90.9%	30.0%	41.7%	85.7%	51.6%
>150 sec.	81.8%	55.0%	50.0%	84.6%	64.5%

Conclusion: A weak correlation between time to reperfusion after SK and the amount of functionally neutralizing SK antibodies was found. However, we conclude that the TAS Streptokinase Test Panel cannot be recommended for clinical use for decision making prior to choice of thrombolytic agent, since the pV(+) for prediction of unsuccessful reperfusion after SK assessed by VCG is low.

P2763 Effect of thrombolysis on plaque morphology in patients with acute myocardial infarction

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Thrombolytic therapy has been confirmed to improve the survival rate in patients (pts) with acute myocardial infarction (AMI). The aim of this study was to examine the differences in plaque morphology (determined by intrvascular ultrasound /IVUS/) between pts with or without thrombolysis in AMI.

Method Clinical (age, gender, coronary risk factors), qualitative (soft/hard plaque, plaque eccentricity, presence of thrombus, rupture, calcification, adaptive/constrictive remodeling) and quantitative (minimal lumen, external elastic membrane /EEM/ and plaque cross-sectional area /CSA/ and plaque burden of the infarct-related lesion, proximal and distal reference segments) IVUS, and angiographic (minimal lumen diameter /MLD/, reference diameter /RD/ and %diameter stenosis /%DS/) data of 27 pts with thrombolysis (85% men, 57 ± 3 y, Group A) were analysed and compared with that of 23 pts without thrombolysis (70% men, 61 ± 6 y, Group B) 6 ± 3 days after AMI.

Results There were no differences in clinical data between the two groups. Intracoronary thrombi and soft plaque were found significantly more frequently in Group B, however, despite thrombolysis, 56% of pts in Group A also exhibited thrombi in IVUS (Table 1; $^*p < 0.05$).

Table 1

	Eccentric	Soft	Rupture	Thrombus	Calcification	Adaptives remodeling	Constrictives remodeling
Group A	59%	48%	37%	56%	37%	37%	22%
Group B	48%	**70%***	52%	**70%***	26%	22%	22%

Minimal lumen CSA of the target lesion, proximal and distal reference segments were significant greater after thrombolysis (Table 2; $^*p < 0.05$).

Table 2

	Infarct-related lesion				Proximal ref.	Distal ref.
	lumen CSA [mm²]	EEM CSA [mm²]	plaque CSA [mm²]	plaque burden [%]	lumen CSA [mm²]	lumen CSA [mm²]
Group A	**4.47 ± 2.71***	15.44 ± 3.57	9.87 ± 4.28	69.8 ± 15.8	**9.77 ± 3.78***	**7.81 ± 3.69***
Group B	3.84 ± 1.81	13.88 ± 4.43	10.03 ± 4.31	70.7 ± 13.2	8.91 ± 3.93	6.61 ± 2.7

Quantitative coronary angiography did not show any differences between the two groups (MLD 1.81 ± 0.66 vs 1.71 ± 0.58 mm, RD 2.86 ± 0.93 vs 2.81 ± 0.53 mm, %DS 67.5 ± 18.3 vs 57.0 ± 16.2% in Group A vs B).

Conclusions Despite thrombolysis, 56% of pts exhibited intracoronary thrombi after AMI. Quantitative IVUS, but not quantitative angiography exhibited a significantly better lumen dimensions after thrombolysis in AMI.

MECHANISMS OF PLAQUE INSTABILITY

P2764 Unstable plaques have increased temperature compared with stable plaques

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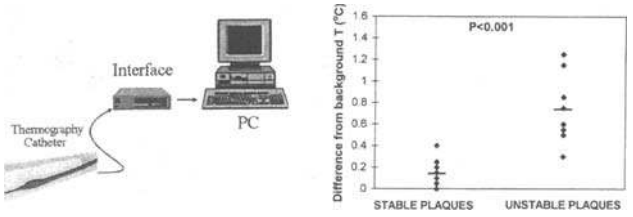
We have shown in vivo that temperature (T) heterogeneity is increased in acute ischemic syndromes (*Ann Intern Med 1998; 129: 1079–80*). To compare the thermal status of unstable and stable plaques, we measured the T of the coronary arteries in 8 patients with unstable angina who were catheterized for coronary intervention on an emergency basis and were found to have except for the culprit lesion an additional lesion (with similar % stenosis) to another vessel. Seven RCAs, 6 LADs and 3 LCxs were studied. The culprit lesion was identified with ECG, angiographic and IVUS criteria. T was measured with a catheter-based technique that was designed and developed in our laboratory (left figure). The 3F thermography catheter incorporates a thermistor at its distal end (accuracy: 0.05 °C, time constant: 300 msec; spatial resolution 0.5 mm).

Results: Difference of plaque T from healthy wall T (background T) was larger in the unstable plaques (right figure).



Conclusions: Unstable plaques have increased temperature compared with stable plaques. This new insight into the pathophysiology of unstable ischemic syndromes may prove useful in predicting plaque rupture and thrombosis.

P2765 Infection burden in acute coronary syndrome: predominant role of Chlamydia pneumoniae

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Introduction: There is growing evidence that previous and recurrent infection play a role in the development of acute coronary syndrom. We evaluated the prevalence of anti Chlamydia pneumoniae IgG (Cp_IgG, previous infection), anti Chlamydia pneumoniae IgA (Cp_IgA, recurrent activity) and anti Respiratory Syncytial Virus IgG (RSV_IgG) as respiratory tract infection markers as well as anti Cytomegalovirus IgG (CMV_IgG) and anti Cytomegalovirus IgA (CMV_IgA) in stable (SAP), unstable anigna (UAP), acute myocardial infarction (AMI), and a control group (CG).

Methods: In 950 patients (pts) with angiographically documented coronary artery disease (CAD) – at least one stenosis > 50% – and in a CG antibody levels of Cp_IgG [Ratio; cut off: 1.5], Cp_IgA [Ratio; cut off: 1.5], CMV_IgG [Relative Units (RU); cut off: 20], CMV_IgA [Ratio; cut off: 1] and RSV_IgG [RU; cut off: 100] were determined on admission to hospital. Pts were divided by clinical event into the groups: SAP, UAP (classified by Braunwald classification) and AMI.

Results: 566/950 (59.6%) of the pts had SAP, 207/950 (21.8%) UAP, 177/950 (18.6%) AMI. The power of the CG was n = 158.

Infection and acute coronary syndrome

Mean	CG	SAP	UAP	AMI	p
Cp_IgA [Ratio]	1.68	1.96	1.92	2.05	0.026
Cp_IgG [Ratio]	1.54	1.72	1.73	1.58	0.054
CMv_IgA [ratio]	0.49	0.5	0.52	0.55	n.s.
CMv_IgG [RU]	107.4	119.6	121.2	121.9	n.s.
RSv_IgG [RU]	92.1	93.2	88.1	84.8	n.s.

data presented are mean Ratio/Relative Units of antibody titers

Conclusion: CAD and acute coronary syndrom is not associated with a burden of several here tested infectious agents. Only recurrent infection of Cp demonstrated by elevated antibody levels of Cp_IgA is related to the prevalence of CAD, especially acute coronary syndrom. This strengthens the hypothesis of a pathognomonic role of infection with Cp in the development of CAD.

P2766 Helicobacter pylori infection influence the extent of coronary artery disease: results of a cross-sectional study

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Background: The causative role of Helicobacter pylori (Hp) infection in pathogenesis of coronary artery disease (CAD) is discussed controversially. No association was found between previous Hp infection and prevalence of myocardial infarction whereas elevated hp antibody titers could be demonstrated in patients (pts) with angiographically proven CAD. We aimed to examine the influence of severity of Hp infection on the extent of coronary atherosclerosis.

Methods: In 1035 patients (pts) with suspected CAD we performed angiography. Antibody titers of Hp_IgG were measured by ELISA technique. Severity of infection was determined by anti Hp_IgG Relative Units [RU]. We developed a coronary atherosclerosis score by determing for each angiogram the number of affected vessel area (stenosis > 50% in a vessel area) (vessel score), the number of stenosis > 50% (0 = 0; 1 = 1; 2–4 = 2; >4 = 3) (stenosis score) and the number of atherosclerotic altered segments (0 = 0; 1 = 1; 2–7 = 2; 8–15 = 3) (segment score).

Results: 244/1035 (23.5%) of the pts had one vessel disease, 249 (24.1%) two vessel disease, 397 (38.4%) three vessel disease, and 145 (14%) no CAD.

Hp infection and extent of CAD

Mean anti Hp_IgG	0	1	2	3	p
Vessel score	86.5	99.4	112.4	111.7	0.01
Stenosis score	88	99.6	114.2	109.6	0.003
Segment score	85.6	93.6	111.9	108.6	0.007

Data shown are mean values of anti Hp_IgG [Relative Units] depending on the different atherosclerosis scores

Conclusion: In pts with angiographically documented CAD there is a significantly higher prevalence of Hp-infection. Furthermore we could demonstrate that the extent of angiographically documented atherosclerotic lesions defined by three different scores is significantly associated with the severity of previous Hp-infection.

P2767 Inflammation and coronary restenosis postangioplasty, hunting for genetic links

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Restenosis is the major complication of percutaneous transluminal coronary angioplasty (PTCA), occurring in about 20–50% of all initially successful procedures. The involvement of inflammatory-mediator cascades in the pathophysiology of restenosis post-PTCA is receiving increasing attention. The genes for E-selectin (E-sel), tumor necrosis factor-alpha (TNF-α) and -beta (TNF-β) have been recently implicated. We had the opportunity to investigate this question in a large, prospective cohort characterized by two quantitative coronary angiographic studies in all subjects.

Methods and Results: Common allelic polymorphisms for these genes were characterized in a cohort of 779 patients of whom 342 patients ("cases") had developed restenosis (as defined by >50% loss of lumen compared to immediate post-procedure results) a follow-up angiography at 6 months post-PTCA. Allele frequencies for the E-sel E1 and E2 alleles (allele E1/E2, absence/presence of PstI restriction site) were 0.11 and 0.89 in cases, and 0.09 and 0.91 in controls. Allele frequencies for TNF-α N1 and N2 alleles (allele N1/N2, absence/presence of NcoI restriction site) were 0.15 and 0.85 in cases, and 0.14 and 0.86 in controls. Allele frequencies for TNF-β N3 and N4 alleles (allele N3/N4, absence/presence of NcoI restriction site) were 0.70 and 0.30 in cases, and 0.74 and 0.26 in controls, respectively. All observed genotype frequencies were in Hardy-Weinberg equilibrium. There was no evidence for an association between genotype and restenosis or degree of lumen loss (adjusted for covariates).

In conclusions: Our data, collected in the largest study of its kind so far, indicate that the common polymorphisms tested of E-selectin, tumor necrosis factors-alpha, and -beta are not associated with incidence of restenosis following PTCA and are therefore not useful markers for risk assessment.

P2768 Alterations in leukocyte adhesion molecule expression and function in the acute coronary syndromes

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The adhesion of leukocytes to vascular endothelium is an important factor in the pathophysiology of the acute coronary syndromes (ACS). One of the principal mediators of this process is the $\alpha_M\beta 2$ leukocyte integrin, composed of CD11b and CD18 chains. The aim of the current study was to identify whether CD18/CD11b expression by neutrophils (PMN) and monocytes (Mø), and PMN CD18 *function*, is altered in patients with an ACS.

Methods: Subjects included 22 patients with an ACS, 12 patients with angiographically proven coronary artery disease (CAD) but stable symptoms and 12 healthy controls (HCs). All patients were, taking maintenance aspirin and all controls took 325 mg daily for >72 h prior to blood sampling. Cell surface CD18 and CD11b expression on PMNs and Mø was determined by flow cytometry. PMN CD18 function was measured by passing whole blood through scrubbed nylon columns and calculating percentage adhesion. In this assay 98% of adhesion is mediated by CD18. Adhesion results are expressed as percentage (±SEM). Groups were compared using the Mann-Whitney U test.

Results: There were no significant differences in PMN CD11b or CD18 expression between the three groups. PMN adhesion is, however, lower in patients with an ACS (9.5 ± 2.1) compared to HCs and patients with stable CAD (9.5 ± 2.7 and 15.3 ± 2.1 respectively, $p < 0.05$). Mø from patients with an ACS express higher levels of CD11b and CD18 than those from either HCs or patients with stable CAD ($p < 0.05$ for both chains and groups).

Conclusion: The expression of CD18/CD11b on peripheral PMNs is unaltered in stable CAD or the ACS (though other work suggests that extensive myocardial necrosis results in activation). PMN adhesion is reduced in the ACS, in keeping with reported changes in sepsis. In contrast, CD18/CD11b expression on Mø is increased. The explanation for these complex changes remains to be fully elucidated but may shed light on the pathophysiology of the ACS.

P2769 Overexpression of tissue factor in unstable angina and myocardial infarction

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Many studies suggest a role for inflammation and thrombosis in the physiopathology of coronary disease. Increased expression of activation markers (Mac-1, tissue factor (TF)) have been detected on leukocyte membrane during inflammatory response. TF, initiator of clotting cascade, plays a central role in the evolution of a stable coronary disease to an acute ischaemic syndrome. The aim of this study was to detect TF on circulating leucocytes and soluble TF in plasma from patients with coronary disease according to their clinical status.

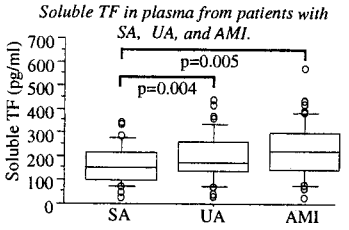
Methods: 147 consecutive patients addressed for coronary angiography were included and classified, according to Braunwald criteria, in stable angina (SA, n = 40), unstable angina (UA, n = 51), and acute myocardial infarction (AMI, n = 56). Circulating blood leucocytes were stained for TF molecules with fluoresceine-conjugated monoclonal antibodies, and were analysed in flow cytometry. Soluble TF was measured in plasma using Elisa assay.

Results: only results concerning monocytes were significant.

Number of patients with high and normal monocyte TF expression according to clinical status.

	SA		UA		AMI	
	n	%	n	%	n	%
High	2	5	12	24*	12	21**
Normal	38	95	39	76	44	79
Total	40	100	51	100	56	100

*$p = 0.018$ SA vs UA; **$p = 0.037$ SA vs AMI; High is ≥ mean + 2 SD in SA group



Soluble TF in plasma from patients with SA, UA, and AMI.

Conclusion: Increase of TF in plasma and on monocyte surface in patients with UA or AMI suggests a role of circulating monocytes in acute ischaemic syndromes. However, absence of correlation between monocyte membrane and plasma TF (data not shown) indicates the possible role of other cells (as endothelial cells) for TF production.

P2770 Chlamydia pneumoniae antibodies and their relationship with restenosis in coronary heart disease patients

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The aim of this study was to investigate the presence and clinical importance of Chlamydia Pneumoniae (CP) antibodies in coronary heart disease (CHD) patients who had undergone percutaneous transluminal coronary angioplasty (PTCA) and coronary stenting (CS). The study population consisted of 32 CHD patients (7 women, 25 men, 55.7 ± 10.1 years) who had PTCA (13 pts, 40.6%) and CS (19 pts, 59.4%) and 25 healthy subjects (5 women, 20 men, 51.6 ± 8.3 years) as the control group. Sera just obtained before PTCA and CS and 3 and 6 months later were stored at −20°C until being tested. Spesific IgG and IgM antibodies against CP were detected by microimmunofluorescence method. Sera with a dilution of 1/128 with which the elementer bodies of CP gave fluorescence were accepted CP IgG positive. CP IgM antibodies were negative in all of the three sera of all the patients. CP IgG antibodies were detected in 3 of 25 (12%) healthy subjects and 17 of 32 (53%) CHD patients ($p = 0.013$). Control coronary angiographic investigation applied six month later revealed restenosis in 16 of the 32 patients (50%). Restenosis was detected in 12 of the 17 patients who had CP IgG antibodies (70.6%) were as in 4 of the 15 patients (26.6%) who were negative CP IgG antibodies ($p = 0.013$). In our study it was found out that CP IgG antibody positivity was higher in CHD patients than the healthy control group. This supports recent findings describing the CP infection in the pathogenesis of atherosclerosis. Prospective and cohort studies are needed to explain the role of CP IgG antibodies in the pathogenesis of coronary atherosclerosis and restenosis.

P2771 An inflammatory, but not an anti-inflammatory, cytokine profile is present in patients with unstable angina and correlates with prognosis

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Background: Inflammation plays a major role in the pathophysiology of acute coronary syndromes. In unstable angina (UA), IL-6 plasma levels are known to be elevated, and the degree of elevation seems to correlate with prognosis. Recently, an anti-inflammatory cytokine profile (high IL-10 to tumor necrosis factor-alfa (TNF-α) ratio) has been observed to be associated with prognosis in infectious disease, and also in patients (pts) with UA.

Objectives and methods: To assess if an anti-inflammatory cytokine profile is present in pts with UA, we prospectively studied 104 consecutive pts with Braunwald Class IIIB UA. Blood samples were drawn at admission and before therapy was initiated. Mean age of pts was of 65 years, and 29% were female.

Results: Sixty-five per cent of pts had plasma IL-10 levels below the detection level of ≥5 pg/mL. During a 3 month follow-up 18 pts died, had a myocardial infarction or were readmitted for a new episode of unstable angina. Compared with pts with good clinical evolution, pts with cardiac events had similar levels of TNF-α (30 ± 30 vs 29 ± 29, p = NS), and lower levels of IL-10 (3.4 ± 6 vs 19 ± 40, $p < 0.001$). Also, the frequency of pts with IL-10 levels ≥ 5 pg/mL was less in the group with cardiac events (16.7% vs 36.4%, p = 0.07). Furthermore, TNF-α to IL-10 ratio was of 6.4 ± 6.3 vs 2.5 ± 4.5, $p < 0.05$, and the IL-1β to IL-10 ratio was of 6.3 ± 9 vs 1.8 ± 4, $p < 0.05$, in pts with and without events.

Conclusion: An anti-inflammatory cytokine profile has not been observed in pts with UA. On the contrary, low levels of IL-10 and high TNF-α and IL-1β to IL-10 ratios seem to be associated with a poor prognosis in pts with UA.

P2772 Different inflammatory response after stent implantation in unstable versus stable angina

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Plasma levels of cytokines and inflammatory mediators are frequently increased in acute ischemic syndromes, yet their time course after successful PTCA is unknown. The purpose of this study was to compare changes of interleukin (IL)-6, an index of inflammation, and von Willebrand factor (vWF), an index of endothelial activation, after successful PTCA with stent implantation in pts with unstable and stable angina.

Methods: Thirty-one pts (23 men, 8 women, mean age 69 years, range 49–88) had unstable angina, defined as angina at rest, Braunwald Class IIB–IIIB or IIC–IIIC (UA group); 21 pts (19 men, 2 women, mean age 58 years, range 50–76) had stable angina, defined as exercise-induced chest pain with positive exercise stress test (SA group). All pts underwent successful PTCA of 1 vessel, followed by stent implantation. Plasma levels of interleukin-6 (IL-6) and vWF antigen were measured by ELISA prior to PTCA, 24 hours after PTCA and 30 days (d) thereafter.

Results:

(mean + SD):

	pre-PTCA		24 h post-PTCA		30-d post-PTCA	
	UA	SA	UA	SA	UA	SA
IL-6 (pg/ml)	7.1 ± 7.4*	2.9 ± 3.6	7.5 ± 6.5	5.0 ± 6.6	2.9 ± 3.1§	3.2 ± 3.5°
vWF (%)	120 ± 38	104 ± 40	127 ± 28	107 ± 23	107 ± 20§	108 ± 15

*p = 0.02 pre-PTCA UA vs pre PTCA SA; §p < 0.005 30-d UA vs pre-PTCA UA; °p = 0.005 30-d SA vs pre-PTCA SA.

In conclusion, although plasma baseline levels of IL-6 are higher in UA pts than in SA pts, they equalize 30 days after a successful PTCA followed by stent implantation. A similar trend is observed for vWF changes. IL-6 levels increase early after PTCA in SA pts, but not in UA pts: it is likely that in the latter group, the inflammatory reaction induced by the procedure is counterbalanced by the remotion of the cause of the raised baseline levels (unstable plaque).

INFLAMMATION IN ACUTE CORONARY SYNDROMES

P2773 Soluble intercellular adhesion molecule-1 levels are of diagnostic, but not prognostic, value in patients with chest pain

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C-reactive protein (CRP) is a non-specific marker of inflammation, which is often raised in patients with unstable angina and appears to be associated with an adverse outcome. Soluble intercellular adhesion molecule-1 (sICAM-1) is, however, a sensitive and specific marker, released from activated endothelium. We hypothesised that plasma sICAM-1 levels would be of diagnostic and prognostic value in patients presenting to the emergency department (ED) with chest pain.

Methods: A convenience sample of 123 patients were studied prospectively. Eligible patients had >15 min of chest pain within the prior 24 h, thought clincally to represent myocardial ischaemia and requiring hospital admission. Subjects with a history of conditions which affect sICAM-1 levels were ineligible and 4 patients who had such conditions diagnosed during admission were excluded. All eligible patients who gave consent were included in data analysis (n = 119). Cardiac troponin I, creatine kinase-MB_{mass}, CRP and sICAM-1 were assayed on arrival to the ED. On the basis of previous data, positive levels were prospectively defined as >2 ng/ml, >5 ng/ml, >1 mg/dl and >260 ng/ml respectively. Study end-points were a discharge diagnosis of an acute coronary syndrome (ACS) and/or an adverse event (AE) in hospital (death, acute myocardial infarction or coronary revascularisation), determined by investigators blinded to study blood results. The relationship between these end-points and a diagnosis of an ACS and/or suffering an AE was assessed by logistic regression.

Results: Fifty-two (of 119; 44%) patients had an ACS and 30 (25%) experienced an AE. When all markers were entered into the regression equation the only independent predictors of a patient having an ACS were cTnI and sICAM ($p < 0.01$ and 0.05 respectively). Only cTnI, however, was an independent predictor of a patient experiencing an AE in hospital ($p < 0.001$).

Conclusion: Elevated sICAM levels assist in the early detection of patients with cardiac chest pain but are not independent predictors of AEs in hospital.

P2774 Development of auto-antibodies in acute coronary syndromes: prognostic implications of cardiac injury and humoral immunity

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Background. During myocardial injury, intracellular proteins are released into the circulation and may trigger the development of auto-antibodies (AAb) as has been described after surgery. The clinical significance of these AAb is unknown. We hypothesized that ischemic injury may be in part related to AAb, which may have prognositc implications.

Methods. We investigated the presence of IgG AAb against actin, myosin, and troponin after an acute ischemic clinical event, and their correlation with CPK and Troponin-I (TnI) in 33 consecutive patients hospitalized for acute coronary syndromes (ACS) without a history of myocardial infarction, and 25 in controls who had no evidence of coronary disease. Measurements were done in-hospital, at 1 and 3 months, and patients were followed clinically for 2 years. The non-parametric Wilcoxon z-test was used for comparisons.

Results. In-hospital, the group with ACS was 39% antiactin+, 44% antimyosin+, and 27% troponin+. In contrast, the respective AAb+ of the controls were 13%, 18%, 9% ($p < 0.04$, ACS vs. control). At 1 month, 50% were actin+, 44% myosin+, and 33% troponin+, and no further change was observed at 3-month follow-up. At 1 and 3 month follow-up, persistence of either antiactin or antimyosin AAb correlated with elevated in-hospital TnI ($z < 0.03$) and CPK ($z < 0.01$). Conversely, elevated TnI at 1 or 3 months correlated with positive AAb in-hospital: antimyosin ($z = 0.03$), antitroponin ($z = 0.02$) and antiactin ($z = 0.08$). AAb+ at 1 or 3 months correlated with reinfarction at 2 year follow-up (100% vs. 25% for AAb−, p = 0.01).

Conclusions. (1) Ischemic myocardial injury is associated with presence of AAb. (2) Patients with elevated TnI and CPK develop AAb at follow-up. (3) Persistence of AAb correlates with elevated TnI at 3 month follow-up, which may signify sub-clinical cardiac injury, and with reinfarction at 2 year follow-up.

P2775 Acute phase proteins in the prognostic classification of unstable angina pectoris

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Inflammatory process has been found to play an important role in the pathogenesis of coronary heart disease (CHD) and in the prognosis of CHD patients. We examined the prognostic value of acute phase proteins C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-alpha) and fibrinogen in patients with unstable angina pectoris (UAP).

Methods: This study is based on a series of 263 patients with the diagnosis of UAP admitted to the Kuopio University Hospital (159 men and 104 women, median age 68 years). Blood samples for the measurement of CRP, IL-6, TNF-alpha and fibrinogen were drawn at admission. Maximum troponin T (TnT) levels were used in data analyses. Median follow-up time with regard to CHD mortality was 17 months.

Results: Age-standardized incidence rates for CHD death in tertiles 1–2 and tertile 3 for CRP were 2.2% and 13.0%, for IL-6 2.3% and 13.7%, for TNF-alpha 3.2% and 11.2%, and for fibrinogen 3.1% and 10.7%, respectively. Cox hazard ratios and 95% CIs (tertile 3 vs tertiles 1–2), adjusted for age, were: 2.51 (1.41–4.45) for CRP, 2.38 (1.31–4.34) for IL-6, 1.88 (1.09–3.24) for TNF-alpha, and 1.99 (1.16–3.41) for fibrinogen. Hazard ratios remained essentially unchanged after further adjustment for the duration of chest pain during hospitalisation and TnT levels.

In conclusion, elevated levels of acute phase proteins, in particular CRP and IL-6, are strong predictors of CHD death in patients with UAP, independently of the duration of chest pain and TnT levels in the acute phase.

P2776 Evidence of antiviral and/or antiself activity of the immune system in severe unstable angina

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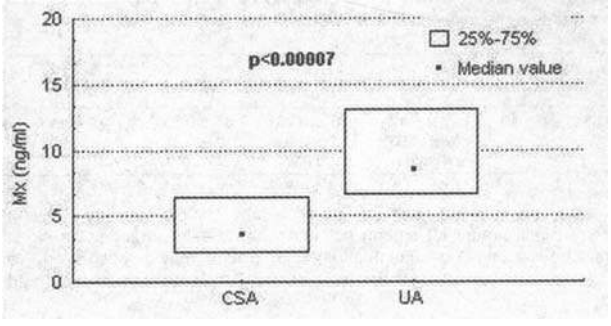
Background: A growing body of evidence suggests an involvement of systemic activation of inflammatory response in the pathogenesis of acute coronary syndromes. However the mechanism which leads to the activation of this inflammatory response is still unclear. We therefore studied the activation of the Interferon-1 (IFN-1) system (which consists of IFN alfa and IFN beta), typically involved in viral and autoimmune diseases, as a possible mechanism.

Materials and methods: As a marker of IFN-1 pathway activation we measured Mx-protein serum levels, obtained through peripheral venous sample, in 22 patients (pts) with Unstable Angina (UA) admitted to our Coronary Care Unit, in 29 pts with Chronic Stable Angina (CSA). Mx is an intracellular protein principally produced by leukocytes, directly and exclusively induced by IFN-1 system. We used the Magic Lite Mx Immunoassay, developed by Chiron Diagnostic. Inclusion criteria for UA was angina (Braunwald class IIIb), no more than five days before blood samples collection. Exclusion criteria were recent viral infection (fever or influenza-like symptoms within 30 days), autoimmune diseases or neoplasia.

Results (median and quartiles): Mx-protein serum levels were significantly higher in UA pts vs. CSA pts, being respectively 14.4 (5.6–13.7) ng/ml, 4.4 (2.04–6.4) ng/ml ($p < 0.00007$).



Mx blood concentration; CSA vs. UA

Conclusion: Our data show a significant activation of INF-1 pathway in UA pts vs CSA pts. However this activation is much smaller then that elicited by a systemic viral infection or by a systemic autoimmune disorder (in which MX protein reaches level of ≥100 ng/ml). Our finding suggest that a mild or localized activation of the immune system versus viral or self antigens might be a component of the inflammatory activity commonly detectable in UA.

P2777 Neopterin, C-reactive protein, cardiac troponin I and coronary events in patients with unstable angina

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Background: Prognosis in patients with unstable angina (UA) is worse in the presence of raised cardiac troponin I (cTnI) and C-reactive protein (CRP) concentrations. Complex coronary stenoses (CCS) are a marker of risk in patients with rapidly stabilized UA. This study investigated whether cTnI is related to CCS and inflammation markers in patients with rapidly stabilized UA.

Methods: We studied 88 consecutive UA patients (57 men) who stabilized within 24 hours of admission, and with normal CK levels during the first 48 hours of coronary care admission. In 55 patients who underwent coronary angiography all coronary stenoses ≥30% were assessed and classified as 'complex' or 'smooth'. Serum cTnI, CRP and neopterin concentrations were measured within 24 hours of admission.

Results: Patients with high cTnI serum concentration (≥0.4 μg/L) were significantly older ($p = 0.002$), had a higher prevalence of diabetes mellitus ($p = 0.019$) and hyperlipidaemia ($p = 0.034$), and had higher CRP ($p = 0.020$) and neopterin levels ($p = 0.032$). Angiographic disease severity was similar in patients with normal cTnI compared to those with high cTnI, but patients with high cTnI had a significantly larger number of CCS ($p < 0.0001$). We observed a correlation between cTnI and neopterin ($p = 0.014$) and also with CRP ($p = 0.096$). cTnI ($p = 0.002$) and neopterin ($p = 0.45$) but not CRP ($p = 0.98$) were independently associated to the number of CCS in a multiple regression analysis.

Conclusions: cTnI is associated with the number of CCS and inflammation markers in patients with rapidly stabilized UA, which may explain the long term prognostic value of cTnI in these patients.

P2778 Is there a difference in the role of inflammation between patients with recent onset angina and patients with progressive angina?

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The pathophysiological mechanisms in the different types of clinical presentations of unstable angina are controversial. Our objective was to explore the role of the markers of inflammatory activity in patients with recent onset angina (ROA) and with progressive angina (PA).

Methods: 210 consecutive patients with unstable angina and no prior myocardial infarction nor total CK elevation post admission were included. Measurements of C-reactive protein (CRP) level at admission, at 48 hours and at discharge were performed, as well as a continuous Holter ECG recording during the initial 24 hours. In 101 (48.1%) patients, the episode of unstable angina was the first manifestation of coronary heart disease (ROA). The remaining 109 patients (51.9%) had prior history of chronic stable angina (PA).

Results: Mean age was 66.1 ± 11.1 years, 62.9% were male; 63.3% received prior treatment with aspirin, and 43.8% had ST segment depression on admission ECG. Overall levels of C-reactive protein* at admission, 48 hours and at discharge were 0.5 (0.3–1.0), 0.7 (0.3–1.6) and 0.8 (0.3–2.4) mg/dl and those of fibrinogen† were 333.9 ± 89.6, 353.5 ± 94.4 and 372.4 ± 109.7 mg/dl respectively. Univariate analysis of baseline characteristics showed:

	ROA	PA	p
CRP at admission* (mg/dl)	0.6 (0.3–1.1)	0.3 (0.15–0.8)	<0.05
CRP 48 hours* (mg/dl)	0.7 (0.3–2.2)	0.8 (0.3–1.5)	ns
CRP at discharge* (mg/dl)	0.8 (0.4–3.1)	0.8 (0.3–2.0)	ns
Fibrinogen at admission† (mg/dl)	324.9 ± 89.4	342.2 ± 89.5	ns
Prior treatment with aspirin	37 (36.6%)	96 (88.0%)	<0.001
Age (years)†	65.3 ± 12.3	66.8 ± 10.2	ns
Silent Ischemia	20 (19.8%)	34 (31.2%)	0.08 (ns)
Heart Failure	7 (6.9%)	16 (14.7%)	0.11 (ns)

(*median and 25–75% interquartile ranges, †mean ± SD).

When logistic regression analysis was performed adjusted to aspirin intake before admission, the difference in CRP levels at admission between patients with ROA and PA was no longer observed.

Conclusion: These results suggest that the role of inflammation is similar in the different subgroups of patients with unstable angina. Previous treatment with aspirin seems to delay the crescendo pattern of evolution of the acute phase reactants during the clinical period of instability.

P2779 Interleukin-6 response during acute myocardial infarction: overall reduction of postinfarct inflammation by early reperfusion?

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Background: Animal studies convincingly have demonstrated that reperfusion of ischemic myocardium induces local inflammatory reactions in infarcted myocardial tissue. To what extent this occurs in humans is not fully clear.

Methods: We investigated the course of Interleukin-6 (IL-6) in relation to early successful reperfusion after acute myocardial infarction (AMI) in 44 patients with a first AMI. The course was examined by assessing peak levels of IL -6 during AMI, as well as its total release, as was calculated from time-integral analysis adjusted for elimination. This method was chosen as it was shown in individual patients that peak levels of IL-6 rather poorly reflected the total amount of IL-6 produced. Twenty-nine patients fullfilled clinical and biochemical criteria of early reperfusion (+).

Results:

	n	Total	Peak IL-6		
			≤12 hours	>12 hours	P
Peak IL-6 (ln, ng L^{-1})					
Reperfusion (+)	29	$1.9 \pm 1.0^{*}$	$1.6 \pm 1.1^{\#}$	$2.3 \pm 0.7^{\dagger}$	0.05
Reperfusion (−)	15	$2.7 \pm 0.8^{*}$	$2.8 \pm 0.7^{\#}$	$2.6 \pm 0.8^{\dagger}$	NS
IL-6 release (ln, ng L^{-1}·hrs)					
Reperfusion (+)	29	$8.3 \pm 1.3^{**}$	$7.9 \pm 1.5^{\#\#}$	$8.7 \pm 0.8^{\dagger\dagger}$	0.05
Reperfusion (−)	15	$9.2 \pm 0.9^{**}$	$9.2 \pm 0.5^{\#\#}$	$9.3 \pm 1.1^{\dagger\dagger}$	NS

$^{*}P = 0.02$, $^{\#}P = 0.02$, $^{\dagger}P$ = NS, $^{**}P$ = NS, $^{\#\#}P = 0.04$, $^{\dagger}P$ = NS

Peak IL-6 levels occurred significantly earlier after onset of chestpain in patients with reperfusion than in those without (17.5 ± 10.5 (n = 29), versus 26.8 ± 15.0 hours (n = 14), respectively, P = 0.04). IL-6 release, and to less extent peak levels, were best (positively) correlated with infarct size in patients without reperfusion.

Conclusions: Both peak and release levels of IL-6 after AMI are significantly lower in patients with early successful reperfusion. We conclude that the extent of the overall inflammatory reactions after AMI are limited by early successful reperfusion.

VIABILITY AND VENTRICULAR FUNCTION AFTER ACUTE CORONARY SYNDROMES

P2780 Electromechanical 3D endocardial mapping: follow-up study after successful myocardial revascularization

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Nonfluoroscopic three-dimensional endocardial mapping using the NOGA™ system has been suggested as a new method for electromechanical assessment of the left ventricle. We performed NOGA mapping before and after successful myocardial revascularization in patients with prior myocardial infarction.

Methods: Nine patients (pts, 7 male, 59 ± 9 years) with prior (>2 weeks) myocardial infarction and corresponding wall motion abnormalities undergoing single- or multi-vessel PTCA were studied before and 6 month after revascularization. All patients underwent metabolic imaging with F-18 FDG PET prior to PTCA. For electromechanical assessment the left ventricle was divided into 12 regions and the regional unipolar electrogram amplitude (UA) and regional linear shortening (LS) were measured and calculated by the NOGA system.

Results: All patients had a sufficient PTCA result at 6-month follow-up. As assessed by PET, 29 of 108 ventricular regions were hypoperfused but displayed preserved metabolism (mismatch). In mismatch regions LS increased from 5.6 ± 3.4% to 10.4 ± 4.5%, in the remaining regions from 7.1 ± 4.7% to 10.3 ± 3.5%. The UA in mismatch regions was 9.9 ± 4.1 mV prior to PTCA and 10.5 ± 3.5 mV at follow up (correlation r = 0.23). In the remaining 79 regions the UA was 10.6 ± 4.8 mV at baseline and 10.7 ± 3.6 mV at follow up (r = 0.71, $p < 0.001$). The UA increased in regions with a difference in LS (ΔLS) between baseline and follow up >2% (9.8 ± 4.8 mV to 10.8 ± 3.9 mV) whereas it decreased in regions with a ΔLS < 2% (11.7 ± 3.6 mV to 10.4 ± 2.6 mV).

Conclusion: Serial endocardial electromechanical mapping can detect improvement in regional left ventricular function after successful myocardial revascularization. Hypoperfused but viable regions benefit more from revascularization. Improvement of regional mechanical function is associated with an increase of the unipolar electrogram amplitude in these regions.

P2781 Myocardial infarct size and the risk of left ventricular remodelling: clinico-orphopathological study

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Background: Multiple studies suggest that the QRS scoring system (QRSs)using observation of Q-and R-wave duration, R/Q and R/S amplitude ratios in the standard 12-lead electrocardiogram (ECG) and precordial ECG mapping is useful in estimating left ventricular (LV) function after myocardial infarction (MI).

Methods: The correlation of QRSs with quantitative autopsy was examined in 1269 cases of intrahospitally deceased patients (pts) with acute MI (age 67.9 ± 0.55 yrs). The 1st group included 1108 (87.3%) pts without anatomic signs of left ventricle aneurysm (LVA). The 2nd group included 161 (12.7%) pts with LVA (gr. 2a – 56 pts with acute LVA, gr. 2b – 105 pts with chronic LVA). Anterior location of MI was 58.9% in gr. 2a and 39.6% in gr.2b. The QRS score of the MI size at the moment of decease did not differ significantly, but its evolution from the debut of MI has been +3.18 ± 0.89% ($p < 0.001$) in whole, respectively +2.60 ± 1.47% in gr.1, +5.24 ± 1.9 in gr. 2a, +2.01 ± 1.27 in gr.2b. ST segment depression (Sum ST/nST)dominated in gr. 2a, demonstrating a larger injury of potentially viable periinfarct region. The morphological parameters signified the predominant presence of cardiac spheric remodelling signs in pts with chronic LVA. This was accompanied by differences in volume (gr. 1 – 400+11.0 mm^3, gr. 2a – 411 ± 15.8 mm^3, gr. 2b – 433 ± 16.0 mm^3) and heart mass (resp. 537 ± 10.8 g, 531 ± 19.5 g, 570 ± 21.7 g).

Conclusion: It is concluded that the QRSs will be clinicaly usefull in the early identification of LV postinfarct aneurysm and cardiac remodelling.

P2782 Left ventricular function in patients with and without persistent myocardial viability after acute myocardial infarction

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Acute myocardial infarction (MI) may elicit left ventricular remodelling and subsequent left ventricular dysfunction. The aim of the present study was to evaluate the influence of persistent myocardial viability on left ventricular function and dimension after MI.

Twenty-seven patients with a first acute MI were included and went through low-dose dobutamine echocardiography (LDDE) (0, 5 and 10 mcg/kg/minute) on day 6, 30 and 90 after the MI. Echocardiographic assessment of wall motion index (WMI), left ventricular enddiastolic volume index (EDDi), endsystolic volume index (ESDi) and ejection fraction (EF) was made. Patients with positive response in more than 2 myocardial segments at LDDE on day 90 were regarded as possessing persistent viability.

Of the 27 patients, 9 patients had persisting viability on day 90, 18 had not. No significant difference between patients with or without persistent viability was found with reference to infarct location, Q-waves or frequency of thrombolytic treatment. Patients without persistent viability had significantly more myocardial segments affected by the infarction ($p = 0.01$). No significant differences in EDDi, ESDi or EF appeared between the groups, but a trend of increase in EDIi ($p = 0.07$) as well as ESDi ($p = 0.08$) among patients without viability was seen. Patients without persistent myocardial viability had significantly higher WMI at all examinations and a significant increase in WMI from day 6 to day 90. The viable patients remained with stable WMI.

		WMI			
Day		6	30	90	
Non-viable	n = 18	1.29 ± 0.17	1.35 ± 0.26	1.38 ± 0.28	p = 0.04 day 6–90
Viable	n = 9	1.16 ± 0.05	1.13 ± 0.09	1.10 ± 0.11	ns
		p = 0.005	p = 0.006	p = 0.002	

In conclusion, a deterioration of left ventricular contraction occurs during the first 3 months after MI among patients with no echocardiographic signs of persisting viability. Subsequent left ventricle dilation may be suspected. No signs of reduced function or dilation were seen among patients with preserved viability.

P2783 Myocardial viability without biphasic response during dobutamine stress echo predicts a favourable left ventricular remodelling after myocardial infarction

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Recent data suggest a favourable influence of myocardial viability (MV) on left ventricular remodeling (LVR) process after acute myocardial infarction (MI) and primary angioplasty. The aim of this study was to evaluate the LVR phenomenon after a first, uncomplicated MI in relation to the presence of MV, inducible ischemia and biphasic response during dobutamine stress echo (DSE).

Methods: 145 consecutive patients (pts) referred for DSE were considered (age: 57, M = 127). All were free from recurrent MI or coronary surgery procedures in the first 6 months after their MI. DSE (5 to 40 μg/kg/m′ + atropine when needed; 3′ steps) was performed 8 ± 4 days after MI. A >1 wall motion score (WMS) decrease at low doses of dobutamine (5–20 mg) identified MV. Ischemia was present in case of >1 WMS increase at high doses of dobutamine. The presence of both MV and ischemia was defined as biphasic response. Indexed end-diastolic and end-systolic volumes (EDV, ESV, ml/m2) from the baseline DSE and from a 2D echo performed 6 months after MI were separately calculated in blinded conditions (modified Simpson's rule). Changes of LV volumes (Δ) were calculated and compared for absolute (ΔEDV, ΔESV) and relative values (Δ% EDV, Δ% ESV). MI site, thrombolysis, CK peak, rest ejection fraction and WMS were also considered.

Results: Pts were divided according to DSE results (Gr 1: no MV, no ischemia; Gr 2: no MV, ischemia+; Gr 3: MV+, no ischemia; Gr 4: MV+, ischemia+). All basic clinical variables were comparable in the four groups.

	ΔVTD	Δ%VTD	ΔVTS	Δ%VTS
Gr 1 (50 pts)	2.7 ± 10.5	5.4 ± 18.2	1.2 ± 8.1	6.8 ± 25.8
Gr 2 (30 pts)	6.9 ± 17.1	13.0 ± 24.9	1.7 ± 10.3	5.5 ± 29.5
Gr 3 (34 pts)	−3.9 ± 9.7§	−6.4 ± 13.9§	−4.8 ± 7.5§	−13.7 ± 19.1§
Gr 4 (31 pts)	7.2 ± 10.5*	13.3 ± 16.7*	3.5 ± 7.4*	10.1 ± 22.7*

§ = p < 0.005 Gr 3 vs Gr 1 and Gr 2; * = p < 0.0001 Gr 4 vs Gr 3

Conclusions: Post-infarction pts with MV during DSE present a different LVR depending on residual dobutamine-inducible ischemia: 1) In pts without inducible ischemia, LV dilatation does not occur; 2) In patients with biphasic response LV dilatation is present and comparable to pts without MV.

P2784 History of hypertension improves left ventricular function early after acute myocardial infarction: analysis by Doppler echocardiography

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We assessed the influence of history of arterial hypertension on left ventricular (LV) systolic and diastolic functions and their reciprocal interactions early after acute myocardial infarction (AMI).

Methods: Standard Doppler-echo was performed in pre-discharge period to 86 patients with AMI, divided in 2 groups: 52 normotensives (N) and 34 hypertensives (H, based on previous evidence of diastolic blood pressure > 90 mmHg and/or of antihypertensive therapy). Twenty healthy subjects were the control group. Patients were excluded for previous AMI, clinical signs of heart failure or cardiogenic shock, valvular heart disease, atrial fibrillation, post-AMI angina. M-mode LV mass was indexed for height. Two-dimensional LV volumes and ejection fraction (EF) were determined. Doppler-derived stroke volume (SV) was calculated. Transmitral diastolic peak velocity E/A ratio, atrial filling fraction (AFF) and E wave deceleration time (DT) were measured.

Results: H had comparable age and heart rate but higher blood pressure and LV mass index than the other 2 groups (all $p < 0.001$). H had also larger end-diastolic volume, reduced end-systolic volume, greater EF and SV (all $p < 0.01$) in comparison with N. E/A ratio was higher (1.3 ± 0.2 and 1.4 ± 0.3 respectively) and DT shorter in both H and N than in controls (all $p < 0.001$) but AFF was greater and DT longer (158 ± 15 msec vs. 149 ± 12 msec) in H vs. N (both $p < 0.01$). Significant relations of SV with both AFF ($r = 0.40$, $p < 0.01$) and DT ($r = 0.53$, $p < 0.001$) were found in H but not in N ($r = 0.19$ and $r = 0.15$, both NS).

In conclusion, diastolic pseudonormalization is detectable in both groups early after AMI, but prolonged DT and increased AFF characterize H, as imprint of previous diastolic dysfunction due to both increased afterload and LV mass. Based on the relations found between SV and both AFF and DT, the improvement of LV systolic observed in H is supported, throughout a greater atrial contribution to LV filling, by greater utilization of Starling mechanism.

P2785 Differentiation between hibernating myocardium and dysfunctionating left ventricular segments caused by remodelling, using polar map integration of imaging techniques

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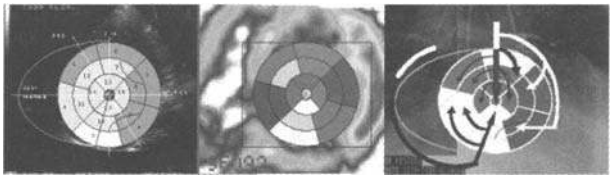
The aim of this study was to integrate the wall motion, the perfusion and the metabolic results. Data from echocardiography, coronary angiography and SPECT/PET in 16 left ventricular segments were compared in a polar map display. 10 patients with previous myocardial infarction were selected (mean age: 50.1 ± 12.2 years, EF: 34.1 ± 12.7%). The segments showing wall motion abnormality with less than 50% ^{18}FDG activity were regarded as infarcted (scarred) regions. The cases with more than 50% relative ^{18}FDG activity in the dysfunctioning regions, and with more than 70% diameter stenosis in the supplying epicardiac coronary arteries, were defined as hibernating myocardium. Dysfunction caused by remodelling was considered if coronary angiography did not reveal significant coronary artery stenosis in the supplying epicardial artery. The incidence of perfusion- metabolic mismatches in the segments was examined by comparing the Tc-99m-MIBI SPECT with the ^{18}FDG-PET results. The data revealed 48 (46.6%) dysfunctioning segments with low metabolic activity (infarction-I). In 29 (28.2%) segments with significant coronary stenosis on the supplying coronary artery, the metabolic activity was maintained (hibernation-H). In 26 (25.2%) segments, the hypo- or akinesia was associated with (nearly) normal epicardial coronary branch (remodelling-R).



Wall motion, FDG and coronary polar map.

A significant correlation ($r = 0.77$, $p = 0.01$) was found between the incidencies of R and I segments. No correlation was noted for the incidences of the H and I segments ($r = 0.11$, $p = 0.76$). The presence of perfusion-metabolic mismatch was detected only in 45% of the H regions (13/29). The results show that remodelling is more frequent after large myocardial infarction, and mismatch pattern can be demonstrated only in a part of hibernating myocardium.

P2786 Echocardiographic assessment of left ventricular remodelling following closed-chest infarction in the rabbit: a physiologically relevent model

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Introduction: Ventricular dynamics following myocardial infarction (MI) is critically dependent on the presence of an intact pericardium However, current small animal models of infarction involve breach of the pericardium. We have developed a novel closed-chest model of MI in the rabbit and characterised the changes in left ventricular function and geometry using transthoracic echocardiography (TTE).

Methods: 8 adult New Zealand White rabbits underwent coronary angiography followed by MI by placement of a thrombogenic coil in the proximal circumflex artery. 6 age and weight-matched rabbits underwent sham procedures. TTE was performed using a 5 mHz transducer. M-mode-derived measurements of end-systolic diameter (ESD), end-diastolic diameter (EDD) left atrial diameter (LA) and % fractional shortening (FS) were performed at day 0 and days 1, 3, 7, 14, 28 and 84. Mitral doppler signals were also compared pre- and post-MI.

Results: statistically significant ($p < 0.01$) changes in ESD and FS were seen from day 7 post-MI (table). A non-significnt early increase in EDD was observed at day 7 which became significant ($p < 0.05$) by day 84. Non-significant increases in LA were also observed. A striking change in mitral filling pattern was also seen in some infarcted rabbits indicating restrictive physiology.

		Day 1	Day	Day 7	Day 14	Day 28	Day 100
ESD	MI	0.64 ± 0.08	0.65 ± 0.06	0.77 ± 0.05	0.81 ± 0.04	0.88 ± 0.06	1.34 ± 0.14
(cm)	Sham	0.60 ± 0.04	0.63 ± 0.02	0.62 ± 0.01	0.65 ± 0.02	0.67 ± 0.004	0.75 ± 0.04
EDD	MI	1.11 ± 0.05	1.38 ± 0.15	1.43 ± 0.11	1.57 ± 0.06	1.49 ± 0.08	2.10 ± 0.09
(cm)	Sham	1.14 ± 0.03	1.39 ± 0.06	1.40 ± 0.05	1.39 ± 0.04	1.50 ± 0.03	1.66 ± 0.02
FS	MI	53.9 ± 1.8	54.3 ± 2.2	50.9 ± 3.2	44.9 ± 2.4	44.9 ± 2.0	36.94 ± 4.40
(%)	Sham	56.9 ± 1.5	54.8 ± 0.7	55.5 ± 1.0	56.8 ± 2.2	58.3 ± 0.8	54.5 ± 2.22

Conclusions: We have characterised the echocardiographic changes in a clinically relevant small animal model of left ventricular remodelling following myocardial infarction. Dilatation was associated with a significant early increase in left ventricular ESD and late increase in EDD similar to the situation in humans. This model, we believe, will provide a powerful tool in the investigation of experimental heart failure.

P2787 Relationship between Q-wave regression and viability in the anterior myocardial infarction

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The meaning of Q-wave regression after an acute myocardial infarction (AMI) has not yet been completely established. Particularly the relationship between Q-wave regression and viability was never reported.

Methods: We studied 26 pts with first Q-wave anterior AMI, retrospectively selected. A standard 12-lead ecg was registered on the hospital admission, before the hospital discharge and at follow-up; nitrogen-13-ammonia (NH3) and fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) was also performed within one month of the onset of symptoms. An ecg-score (following the millimetre of regression of Q-wave and/or increase of R-wave in corresponding leads from V1 to V4, from discharge to follow-up) was attributed at every pt. PET viability was defined as an FDG uptake $\geq$ 50% of the maximum, whereas a perfusion-metabolic mismatch was considered present when the NH3 uptake was significantly lower than FDG uptake.

Results: The mean follow-up was 22 ± 13 months. In the 11 pts without viability (group 1) the attributed mean ecg-score was of 2.62 ± 3.88 mm. In the 15 pts with viability (group 2) the mean ecg-score was of 14.63 ± 10.44 mm ($p = 0.001$ vs group 1). In the 7 pts with viability and without mismatch (group 2a) the ecg-score increased of 22.4 ± 8.5 mm ($p < 0.0001$ vs group 1) while in the 8 pts with viability and with mismatch (group 2b) the ecg-score increased of 8.16 ± 6.96 mm ($p = 0.003$ vs group 2a and 0.05 vs group 1).

Conclusions: Our study shows that, in the anterior AMI, the regression of the ecg signs of necrosis is related with the presence of viability in the infarcted area. Moreover, in presence of a metabolic-perfusion mismatch, the regression is lower.

P2788 Prediction of cardiac events with cardiopulmonary exercise testing soon after myocardial infarction

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Aim of this investigation was to assess the prediction of cardiac death, re-infarction or heart failure (IV NYHA), in the subsequent clinical course after an uncomplicated myocardial infarction. We explored the predictive power of clinical variables and variables derived from exercise testing, performed one month after infarction. We studied 164 consecutive patients (131 males), their mean age was 60 ± 10 years. Exercise testing with breath by breath gas exchange evaluation was performed with an erect bicycle, with 25 W initial workload and 25 W increases every 3'. In 54 patients unable to cycle, treadmill exercise testing was performed with the Bruce protocol. Patients were followed up for 11.5 ± 10 months. Their data were also compared with our population of 74 healthy volunteers (46 males, mean age 43 ± 12), who also underwent cardiopulmonary exercise testing.

Results: In the healthy volunteers, peak VO_2 was 30 ± 9 ml/kg/min, the 95th inferior percentile being at 18 ml/kg/min. Anaerobic threshold (measured with the V-slope method, operator-controlled) was at a VO_2 of 16 ± 7 ml/kg/min, the 95th inferior percentile being at 10.5 ml/kg/min. In the patients, peak VO_2 was 19 ± 5 ml/kg/min ($p < 0.001$ vs normal volunteers), anaerobic threshold was at 11 ± 3 ml/kg/min ($p < 0.001$ vs normal volunteers). Twenty-three patients had cardiac events (death, reinfarction or heart failure). At univariate analysis, age ($p = 0.01$), peak VO_2 ($p < 0.0001$) and VO_2 at the anaerobic threshold ($p < 0.001$) were associated with cardiac events. At logistic regression analysis, the sole variable significantly and independently associated with cardiac events (and also with cardiac death alone) was VO_2 at peak exercise. The best cut-off limit to subdivide patients at different risk of events was 12 ml/kg/min: 18 patients with less than 12 ml/kg /min VO_2 at peak exercise had 36% and 68% risk of a cardiac event at 1 and 2 year follow up, compared with 3% and 10% risk in the remaining patients ($p = 0.0001$).

Conclusions: Soon after myocardial infarction, peak VO_2 is an extremely powerful predictor of subsequent cardiac death, reinfarction or heart failure during medical therapy, and adds significant information to clinics and exercise test data. The best cut-off value of peak oxigen consumption for the prediction of the individual risk of cardiac events is 12 ml/kg/min.

P2789 The interactive effect of age and right ventricular involvement on the increase in mortality in patients with inferior myocardial infarction is restricted to the early phase

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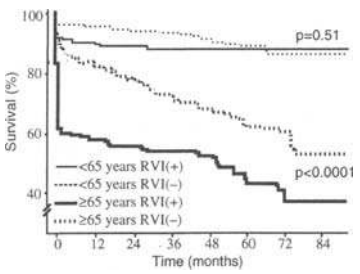
Right ventricular involvement (RVI) increases mortality in patients with inferior myocardial infarction (IMI), particularly in those of advanced age. The duration of the interaction between age and RVI on the increase in mortality in patients with IMI is unknown.

Methods. The short- and long-term mortality of 798 consecutive patients admitted to our CCU with an IMI of less 48 hours of evolution was studied. We performed an stratified analysis according to the patients' age (≥65 years old versus <65 years) and to the presence of RVI (defined by echocardiographic and/or electrocardiographic criteria). A complete follow-up was obtained in 98% of patients.

Results. In the whole group, the mean age was 64 years, 78% were men and 54% received reperfusion therapy. The median follow-up time was 45 months. Survival curves by each stratum are shown in the graph.



Conclusions: In IMI, RVI is associated with a lower long-term survival only in elderly patients. However, this difference in survival is a consequence of the increase in mortality produced in the early phase.

P2790 Perioperative prognostic value of dipyridamole echocardiography in vascular surgery: a large-scale multicenter study on 509 patients

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Background: Patients undergoing major vascular surgery are at relatively high risk of cardiac events, and pharmacological stress echocardiography is increasingly used for perioperative risk stratification.

The aim of the study was to evaluate the value of dipyridamole echocardiography test (up to 0.84 mg/kg over 10') in predicting cardiac events in a large scale, multicenter, prospective, observational study design.

Method and Results: 509 patients (mean age 66 ± 10 years) were studied prior to vascular surgery by dipyridamole stress echocardiography in 11 different centers. All patients underwent preoperative clinical risk assessment according to the American Heart Association guidelines. No major complications occurred during dipyridamole stress echocardiography. Technically adequate images were obtained in all patients; however, in four patients only the low dipyridamole dose (0.56 mg/kg over 4 min) was given for limiting side effects. Eighty-eight (17.3%) had a positive test. Perioperative events occurred in 31 patients (6.1%): 6 deaths, 11 myocardial infarctions and 14 unstable angina. Sensitivity and specificity of dipyridamole stress echocardiography for predicting spontaneous cardiac events were 81% and 87%, respectively, with a positive predictive value of 28% and negative predictive value of 99%. By multivariate analysis the difference between wall motion score index at rest and peak stress, test positivity and ST segment depression during dipyridamole infusion were independent predictors of any perioperative cardiac event.

Conclusion: Dipyridamole stress echocardiography is safe and well tolerated in patients undergoing major vascular surgery, and provides an effective preoperative screening test for the risk stratification of these patients, mainly due to the extremely high negative predictive value, which is a potent predictor of complication-free procedure.

P2791 Can doppler myocardial imaging segmental velocities predict regional contractile recovery 3 months post successfully treated Q-wave acute infarction?

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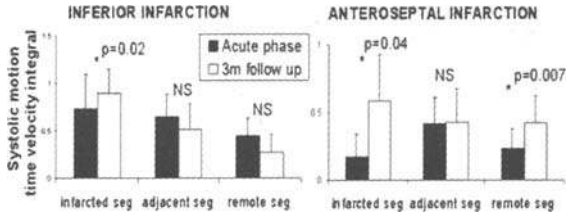
The LV recovery after acute myocardial infarction (AMI) is related to successful reperfusion. Both global and regional indices can be useful for LV function monitoring. Since Doppler Myocardial Imaging (DMI) measures segmental velocities it can provide valuable information on regional changes of reperfused myocardium.

Aim: The aim of this study was to assess feasibility of Doppler Myocardial Imaging technique in monitoring the regional recovery in patients post AMI.

Methods: 20 pts (aged 49–81 y, 10F) with AMI were evaluated by Colour DMI within 24 h since onset of the symptoms and 3 months post AMI. Only patients with first Q wave AMI and without ischemic events during the follow up period were enrolled to this study. Successful reperfusion was confirmed in 14 pts (gr.III). The infarcted, adjacent and remote segments were established on the base of 2 D grey scale image in 10 pts with anteroseptal (Gr. I) and 7 pts (Gr. II) with inferior AMI. A 70–80 fps colour DMI data set was acquired and peak systolic velocity (Vel), time velocity integral (Integr) were computed.

Results: In all patients the 3 months follow up study showed an increase in segmental Vel and Integr for infarcted segments in both Gr I and II(see Figure). LV FS increased from 24.9 ± 3.4 to 30.8 ± 6.7% (p = ns). Negative correlation was found between CKMB level and Integr measured in acute phase of AMI (R = −0.52, p = 0.01). In Gr.III an increase in both Vel (2.2 ± 1.5 vs 3.4 ± 2.1, p < 0.05) and Integr (0.32 ± 0.31 vs 0.71 ± 0.3, p < 0.001) was also noted.



Conclusions: Despite nonsignificant global function improvement significant increase in peak systolic velocity and velocity integral was observed in infarct/reperfused segments. Thus DMI can identify segmental functional recovery after successful reperfusion.

P2792 Does the presence of significant mitral regurgitation protect against left ventricular thrombus formation after acute myocardial infarction?

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Rationale: A role of mitral regurgitation in protecting against left ventricular thrombosis (LVT) after acute myocardial infarction has been previously suggested, but this hypothesis is still controversial.

Methods: From the GISSI-3 echo sub-study population, 757 patients with their first myocardial infarction were studied by echocardiography performed (1) from 24 to 48 hours, (2) at discharge, (3) after 6 weeks and (4) after 6 months. The diagnosis of LVT was based on the dectection of an echo-dense mass with defined margins visible throughout the cardiac cycle in at least two orthogonal views.

Results: In 64 patients (8%) left ventricular thrombosis was detected in one or more examinations. Compared to the remaining 693 patients, subjects with left ventricular thrombosis were significantly older (64.6 ± 13.0 vs 59.8 ± 11.7 years, p < 0.005), had larger infarction (extent of wall motion asynergy: 40.9 ± 11.5 vs 24.9 ± 14.0%, p < 0.001), more depressed left ventricular ejection fraction at admission (43.3 ± 6.9 vs 48.1 ± 6.8%, p < 0.001) and greater left ventricular volumes at admission (87 ± 22 vs 78 ± 18 ml/m^2, p < 0.001; 50 ± 17 vs 41 ± 14, p < 0.001; for end-diastolic and end-systolic respectively). The use of thrombolysis and aspirin did not differ between the 2 groups (respectively 71% vs 74% and 81% vs 86%, p NS). The prevalence of moderate to severe mitral regurgitation at Color Doppler at admission was higher in patients who had left ventricular thrombosis at any time (10.2% vs 4.2%, p < 0.05). A stepwise multiple logistic regression analysis established that the only independent variable related to the presence of left ventricular thrombosis was the extent of wall motion asynergy (p < 0.0001).

Conclusions: Moderate to severe mitral regurgitation in patients after myocardial infarction does not seem to protect against left ventricular thrombus formation; on the contrary its prevalence is higher in these patients. The only independent determinant of left ventricular thrombosis is the extent of the akinetic-diskinetic area detected at the echo performed between 24 and 48 hours from symptoms onset.

P2793 Left atrial remodelling after acute myocardial infarction: an analysis of the GISSI-3 echo substudy

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Background: While several studies have tried to assess the remodeling process of the left ventricle after acute myocardial infarction (AMI), no significant information is available of the related changes of the left atrium.

Methods: 757 patients from the GISSI-3 Echo substudy with their first AMI aged from 22 to 88 years (mean 60 ± 12 years) were considered. Echocardiograms were performed at 24–48 hours after AMI (T1), before discharge (T2), after 6 weeks (T3) and after 6 months (T4). Left atrial remodeling was defined as early (T1–T2) and late (T2–T4). Maximal left atrial area (A) was obtained from the apical 4 chamber view at end-systole.

Results: Early left atrial remodeling (T1–T2) was characterized by an increase of A from 17.2 ± 3.7 to 17.6 ± 3.8 cm^2 (repeated measures analysis of variance, time effect: F = 8.8, p < 0.005; inter-observer difference: 0.08 ± 1.53 cm^2). In the univariate analysis the increase of A was positively related to the increase in left ventricular sphericity (r = 0.09, r = 0.08 for diastolic and systolic respectively, p < 0.05). In a stepwise multiple linear regression the only variable independently related to this change was left ventricular ejection fraction at T1 (variables at T1 considered in the model were: age, max cpk plasma level, extent of a-diskinetic area, left ventricular volumes, ejection fraction and sphericity indexes, peak E and A wave and E wave deceleration time at Doppler mitral inflow). Similarly, late left atrial remodeling (T2–T4) was characterized by an increase of A up to 17.9 ± 3.5 cm^2 (F = 5.9, p < 0.005). The variable independently related to the late changes was E wave deceleration time at Doppler mitral inflow. When variables at T2 were considered, late remodeling was independently related to E wave peak velocity at Doppler mitral inflow. Patients with moderate to severe mitral regurgitation at Color Doppler at T1 had higher A (18.5 ± 3.5 vs 17.1 ± 3.7 cm^2, between subjects effect: F = 8.6, p < 0.005) but the increase over time did not differ from that in patients with mild or absent mitral regurgitation (interaction F = 0.1, p NS).

Conclusions: Both early and late left atrial remodeling occur after AMI. The main factors related to the remodeling were left ventricular ejection fraction (early remodeling) and left ventricular filling characteristics (late remodeling). Although patients with significant mitral regurgitation had greater left atrial dimensions, the pattern of left atrial remodeling in these patients was not significantly different from the overall population.

HOW TO FIGHT WITH THE THROMBUS DURING INTERVENTION

P2794 The Rescue PT catheter: a simple and effective alternative for the removal of intracoronary thrombus

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Thrombus is by far the most frequent cause of acute coronary syndromes. Removal of the thrombus by thrombolytic agents carries the risk of severe bleeding, primary PTCA the risk of distal embolisation.

The aim of this study was the evaluation of the safety and efficacy of thrombus aspiration using the Rescue PT catheter, a 4.5 F polyurethane semi monorail catheter with an oblique end. It can be advanced over a 0.014 inch guide wire. Vacuum is applied by a small suction device.

Methods: Angiographic and clinical aspects were evaluated in 50 pts (51 vessels; 46 coronary arteries and 5 bypass grafts) with angiographic suspicion of a considerable amount of fresh intravascular thrombus (<10 hours). 44 Pts were treated in the acute phase of a myocardial infarction, 29 pts after failed thrombolysis. In 7 pts thrombosuction was performed because of distal embolisation, in 4 alredy present before and in 3 after initial thrombosuction.

Results: Thrombus could be removed in 46/51 vessels and TIMI 3 flow was present in 9 vessels before, 42 after thrombosuction and 47 after additional therapy. In 42 vessels additional therapy (PTCA, stent, thrombolysis) was applied. Angiographic signs of distal embolisation possibly caused by thrombosuction occurred in 3 vessels. Distal embolisation was successfully treated by thrombosuction in 5/7 Pts. 2 Pts died in-hospital because of cardiogenic shock that was already present before the procedure.

Conclusion: The Rescue PT catheter proved to be an effective and safe alternative for the removal of fresh thrombus from coronary arteries and bypass grafts. It is also particularly useful if distal embolisation is present.

P2795 Cost-effectiveness of rheolytic thrombectomy for thrombus-containing coronary lesions: final results from the VEGAS 2 trial

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Despite advances in mechanical and pharmacological therapy, thrombus-containing lesions are at high risk for adverse events and remain a challenging subset for percutaneous coronary revascularization. Rheolytic thrombectomy with the Angiojet device can safely remove intracoronary thrombus, but the overall cost-effectiveness of this technique is unknown.

Methods: We determined in-hospital and 1-year follow-up costs for 347 patients with thrombus-containing lesions who were randomized to treatment with intracoronary urokinase (UK; 6 to 30 hour infusion, n = 169) or immediate thrombectomy with the Angiojet device (AJ; n = 178). Catheterization laboratory costs were based on measured resource utilization and 1998 unit costs, while all other costs were estimated from hospital charges and cost-center specific cost-to-charge ratios.

Results: Compared with UK, AJ reduced the incidence of periprocedural MI (12.2% vs. 30.3%, $p < 0.001$) and major vascular complications (4.5% vs. 17.7%, $p < 0.001$) and shortened length of stay by nearly one day (4.2 vs. 4.9 days, $p = 0.02$). As a result, AJ reduced procedural costs, ancillary costs, and physician fees (see Table) and produced net cost savings of more than $5000 per patient ($16,803 vs. $22,723, $p < 0.001$). Regression analysis demonstrated that the in-hospital cost savings with AJ were explained by reduced ischemic complications (15%), reduced vascular complications (19%), and avoidance of multiple procedures (66%). These cost savings were maintained at one year follow-up ($21,657 vs. $27,372, $p < 0.001$).

In-hospital and 1-year costs

	Angiojet	Urokinase	P-value
Initial procedure	$8064 ± 2730	$9733 ± 4108	<0.001
Repeat procedures	$392 ± 1413	$847 ± 1927	<0.001
Hospital stay	$6732 ± 5926	$8637 ± 5843	<0.001
MD fees	$1615 ± 490	$3506 ± 1138	<0.001
Initial hospitalization	$16803 ± 7397	$22723 ± 8998	<0.001
Subsequent hospitalizations	$4853 ± 11,085	$4649 ± 10852	NS
1-year total	$21657 ± 14966	$27372 ± 14022	<0.001

Conclusions: Compared with standard treatment with intracoronary UK, rheolytic thrombectomy both improves clinical outcomes and reduces overall medical care costs for patients with thrombotic coronary lesions.

P2796 Influence of lesion morphology on markers of blood coagulation and ischaemia before and after PTCA

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The aim of the study was to evaluate the influence of lesion morphology on markers of blood coagulation and ischemia before and after PTCA.

Methods: 187 patients with angina pectoris were pre-PTCA divided in three groups on the basis of the ischemia related artery according to angiographic lesion morphology. The classification follows the criteria by Ambrose. Group I: stenosis >50% with smooth or slightly irregular morphology. Group II: asymmetric stenosis >50% with irregular contours/ulcerations. Group III: stenosis with an intracoronary thrombus. Fibrinogen, thrombin antithrombin III complex (TAT) and troponin-I (Tn-I) levels were determined pre- and 4, 8 and 24 hours post-PTCA. The highest values post-PTCA are given in the table. The groups were compared using Wilcoxon's test.

Results:

	Group I n (%)	Group II n (%)	Group III n (%)	p
fibrinogen > 350 mg/l pre-PTCA	16 (20%)	20 (36%)	4 (27%)	n.s.
fibrinogen > 350 mg/l post-PTCA	22 (30%)	14 (36%)	*6 (75%)*	0.039
T A T > 4.1 μg/l pre-PTCA	48 (54%)	35 (49%)	11 (55%)	n.s.
T A T > 4.1 μg/l post-PTCA	18 (22%)	13 (24%)	*7 (54%)*	0.047
Tn-I ≥ 0.4 μg/l pre-PTCA	9 (19%)	8 (26%)	*5 (63%)*	0.043
Tn-I ≥ 0.4 μg/l post-PTCA	13 (28%)	10 (32%)	*6 (75%)*	0.037

Conclusion: Patients with thrombotic lesions show significant higher levels of fibrinogen and TAT post-PTCA in comparison to patients with non-thrombotic lesions (group I + II). Tn-I levels were pre- and post-PTCA significantly higher in group III than in group I + II.

P2797 Improved outcome of diabetics submitted to coronary angioplasty with concomitant use of abciximab? A practical insight

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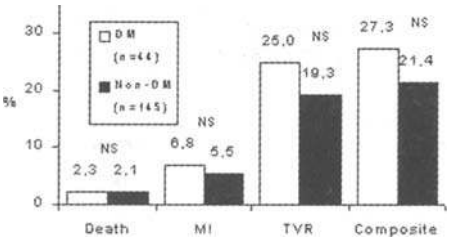
Background: Diabetics have a particularly important cardiac event rate after coronary angioplasty (PTCA). It is unknown if recently introduced IIb/IIIa receptor antagonists can modify this ominous prognosis.

Aim: To analyse safety and efficacy of abciximab in the outcome of diabetics (DM) submitted to PTCA compared with non-DM patients (pts).

Methods: We evaluated 189 pts (mean age 59 ± 10 years, 14% female) submitted to PTCA with abciximab from June 1996 to March 1998. DM was present in 44 pts (23%). Baseline demographic and clinical characteristics were similar in DM and non-DM pts. Clinical presentation for PTCA was an acute coronary syndrome in 45% of pts in DM versus 32% in non-DM pts (NS). Stent implantation was 89% in DM versus 83% in non-DM pts (NS). Unplanned ("rescue") use of abciximab was 41% in DM versus 37% in non-DM pts (NS).

Results: The rate of hemorrhagic complications requiring blood transfusion therapy was 6.8% in DM versus 0.7% in non-DM pts ($p = 0.06$). Thrombocytopenia (<50' 10^9/L) occurred in 2.3% of DM versus 2.8% of non-DM pts. Follow-up at 6-months was (figure):



Conclusions: In this study, the occurrence of major acute coronary events at 6-months follow-up did not differ significantly between diabetic and non-diabetic patients undergoing PTCA with abciximab.

P2798 In-hospital predictors of major complications following intracoronary stenting with ticlopidine-aspirin in patients with unstable angina: a rational basis for the selected use of glycoprotein IIb/IIIa inhibitors

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Prior studies have shown a significant reduction of major complications using abciximab during intracoronary stent placement, especially in acute coronary syndromes. Nonetheless, particularly because of its cost, the use of this treatment in a prophylactic way remains limited. The aim of our study was to assess in-hospital predictors of major complications in patients with unstable angina, in order to determine in which subset this treatment would be the more beneficial. We studied 287 consecutive pts (220 men, mean age 64 years) with rest unstable angina (Braunwald class II and III) who underwent intracoronary stent placement followed by ticlopidine-aspirin therapy, whitout planned use of abciximab in our 2 centers in 1995–96. Indication for stent placement was bail-out in 17 pts (6%), sub-optimal results in 189 pts (66%) and elective in 81 pts (28%). Successful stent placement was achieved in 96%. Our end-point for major in-hospital complications was the cumulative rate of death, Q-wave MI, large non Q-wave MI (CK > 5 × ULN) and emergency CABG. A major complication occurred in 16 pts (5.6%). Univariate predictors were Braunawald class III (9.3 vs 3.3%, $p < 0.03$), 3-VD (10.3 vs 3.3%, $p < 0.009$), female gender (10.4 vs 3.8%, $p < 0.03$), bail-out procedure (35 vs 3.7%, $p < 0.00001$) and age (mean age in case of a major complication 70 ± 8 vs 64 ± 11, $p < 0.02$). On multivariate analysis, Braunwald class III ($p < 0.05$), female gender ($p < 0.01$) and 3-VD ($p < 0.03$) were predictors of major complications.

Thus in the setting of rest unstable angina ceratin subsets of patients were at high risk of developing a major complication following intracoronary stent placement with ticlopidine-aspirin. In these selected cases, prophylactic use GP IIb/IIIa inhibitors might be advisable.

P2799 The use of clopidogrel instead of ticlopidine after intra-coronary stent insertion: initial results in stents of ≤3 mm diameter

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Patients with small stents (≤3 mm diameter) are at increased risk of stent occlusion. Ticlopidine is now used routinely in addition to aspirin to prevent stent thrombosis but is unlicensed in the UK and causes neutropaenia in 2.4% of patients. Clopidogrel, which is chemically related to ticlopidine, has recently become available. It has no increased risk of neutropaenia and is cheaper than ticlopidine. In all patients treated in our institution with stents ≤ 3 mm we compared outcome in those treated with aspirin and ticlopidine (Dec–Jul 97/98, Group T) and those treated with aspirin and clopidogrel (Aug–Dec 98, Group C). In Group T there were 190 patients (253 lesions, 274 stents, age 59.1 ± 10.7 yrs, 72% male, 31% unstable angina). 64% had 1 stent, 36% had >1 stent. In Group C there were 118 patients (157 lesions, 173 stents, age 60.6 ± 9.4 yrs, 75% male, 20% unstable angina). 68% had 1 stent, 32% had >1 stent. All patients had heparin during stent insertion and similar stents were used in both groups. Vessels treated (Group T vs C): LAD 47% vs 51%; Cx 25% vs 22%; RCA 22% vs 20%; D1 2.4% vs 1.2%; 1x 1.2% vs 2.4%; L main 0% vs 1.9%; vein graft 2.4% vs 1.9%. Lesion characteristics: A 37% vs 41%, B1 33% vs 34%, B2 16% vs 16%, C 14% vs 9%. Indication for stent: elective 65% vs 60%, sub-optimal result 30% vs 38%, bail-out 2.5% vs 1.2%, restenosis 1.8% vs 0.8%. Length of hospital stay was 1.8 vs 1.6 days. In Group T complications at 30 days were: cardiac death 1, stent occlusion 3 (1.6%), non-Q wave MI 2, urgent revascularisation 4 (Major adverse cardiac & cerebral events (MACCE) 5.2%) In Group C complications at 30 days were cardiac death 1, non-cardiac death 1, stent occlusion 0, non-Q wave MI 2, urgent revascularisation 0 (MACCE 3.4%). Follow-up was available in 100% of patients in Group T and 98% of patients in Group C and was 203 ± 79 and 61 ± 25 days respectively. Although the follow-up period is short in Group C at present, early indications are that clopidogrel can be used safely instead of ticlopidine in patients with stents ≤ 3 mm in diameter.

P2800 Geographic variability in outcomes within an international trial of glycoprotein IIb/IIIa inhibition in patients with acute coronary syndromes: results from PURSUIT

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Aims The aim of the present study was to analyze the factors that might contribute to the geographic variations in patient outcome and treatment effect as observed in the PURSUIT trial.

Methods In PURSUIT, 9461 patients with acute coronary syndromes were randomized to the platelet inhibitor eptifibatide or placebo for 72 h in 27 countries in 4 geographic regions including Western (WE, n = 3697) and Eastern Europe (EE, n = 1541) as well as North (NA, n = 3827) and Latin America (LA, n = 396). Endpoint was the 30-day composite of death or MI. In the initial univariate analysis, the treatment effect appeared greater in NA than in WE, while no effect was apparent in LA and EE. However, the confidence intervals for these effects were wide and overlapping. In order to more precisely study the differences, a subdivision in an early and late outcome and treatment effect was made, analyzed as the rate of death or MI at 72 h censored for percutaneous coronary intervention (PCI) and the rate between 3 and 30 days. Additional analyses were performed with different definitions of MI using higher thresholds of CK-MB elevation. Multivariable analysis was used to evaluate the relation between region and outcome and to determine the adjusted eptifibatide treatment effect.

Results Major differences in baseline demographics were apparent among the 4 regions; in particular, more patients from EE had characteristics associated with impaired outcome. Also, interventional treatment varied considerably with more patients from NA undergoing PCI. Despite differences in the 72-h event rate, eptifibatide consistently reduced the composite of death or MI among all 4 geographic regions and for all definitions of infarction. Absolute reductions ranged from 0.7–1.5% in WE, 0.6–1.2% in NA, −0.1–1.5% in EE, and 3.5–5.6% in LA. After correction for baseline characteristics, the benefit of eptifibatide was similar in all regions. In patients undergoing PCI during study drug infusion in WE (n = 266) and NA (n = 931), there was a dual treatment benefit with eptifibatide. During medical therapy preceding the intervention, an absolute reduction in MI was observed ranging from 2.0–4.8% in WE and 0.9–3.0% in NA, while the reduction in procedure- related events ranged from 2.1–2.9% in WE and 2.7–4.3% in NA for different MI definitions. No rebound occurred. After multivariable adjustment neither benefit nor rebound was apparent after 3 days in all regions, except in LA. In general, the differences in outcome and treatment effect among regions were greatest when the protocol definition of MI (CK-MB > 1) was applied. When stricter definitions were used, differences became smaller and disappeared with the assessment by the investigator.

Conclusion The analysis suggests that the apparent differences in patient outcome and treatment effect can largely be explained by differences in demographics and adjunctive treatment strategies as well as by the methodology of MI definition and the adjudication process.

P2801 Long-term oral glycoprotein IIb/IIIa inhibition with xemilofiban in patients undergoing percutaneous coronary intervention: results from EXCITE

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Background: Intravenous GP IIb/IIIa antagonists have demonstrated efficacy in preventing the thrombotic endpoints of death, MI and urgent revascularisation when administered immediately prior to and for up to 48 hours after PTCR. This trial was set up to investigate whether oral administration has the same acute effect as intravenous GP IIb/IIIa antagonists and whether long-term administration further improves long-term outcome.

Methods: The EXCITE study was an international, multicenter, randomised, placebo-controlled trial of 7232 patients (pts) to test the efficacy of the oral GP IIb/IIIa antagonist xemilofiban (xemi) administered prior to and chronically for up to 6 months after PTCR with and without stent (S) placement. All pts were treated with ASA and heparin; all S pts received xemi continuously, or ticlopidine for 2–4 weeks followed by xemi placebo. Two doses of xemi were tested. The primary endpoint was time to the first occurrence of the composite of death, MI, or urgent revascularisation, and time to death or MI over the 6-month study period. Additional analysis explored the effect of xemi on the same endpoints in pts treated with balloon angioplasty alone, or with additional stent deployment.

Results: Approximately 71% of pts received S at the discretion of the operator. At the end of the 6-month follow-up, 13.6% of pts treated with placebo, and 14.1% and 12.6% of pts treated with 10 mg and 20 mg of oral xemi TID respectively, experienced endpoint events (NS). At 30 days following PTCR, pts treated with PTCR without S had lower event rates than those receiving stents. By 180 days, this trend had reversed and endpoint events had occurred more frequently in pts without S than in those in whom S had been deployed.

Conclusions: Chronic treatment with xemi was not superior to 2–4 weeks therapy with ticlopidine in pts receiving S, or chronic ASA therapy for those receiving balloon angioplasty alone. These findings should provoke further research into the role of chronic platelet GP IIb/IIIa receptor blockade in preventing ongoing thrombotic cardiac events.

P2802 Platelet activation and platelet-monocyte interaction during coronary intervention: is there a genetic influence?

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Background: Coronary intervention may be complicated by acute thrombotic occlusion and late restenosis as a result of events initiated by endothelial trauma and propagated by platelet activation. The aim of our study was to assess the degree and duration of local and systemic platelet activation during coronary intervention; to correlate this with the degree of endothelial damage and the presence of PlA2 polymorphism (a known risk factor for coronary disease) and further to examine the level of platelet-monocyte adhesion (PMA) and monocyte activation which platelet activation may trigger.

Methods: Coronary sinus (CS) and peripheral blood samples were collected at baseline, post-1st balloon inflation and post-angioplasty in 21 patients undergoing successful left system coronary angioplasty. Platelet activation was determined by flow cytometric detection of PAC-1 expression (a marker of platelet activation). Endothelial damage was assessed by measuring solube thrombomodulin (sTM) levels by ELISA. PlA genotype was assessed by PCR of the polymorphic region followed by restriction enzyme digestion and electrophoresis of the PCR product to reveal the allele-specific restriction fragment length polymorphism. PMA was assessed by double staining with CD14 (a monocyte specific marker) and GP1b (a platelet specific marker). Monocyte activation was assessed by quantifying the degree of L-selectin mean channel fluorescence(MCF)down- regulation.

Results: All patients demonstrated significant platelet activation in the CS immediately after the 1st inflation, (20.63 vs 8.13 at baseline, $P < 0.001$), but not in the periphery(14.35 versus 7.7 at baseline P = NS). Platelet activation did not correlate with the degree of endothelial damage as assessed by sTM levels ($P = 0.8$), however, there was a trend towards increased platelet activation in patients polymorphic to PlA2 ($P = 0.08$). There was a significant albeit transient increase in local PMA after the 1st inflation (51.4 ± 4.9 vs 37.7 ± 2.4 at baseline $P = 0.019$) leading to a significant increase in systemic monocyte activation at 24 hours (46.9 ± 6 vs 66.4 ± 5.1 at baseline, $P = 0.02$).

Conclusion: Coronary intervention results in local platelet activation and PMA which in turn may lead to prolonged systemic monocyte activation. Platelet activation does not correlate with the degree of endothelial damage but may correlate with the presence of PlA2 polymorphism. Our results provide new insight into the mechanisms involved in restenosis and therefore possible therapeutic approaches to the thrombotic complications which may follow coronary intervention.

P2803 Successful percutaneous intervention in patients with total coronary occlusions results in increased local platelet activation compared to those with stenoses

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Background: Successfully dilated coronary occlusions have a higher restenosis rate compared to non-occlusive stenoses. Peri-interventional platelet activation correlates with restenosis, but has not been assessed in the context of occlusive versus non-occlusive stenoses.

Aim: to compare the degree and duration of platelet activation in patients with occlusions against those with stenoses during percutaneous transluminal coronary angioplasty.

Method: Platelet activation was prospectively examined in 30 patients undergoing successful left coronary system intervention. Nineteen patients (15 males, mean age 63) had non-occlusive stenoses ($66 \pm 5\%$ (mean $\pm$ SD) stenosis), and 11 patients (4 males, mean age 62) had total occlusions. Coronary sinus blood samples were collected at baseline, post-first balloon inflation and post-angioplasty. Platelet activation was assessed by flow cytometric quantification of percentage platelet PAC-1 expression. PAC-1 is a neoepitope found only on the conformationally active form of the GPIIb/IIIa receptor following platelet activation. Platelets were stained with fluorochrome-conjugated monoclonal antibodies directed against CD42a (a constitutively expressed general platelet marker) and PAC-1 (an activation-dependent marker). Platelets were electronically gated on the basis of staining for CD42a and forward scatter characteristics and the percentage expressing PAC-1 measured.

Results: All patients demonstrated significant platelet activation in the coronary sinus immediately after the first balloon inflation, as measured by the percentage of platelets positive for PAC-1. In the stenosis group, platelet activation increased from $6.3 \pm 1.1\%$ at baseline to $14.3 \pm 2.8\%$ after the first inflation ($P < 0.02$), but returned to baseline ($7.0 \pm 1.8\%$, P = NS) post-angioplasty. By contrast, in the occlusion group, platelet activation increased from $7.9 \pm 1.4\%$ at baseline, to $23.7 \pm 5.0\%$ ($P = 0.007$) after the first inflation and remained high at the end of the procedure ($23.5 \pm 5.4\%$, $P < 0.04$ vs baseline).

Conclusion: Our data shows that patients with successfully dilated total occlusions have more prolonged platelet activation after intervention than those with stenoses. This observation supports the hypothesis that prolonged platelet activation may play a major role in the development of reocclusion and restenosis after successful dilatation of total occlusions. Patients with total occlusions may therefore benefit from a more aggressive anti-platelet regime.

P2804 Reduced procedural risk for coronary catheter interventions in carriers of the coagulation factor-VII Gln353 gene

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Background: Increased coagulation factor VII (FVII) activity represents an independent risk factor for acute thrombotic events in the course of coronary artery disease (CAD). The mutation Arg353Gln of FVII is known to decrease FVII activity. Presence of Gln353 was suggested as protective against CAD and myocardial infarction. It is unclear whether Gln353 mutation reduces susceptibility to develop complications after coronary catheter interventions.

Methods and Results: 666 consecutive CAD patients who underwent coronary catheter interventions (280 coronary angioplasty [PTCA], 104 coronary atherectomy [DCA], and 282 stenting) were observed for a 30-day composite endpoint, including need for target-vessel revascularisation, myocardial infarction, and death. The Arg353Gln polymorphism of FVII was determined by PCR/RFLP assay. The frequencies of homozygotes for Arg353, heterozygotes, and homozygotes for Gln353 in the whole group were 76.4%, 22.2%, and 1.4%, respectively. Composite endpoint appeared in 43 cases (30 target vessel revascularisation, 12 myocardial infarction, and 1 death). These complications occurred with 2.5% in carriers of at least one Gln353 allele (4 out of 157 cases), and with 7.7% in homozygotes for Arg353 (39 out of 409; odds ratio, 0.32; 95% confidence interval, 0.08–0.90; $P = 0.013$). A trend of allele dependent reduction of risk was also observed if we separated complications according to device.

Conclusions: The Gln353 allele of FVII confers significant protection against complications after angioplasty.

P2805 Minimal heparinization in PTCA: is heparin really warranted?

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Objective: To assess the safety of mini-dose (2,500 units intravenous bolus) unfractionated heparin in PTCA.

Methods: 100 out of 113 (88.4%) consecutive patients undergoing PTCA were prospectively enrolled to the study. All enrolled patients received mini dose unfractionated heparin (MDUH), prior to guiding catheter insertion, with no subsequent heparin administration. Two physicians assessed the patient and lesion characteristics as well as PTCA results. Femoral sheaths were removed within 2 hours after PTCA. Patients were followed up by telephone monthly after their discharge.

Results: Angiographic and clinical success were achieved in 94% and 91% respectively. There was one in-hospital death. Emergency coronary bypass surgery and stroke did not occur. One patient experienced acute closure 6 hours after PTCA. 56 patients (56%) received stents (36 of these without previous balloon dilatation). There were 5 cases (5%) of side -branch compromise: two of these resulting in mild CPK rise. 4 patients had reduced TIMI flow after PTCA. One case of mild non-occlusive in-stent thrombosis was detected. No bleeding or vascular complications were detected. Mean follow up of 62 ± 35 days) revealed no additional deaths, one myocardial infarction, and 6% repeat target vessel revascularization (TVR).

Conclusion: MDUH appears to be safe in non-emergency PTCA, and has the potential of reducing bleeding complications, hospital stay and cost, and set the stage for ambulatory trans-femoral PTCA. Larger double-blind heparin dose optimization studies, with long term stringent follow up protocol, need to confirm this impression.

P2806 Bleeding and vascular complications after percutaneous coronary interventions and abciximab

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Hemorrhagic and vascular complications contribute significantly to the morbidity of percutaneous coronary intervention (PCI) and are risk factors for long-term mortality. The safety of adjunctive abciximab has not been documented outside the setting of clinical trials which have involved highly selected pts.

Methods: We prospectively recorded the incidence of bleeding and peripheral vascular complications in 2623 consecutive pts undergoing PCI (841 with and 1782 without abciximab). Heparin was used according to the EPILOG guidelines.

Results: Major bleeding (decrease in Hb > 5 g/dL, decrease in hematocrit > 15% or intracerebral hemorrhage) occurred in 2.1% of pts who received abciximab and 0.7% of pts who did not ($p = 0.002$). Minor bleeding (decrease in Hb > 3 g/dL, decrease in hematocrit > 10%) occurred in 14% of pts who received abciximab and 6% of those who did not ($p < 0.001$). Pseudoaneurysms or AV fistulae occurred in <1% of pts. Among 254 pts treated within 12 hrs of an acute MI, major bleeding occurred in 5.7% of 140 pts who received adjunctive abciximab versus 2.6% in the 114 pts who did not; minor bleeding occurred in 18.6% and 17.5%, respectively.

Conclusions: Adjunctive abciximab was associated with a significantly higher frequency of bleeding in pts undergoing PCI particularly in the setting of acute MI. Although the incidence of major bleeds was relatively low, minor bleeding occurred more frequently than reported from randomized trials. Further strategies to reduce these complications are required.

P2807 Risk for early major adverse cardiac events after coronary stent placement in the era of ticlopidine

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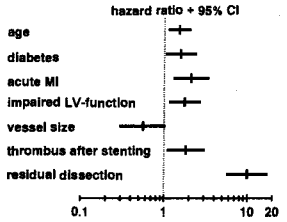
Previous risk analyses for MACE during the first 30 days have stressed the importance of ticlopidine therapy and of an optimal angiographic result. Data focussing on patients with ticlopidine therapy are not available. Therefore we analyzed all 3676 patients with ticlopidine therapy after successful stenting within a 4-year period (without cardiogenic shock). Risk analysis by Cox proportional hazard models included 23 clinical, angiographic and procedural factors.



The overall MACE rate was 3.4% (death, 1.1%; myocardial infarction, 1.0%; TLR, 2.1%); 50.0% of all events occurred during the first 3 days, 77.8% during the first 2 weeks. The significant and independent risk factors identified are illustrated in the graph.

Conclusions: This retrospective analysis illustrates the risk associated with older age, diabetes, acute myocardial infarction, impaired LV function, smaller vessel size and an intracoronary thrombus at the end of a procedure. The most prominent factor however, an uncovered residual dissection, underscores the need for an optimal angiographic result.

P2808 C825T polymorphism in the gene encoding for the β3 subunit of heterotrimeric G proteins is not associated with an increased risk of thrombosis and restenosis following coronary stent placement

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C825T polymorphism in the gene encoding for the β3 subunit of heterotrimeric G proteins (*GBN3*) is strongly associated with a splice variant of Gβ3 lacking 41 amino acids. *In vitro* presence of the splice variant Gβ3-s results in increased G_i signaling. C825T polymorphism has been associated with essential hypertension, coronary artery disease and myocardial infarction. Its role in the processes of vessel thrombosis and restenosis after percutaneous coronary interventions has yet not been studied.

Methods: C825T genotype of 562 consecutive patients who underwent coronary stent placement was determined. In 468 patients (83%) a 6-month follow-up angiography was performed.

Results: CC genotype was present in 46%, CT in 45% and TT in 9% of the patients. No significant differences regarding clinical, angiographic and procedural characteristics were found between carriers of T allele (CT + TT) and homozygous carriers of C allele (CC). Four patients with and three patients without T allele suffered from subacute stent thrombosis ($p = 0.86$). Restenosis (≥50% diameter stenosis in QCA) was found in 33% of CC, 28% of CT and 33% of TT patients ($p = 0.56$). Carriers of the T allele (CT + TT) had a restenosis rate of 29% *verca* 33% in patients homozygous for C allele ($p = 0.40$). Late lumen loss was 1.04 ± 0.77 mm in CT and TT patients and 1.12 ± 0.81 mm in CC patients ($p = 0.27$). No significant difference was found in target vessel revascularization rates between patients with (17.5%) and patients without (19.7%) T allele ($p = 0.50$).

In conclusion, these results do not support a relevant role for C825T *GBN3* polymorphism in the mechanisms leading to thrombosis and restenosis after coronary stent placement.

P2809 Polymorphisms in the fibrinogen and the glycoprotein IIIa genes and recurrent restenosis after second PTCA

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Recurrent restenosis limits the benefits of PTCA in about 30% of cases. We have recently investigated the association of the β-fibrinogen G/A-455 (Fib455 G/A) and the glycoprotein IIIa PI A1/P1 A2 (GP IIIa PIA1/PIA2) gene polymorphisms with the risk of restenosis after coronary angioplasty (PTCA). This study was designed to investigate whether the these polymorphisms are associated with recurrent restenosis after a second PTCA.

Methods: One hundred and fifty-four out of 511 consecutive PTCA patients were re-dilated on a restenotic lesion and investigated prospectively. One hundred and forty-three patients (92.9%) underwent follow-up angiography. Recurrent restenosis was defined as >50% progression of the residual stenosis after the second PTCA. Patients were genotyped using PCR and PCR/RFLP techniques. The frequencies of recurrent restenosis were compared among patients with different Fib and GP IIIa genotypes.

Results: The overall frequency of recurrent restenosis was 31%. Baseline clinical data (sex, age, history for diabetes and hypertension, current blood pressure, current smoking, serum lipid levels) did not differ among patients with and without recurrent restenosis. Patients with different Fib455 and GP IIIa genotypes showed similar frequencies of recurrent restenosis (35% in Fib455GG genotyped patients vs. 27% in C allele carriers; n.s. and 30% in GP IIIa PIA1/A1 genotyped patients vs. 35% in PIA2 allele carriers; n.s.).

In conclusion: These results show that the Fib 455 G/A and the GP IIIA PIA1/PIA2 polymorphisms are not associated with the risk for recurrent restenosis after a second PTCA.

P2810 Loading dose of ticlopidine: a simplified approach to intracoronary stent management

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Backgroun: Ticlopidine (T), in addition to aspirin reduced both stent thrombosis and ischemic complications post percutaneous transluminal coronary angioplasty (PTCA). Action of T is slow and take at least three days to have a full inhibitory effect on platelet aggregation. It has been demonstrated that a loading dose of T (1500 mg a day) exerts the same effect in 24 hours. We hypothesized that a loading dose of T given the day before PTCA, might reduce the hospital stay without more ischemic complication (non-Q-wave myocardial infarction, NQWMI).

Methods: We reviewed outcomes in 376 consecutive patients (pts) treated with ticlopidine prior to stenting. We assessed the occurrence of NQWMI (an elevation in creatine kinase > 220 IU/L with >4% MB fraction) between the group with loading dose and standart dose.

Result: 212 pts received T (500 mg/day) 3 days before and 164 pts received a loading dose (1500 mg) the day before PTCA. There were no major in-laboratory ischemic complication (death, Q wave MI, emergency bypass surgery) within the study population. Characterics of pts were as follow.

	Loading dose	Standart dose
Number of patients	164	212
Mean age (year)	68.3	57.6
Unstable angina (%)	40.8*	23.7
Previous bypass (%)	2	2
B2 or C lesion (%)	63.4*	43.5
Diabetes (%)	31.2	20.2
Average n° of treated vessels	1.7	1.1
Mean left ventricular ejection fraction (%)	37.2*	53.4
Non-Q-wave myocardial infarction (%)	20.1	21.6
Days in hospital (mean ± SD)	5.3 ± 3.8*	9.7 ± 4.2

*$p < 0.05$

Conclusion: Despite high risk criteria for PTCA*, giving a loading dose of T the day before PTCA may reduce the hospital stay without more ischemic complication.

LATE RESULTS OF CORONARY INTERVENTION

P2811 8 years clinical follow-up after intracoronary stent implantation

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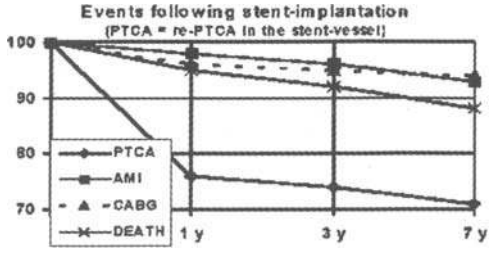
The clinical outcome of the first consecutive 100 patients (mean age 59 y [27–79], 84% male) with intracoronary stent implantation (Palmaz-Schatz) in our hospital since 1990 was studied.

Clinical follow-up was obtained over a mean observation period of 5.8 years (4–8 y). Angiographic controls were performed after 3, 6 or 12 months, clinical controls in 1995 and in 1998.

Indications for stenting were unsuccessful PTCA in 88% (39% total vessel occlusion, 49% recoil > 50%) and restenosis in 12%. Stent implantation was performed in 8.8% of all PTCA procedures in this period. Mean EF was 61% (24–89%). Anti-coagulation consisted of ASS, heparin and coumadine. The percentage of patients with 1, 2 or 3-vessel disease was 42%, 39% and 19%. After 1 y angiographic controls revealed a 26% cumulative rate of restenosis (stenosis > 50%), 94% of these underwent successful re-PTCA. Up to february 1998 the total number of deaths was 12% (including 4 non-cardiac deaths), of myocardial infarctions was 7%, CABG 6%, 16% PTCA in different vessels, re-PTCA in stented vessels 29%.



Events following stent implantation.

Within 8 years after stent implantation, mortality, incidence of myocardial infarction or CABG in unselected patients are low. There is a low rate of re-PTCA after 1 y and in the observation period beyond 1 y. Serious adverse long-term effects of coronary stent implantation were not observed.

P2812 Five-year clinical outcome after coronary stent placement

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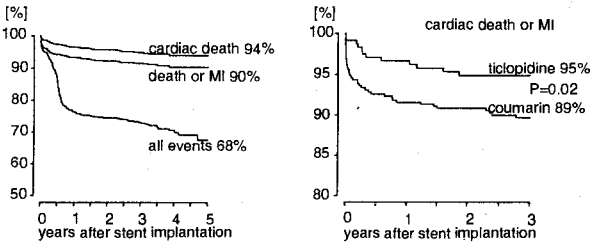
There is still little information about the clinical long-term follow-up after coronary stent placement and whether the initial benefit of antiplatelet therapy is maintained over time. The present study investigates the long-term course (more than three years) of 632 patients (pts) who had successful coronary stent implantation from May 1992 to May 1995. The postinterventional therapy was conventional anticoagulation with coumarin in 62% of the pts and combined antiplatelet therapy (CAT) with aspirin und ticlopidine in 38%. Long-term follow-up was completed in 97% of the pts. Repeat angiography 6 months after stent placement was carried out in 82% of the patients and restenosis rate (≥50% diameter stenosis) was 26.5%. Clinical endpoints were cardiac death, myocardial infarction (MI), repeat angioplasty or coronary artery bypass surgery.

The Kaplan-Meier curves (left) show the event-free survival over 5 years of follow-up. The figure on the right shows the comparison between the two therapy groups after three years.



With a five-year cumulative cardiac death rate of 6%, coronary stenting is associated with a good clinical long-term outcome. The proven initial benefit of pts with CAT is maintained at long-term.

P2813 Ten-year follow-up after intracoronary stenting

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The use of intracoronary stents has rapidly increased within the last decade. Nevertheless, very little is known so far about the long-term outcome of intracoronary stenting. Thus, we examined 58 patients at a mean of ten years after intraoronary stenting.

Method: In 58 patients, who received a Palmaz-Schatz stent at a mean of ten years before follow-up, data was obtained from hospital charts, a contact with the personal doctor and a contact with the patient. The patients were asked to complete a structured interview at our center; if this was not possible the interview was sent to the patient to be completed. Data then was analyzed for the following endpoints: death of any cause (Death), myocardial infarction (MI), Re-PTCA of any vessel (Re-PTCAP), CABG and any of the events mentioned above (Any event).

Results: The table shows the results: 14 patients died within follow up period of 10 years, 7 patients of cardiac death, 3 patients of non-cardiac death and in 3 patients the cause was not known.

	First year	After first year	Overall
Death	2 (3.4%)	12 (20.7%)	14 (24.1%)
MI	2 (3.4%)	4 (6.8%)	6 (10.3%)
Re-PTCA	14 (24.1%)	14 (24.1%)	28 (48.3%)
CABG	6 (10.3%)	8 (13.8%)	14 (24.1%)
Any event	21 (36.2%)	18 (31.0%)	39 (67.2%)

Conclusion: Ten years following Palmaz-Schatz stent implantation we did observe favourable results, especially after the first year. Since nowadays acute complications are less than 10 years ago this data are very promising.

P2814 Long-term results with the Wiktor coil stent: angiographic data from a consecutive series of 300 lesions

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Coil stents have been suspected to be associated with an increased rate of delivery failures, of recoil, and of restenosis due to plaque protrusion. In this study we analyzed the clinical and the angiographical outcome of a consecutive, 'real-world' series of Wiktor™ stent implantations.

A total of 374 stents were implanted in 300 lesions (248 de-novo and 52 restenotic; 128 LAD, 32 CX, 122 RCA, 18 CABG) from 283 patients. The clinical status included 9% acute and 26% recent myocardial infarctions, 31% unstable and 34% stable angina. There were 57% AHA type B2/C stenoses, including 48 total occlusions. Stent indications were an unsatisfying PTCA result in 82%, vessel closure in 5%, and primary stenting in 13%.

Success rates of stent delivery increased from 91.3% (initial 51 lesions) to 98.4%. Post-procedure ticlopidine and ASS was given for 2–3 months. Angiographic follow-up was performed in 81% after 175 ± 47 days. MLD [mm] was 0.48 ± 0.43 pre PTCA, 2.32 ± 0.59 after stenting, and 1.61 ± 0.97 at follow-up, resulting in a late loss index of 0.36 ± 0.55. The balloon-to-artery ratio was 1.24 ± 0.23 with a reference diameter (RD) of 2.66 ± 0.73 mm pre PTCA and a 16.2 ± 8.6% residual stenosis after stenting.

The occurrence of restenoses significantly correlated ($p < 0.05$) with the use of high pressure dilation, the number of stents per lesion, a smaller RD, and a lower MLD post stenting. No impact had lesion type and location, dissection type and the balloon-to-artery ratio.

	RD ≥ 3.0 mm	RD < 3.0 mm	MLD ≥ 2.5 mm	MLD < 2.5 mm
Restenosis	19.6%	41.9%	25.0%	41.8%
Reinterventeion	14.3%	34.4%	15.3%	35.9%

(RD = reference diameter pre PTCA, MLD = minimal lumen post stenting)

We conclude that coil stent delivery failure is much less frequent than suspected. The restenosis rate in an unselected patient group is comparable to more recent multi-cellular stents and remains below 20% in larger vessels.

P2815 Four years follow-up of the start trial, a randomized stenting versus PTCA study

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Background: Randomized trials have conclusively shown that, compared with angioplaty (PTCA), stent implantation reduces restenosis rate in "de novo" coronary artery lesions. Although this seems to translate into early clinical benefit, the impact of stenting on clinical events has not been assessed in the long run.

Objective: The present investigation was conducted with the aim of ascertaining whether the long term clinical outcome of patients (pts) treated with stents was better than those of pts undergoing PTCA.

Methods: Clinical data of START (Stent vs Angioplasty Restenosis Trial), a spanish multicenter randomized study, were analyzed at a mean of 52.4 ± 17 months after randomization in 436 (96%) of 452 pts enrolled. The following end-points were considered: cardiac death, target lesion revascularization (TLR), and non fatal myocardial infarction (MI).

Results:

	Death	TLR	MI	Total
Stent (225)	6 (2.7%)	27 (12%)	5 (2.2%)	38 (17%)
PTCA (211)	5 (2.4%)	52 (24.6%)	6 (2.8%)	63 (30%)
p	ns	<0.00	ns	<0.01

Conclusions: The early clinical benefit of stenting is sustained in the long run, as manifested by a significant reduction in the necessity of further revascularization procedures beyond the ensuing 4 years.

P2816 Five-year follow-up after coronary stenting: survival, event-free survival and freedom from new revascularization

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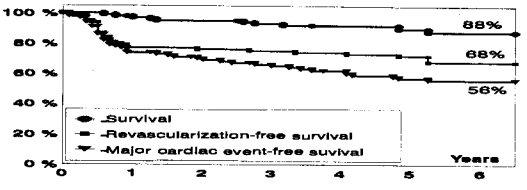
To assess the clinical efficacy of coronary stenting (CS) 5 or more years after implantation we followed 130 consecutive pts (mean age: 61 ± 9 years, 88% males) who underwent successful CS in 138 lesions from January 1991 to January 1993. Angiographic follow-up (FU) was performed in 95% of pts at 6.9 ± 4 months Clinical FU was completed for 97% of pts. Mean time to clinical FU was 5.0 ± 1.2 years (range: 5–6.5 years). Left ventricular ejection fraction was 0.62 ± 0.12 and 48% of pts had multivessel disease. Indication for PTCA was unstable angina in 66% of pts and CS was elective in 56%.

At six months 24% of pts (CI 95%: 17–32%) had angiographic restenosis (>50% QCA-criterion). During FU, 14 pts (11%, CI 95%: 6–18%) died (7 cardiac deaths) and 7 pts (5%) required admission for AMI or unstable angina. Stent failure demanded a new revascularization in 19% of pts (CI 95%: 13–27%). However over the last 4 years of FU, only 1 pts (0.8%) needed new revascularization due to Stent failure. At the end of FU 91% of surviving pts remained asymptomatic whereas freedom from angina or major cardiac events was 61%.



Thus: 1) survival, angina-free survival, and event-free survival 5 o more years after CS are acceptable; 2) After 1 year post-CS, events and revascularization related with the stented vessel are exceptional.

P2817 Immediate and long-term clinical and angiographic results of coronary stenting in stable and unstable angina patients

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Higher rates of major adverse events and restenosis after PTCA have been reported in unstable angina compared to stable angina patients. Aim of our study was to compare clinical and angiographic outcomes following coronary stent implantation in 736 stable (S) and 360 unstable (U) angina pts between May '92 and February '98. The analysis of major coronary risk factors showed a relative increase in male gender (86.5% vs 79.7%, p = 0.004), higher cholesterol levels (52.9% vs 45.5%, p = 0.02) and a previous history of Q-wave MI (41.4% vs 31.9%, p = 0.002) in S compared to U pts. No differences were observed in coronary disease extension (1-VD: 53.8% S vs 51.9% U, ns; 2-VD: 31.8% vs 35.5% U, ns; 3-VD: 14.4% S vs 12.5% U, ns), stented vessel (LAD: 49% S vs 53.4% U, ns; RCA: 30% S vs 28.7% U, ns; LCx: 17.8% S vs 12.8% U, p = 0.02; Graft: 2.9% S vs 5% U, ns) and lesion type (A: 5.7% S vs 7.8% U, ns; B1: 41.7% S vs 32% U, p = 0.05; B2: 40.6% S vs 49% U, ns; C: 12.4% S vs 11.4% U, ns). Coronary lesions were longer in S pts: 16.7 ± 8.6 mm vs 13.8 ± 7.8 mm in U (p = 0.01). Bailout stenting in U pts was twice that observed in S (20.2% vs 11.8%, p = 0.001) due to a more frequent occurrence of flow limiting dissections and abrupt closure. Similar were the number of stent/pt (S: 1.14 ± 0.41, U: 1.15 ± 0.55, ns), maximal inflation pressure (S: 15.3 ± 2.33 atm, U: 14.6 ± 2.96 atm, ns) and final balloon diameter (S: 3.53 ± 0.56 mm, U: 3.54 ± 0.5 mm, ns) in both groups. High procedural and clinical success were achieved in U pts (95.8% and 96.4%), similar to that obtained in stable angina (96.6% and 97.9%, ns). Amongst in-hospital complications, no differences were observed in stent thrombosis (0.5% S vs. 0.9% U, ns) and need for urgent CABG (0.5% S vs 1.4% U, ns) while a greater incidence of death (0.1% S vs 1.6% U, p = 0.006), Q and non-Q wave MI (1.7% S vs 4.7% U, p = 0.009) and major bleeding (0.9% S vs 4.1% U, p = 0.0007) occurred in U pts. Cumulative data of 6-mos F/U, so far available in 70% of S and 72.9% of U pts, showed a three-fold higher incidence of recurrent angina in U pts (4.4% S vs. 10.6% U, p = 0.001) but no difference in the rate of Q-wave MI (0.5% S vs. 0.9% U, ns), death (0% S vs 0.8% U, ns), Re-PTCA (14.5% S vs. 16.2% U, ns) and CABG (2.5% S vs 2.9% U, ns). Angiographic restenosis was 25.8% in S and 35.8% in U pts (p = 0.002).

Conclusions: 1. Stenting was associated with high and comparable acute success in S and U pts; 2. Although MACE were observed more frequently in unstable angina, their incidence was significantly lower than that previously reported for PTCA; 3. Six-month F/U showed higher recurrence of angina and angiographic restenosis in unstable pts.

P2818 Long-term angiographic patency of recanalized chronic coronary total occlusions associated with sub-intimal dilatation

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Successful recanalization of chronic coronary total occlusions (CTO) by PTCA sometimes involves sub-intimal dilatation (SID) which produces pseudo lumen. However, long-term patency of recanalized CTO associated with SID is unknown. This study aimed to examine the long-term angiographic outcomes of recanalized CTO with SID. Five hundred and seven CTO (TIMI flow grade = 0, occlusive duration ≥ 3 months) were successfully recanalized by PTCA. Long-term follow-up angiography was obtained in 427 lesions (84.2%) 215 ± 142 days after the initial PTCA. One hundred and twenty-eight lesions were recanalized with SID (SI group) and 299 lesions without SID (I group). There were significant differences in lesion morphology and procedural results between the two groups (Table). Stents were implanted in 36% of SI group and in 26% of I group. Initial restenosis rate, times of revascularization (TLR) and final patency rate are shown in the table.

	SI group (n = 128)	I group (n = 299)	P value
Reference diameter ≥ 2.5 mm	46.1%	56.9%	0.04
Occlusion length ≥ 20 mm	47.7%	29.1%	0.002
Post MLD ≥ 2.0 mm	17.9%	39.1%	<0.0001
Initial restenosis rate	80.5%	47.8%	<0.0001
Times of TLR	1.5 ± 1.5	0.9 ± 1.1	<0.0001
Final patency rate	89.1%	95.7%	0.03

In SI group, primary stenting provided the patency rate of 100% ($p < 0.01$ vs 84.8% of non-stenting sub-group), and it was the only predictor of final patency detected by multiple regression analysis.

Conclusion: Recanalized CTO with SID has a disadvantage in lesion morphology and procedural results which requires frequent TLR. However, a favorable long-term patency can be expected, especially by primary stenting, even if CTO is recanalized with SID.

TRANSMYOCARDIAL REVASCULARIZATION

P2819 Transmyocardial revascularization and percutaneous myocardial revascularization improve exercise tolerance: results from the cardiogenesis ATLANTIC and PACIFIC trials

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Background: Transmyocardial Laser Revascularization (TMR) and Percutaneous Myocardial Laser Revascularization (PMR) are being investigated for the treatment of patients with intractable angina that is refractory to conventional therapies. The ATLANTIC TMR and PACIFIC PMR prospective randomized trials evaluate whether TMR and PMR can improve functional capacity in patients with CCSAS Class III or IV angina.

Methods: In the ATLANTIC Trial, 182 patients with Class III or IV angina untreatable by conventional therapies were randomized at 16 centers in the US to continuing medical therapy or to continuing medical therapy plus surgical TMR with the CardioGenesis TMR System. In the PACIFIC Trial, 235 patients were randomized at 13 sites (12 in the US, 1 in the UK) to continuing medical therapy or to continuing medical therapy plus PMR with the CardioGenesis PMR System. All patients in both studies showed objective evidence of reversible ischemia by dipyridamole thallium scans and had an LV Ejection Fraction of >30%. Improvement in exercise time under standardized testing was a primary endpoint in both studies.

Results: In the ATLANTIC Trial, treated patients showed an average improvement in exercise tolerance of 31% at 3 months, and a continued improvement of 35% over baseline at 6 months. In the PACIFIC Trial, treated patients showed an average improvement of 28% at 3 months. Furthermore, analysis of data from the ATLANTIC Trial showed that ST segment depression indicative of ischemia occurred at higher work loads at both 3 and 6 month following TMR. This provides objective evidence of improvement in ischemia and functional capacity.

Conclusions: Results indicate that myocardial laser revascularization, whether performed surgically or percutaneously, results in clinically significant improvement in functional capacity in Class III and Class IV patients. 12-month ATLANTIC and 6-month PACIFIC randomized data will be presented.

P2820 Six month follow-up of a prospective randomized trial of percutaneous transmyocardial revascularization vs medical therapy in patients with refractory angina

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Background: Percutaneous Transmyocardial Revascularization (PTMR) has been reported to improve angina in medically refractory patients ineligible for CABG and PTCA. A prospective randomized trial of Eclipse Holmium Laser PTMR vs Medical Therapy in inoperable, Class III–IV patients completed enrollment 10/98.

Methods: 335 patients were randomized 12/97–10/98: 169 to PTMR, and 166 to Maximal Medical Therapy (MM).

Results: Baseline characteristics were similar: Mean age 63 ± 11, 74% male, history of hypertension 75%, MI 67%, PTCA 68%, and CABG 82%, mean EF 47% ± 10, mean angina class 3.4 ± 0.5. 19 ± 7 channels were made in the ischemic myocardium of treated patients. Total procedure time averaged 86 minutes; total laser time averaged 23 minutes. There was one peri-procedural death, 5 other cases of cardiac tamponade (3.0%), and 4 peri-procedural non-Q MIs (2.4%). At 3-months, mean improvement in angina class for PTMR was twice that of the control group (1.6 vs 0.8 classes, class 1.8 vs 2.6, $p < 0.0001$). Exercise tolerance improved 18% (80 secs) in the PTMR group while decreasing 15% (84 secs) in MM ($p < 0.001$) in the 72 patients with complete 6 month data. At 6 months, total deaths are 5 (3.0%) in PTMR and 6 (3.6%) in MM (p = ns).

Conclusions: Initial results of this randomized study suggest that PTMR provides significantly greater angina relief and functional improvement than does medical therapy in patients with Class III-IV refractory angina. Complete 6-month follow-up data will be presented.

P2821 Percutaneous myocardial revascularization: results from the roll-in phase of the PACIFIC trial

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Percutaneous Myocardial laser Revascularization (PMR™) is being investigated for the treatment of patients with severe angina and judged unsuitable for conventional revascularization therapies (CABG or PTCA). Preliminary results from the U.S. and Europe demonstrated the safety of the procedure and suggest improvement in angina class and exercise tolerance following PMR. We present results including 12-month follow-up data from the roll-in (training) phase of the CardioGenesis PMR™ System (PACIFIC) Trial.

Methods: Patients received PMR treatment in the roll-in phase of the PACIFIC trial beginning in July 1997. To be eligible for PMR, patients were required to have: i) stable Class III or Class IV angina refractory to medical therapy; ii) ejection fraction of ≥ 30%, iii) demonstrated ischemia by stress nuclear imaging, and iv) judged to be ineligible for CABG or PTCA. The average patient age at 60, and the incidence of hypertension (69%), hyperlipidemia (79%) and diabetes (44%) were consistent with other TMR trials. The majority of patients had a history of CABG (26%), PTCA (8%) or both therapies (58%).

Results: PMR treatment was successfully completed in 72 patients. The procedural safety profile was encouraging with no procedural or device related deaths and no surgical intervention required. Primary endpoints of angina class (CCSAS) and exercise tolerance time (Modified Bruce Protocol) both demonstrated improvement. Fifty-nine percent of the baseline Class IV patients experienced a drop of 2 or more angina classes at 3 and 6 months post treatment. Exercise tolerance improved in both baseline Class III and IV patients, with Class III patients showing an average increase of 29% and Class IV patients experiencing an average increase of 51% in exercise time at 6 months. Anecdotal 12-month exercise data for these patients also appears promising. PMR patients experienced quality of life improvements as measured by the Seattle Angina Questionnaire. Adverse events were minimal and included one instance of myocardial perforation, treated with pericardiocentesis and one instance of complete heart block (pre-existing RBBB) requiring placement of a permanent pacemaker. There were 3 non-device, non-procedure related deaths in this severely ill roll-in cohort.

Conclusion: PMR may offer interventional cardiologists a new option for treatment of intractable angina secondary to diffuse coronary artery disease. PMR has an excellent safety record and appears to results in angina relief and increased exercise capacity. Further one-year follow-up data will be presented.

P2822 Percutaneous myocardial revascularization (PMR): initial results from the PACIFIC trial

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Background: Percutaneous Myocardial Revascularization is catheter-based approach to create ~6 mm deep laser channels in the myocardium from the endocardial surface. The PACIFIC Trial used the CardioGenesis Axcis System to test the hypothesis that PMR can palliate symptoms and improve exercise tolerance for patients with Class III or IV angina.

Methods: 235 patients with refractory Class III or IV angina untreatable by angioplasty or bypass surgery were randomized at 13 sites to medical therapy or to PMR plus medical therapy with the CardioGenesis Axcis PMR System. All patients had objective evidence of reversible ischemia by dipyridamole thallium, a wall thickness of greater than 8 mm in the targeted region and an LV Ejection Fraction of >30%. Typically 10–18 channels were created in each targeted ischemic region. The primary endpoints of the study were change in angina class and exercise tolerance.

Results: All treatments were completed safely and successfully. There were no procedural deaths, no incidents of procedural VF, and a single incident of procedural VT requiring cardioversion. There were no incidents of myocardial perforation requiring surgical intervention. At 3 and 6 months, the majority of treated patients showed improvement in both angina class and exercise tolerance. Treated patients showed an average 1.3-class drop in angina at 3 months. 47% of treated patients experienced a drop of two or more angina classes, and 28% of treated patients had Class I or no angina at three months, while the angina class of patients in the control arm remained virtually unchanged. On average, exercise tolerance decreased slightly in the control group (−2%) while improving more than 1 minute (28%) in the treatment group at 3 months. Interim analysis suggests continued improvement in the PMR group at 6 months.

Conclusions: Results indicate that PMR with the CardioGenesis system is a relatively safe procedure, is associated with negligible morbidity, and improves the symptoms and exercise capacity of patients suffering from severe angina. Complete six-month randomized study follow-up data will be presented.

P2823 Percutaneous direct myocardial revascularization guided by Biosense™ left ventricular mapping in patients with refractory coronary ischaemic syndromes

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Background: Laser myocardial revascularization has been explored as an alternative treatment strategy for patients with chronic refractory myocardial ischemic syndromes who are not candidates for conventional modes of coronary revascularization.

Methods and Results: We used the Biosense™ 3D magnetic guidance system for direct myocardial revascularization (DMR) in 76 pts with refractory ischemic coronary syndromes (52 men, age 62 ± 11 years, EF = 48 ± 11%) to perform percutaneous DMR using Ho:YAG laser @2 J × 1 pulse per laser channel. Successful laser channels created in pre-specified target zones were achieved in 75/76 pts. Overall major cardiac adverse events were 2.6%; including no death or emergent surgery; 1 post-procedure pericardiocentesis for pericardial effusion, and 1 minor embolic stroke. Treatment zones were: anterior (30), apex (1), lateral (32), inferior (24), and postero-lateral (24). The average number of laser channels was 26 ± 9 (range 11–51). No significant changes in LV function were noted by echo one day and one month post-procedure. One month exercise duration after DMR increased from 388 ± 177 secs (baseline) to 455 ± 170 secs ($p = 0.001$) in the first 56 pts and angina (CCS) improved from 3.2 ± 0.4 to 1.9 ± 0.7 @3 months ($p < 0.001$), with 58% of pts experiencing sustained symptomatic improvement. The improvement in exercise duration @1 month was highly correlated with the number of treatment zones ($p = 0.007$).

Conclusions: Percutaneous DMR guided by Biosense™ LV mapping 1) is feasible and safe; 2) early efficacy endpoints reveal improved angina and prolonged exercise duration at 1 and 3-m follow-up. A blinded randomized clinical trial is underway to establish definitive therapeutic value.

P2824 Acute and long-term results after catheter-based percutaneous myocardial laser revascularization in patients with end-stage coronary artery disease

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Background: Catheter-based percutaneous myocardial revascularization (PMR) is a safe and feasible treatment for patients with refractory angina pectoris due to coronary artery disease which are not candidates for angioplasty or bypass grafting. The study evaluates the acute and long-term results after PMR in patients with end-stage coronary artery disease.

Methods: 60 Patients (P) (64.1 ± 9.0 years) were treated with PMR. Regions with stress induced ischemia were located by thallium scintigraphy in the anterior wall in 32 P, in the lateral wall in 21 P and in the inferior wall in 36 P (25 P had stress-induced ischemia in more than one region).

Results: PMR was successfully performed in all P. 11.4 ± 4.0 (6–21) laser channels were created per region treated. Creatine kinase levels rose from 80 ± 37 U/l before PMR to 149 ± 67 U/l after PMR. Adverse procedural effects included arterial bleeding in 1 P, transient renal failure in 1 P and small pericardial effusions (<5 mm) in 8 P detected echocardiographically not requiring drainage. Clinical symptoms, exercise time on standard bicycle ergometry and thallium uptake in the PMR-treated regions during thallium scintigraphy (compared to the non-treated septum) are given in the table:

	Baseline (n = 60)	3 months (n = 43)	6 months (n = 38)	12 months (n = 24)
CCS-class	3.3 ± 0.5	1.7 ± 1.0*	1.4 ± 0.7*	1.4 ± 0.9*
Exercise time (sec)	346 ± 141	447 ± 183*	460 ± 162*	442 ± 168*
Thallium uptake (%)	76 ± 15	74 ± 14	76 ± 14	74 ± 12

*: $p < 0.01$ vs. baseline

Conclusion: PMR results in significant and persisting improvement of anginal symptoms and increased exercise capacity, but thallium scintigraphy did not show improved myocardial perfusion after PMR.

P2825 Percutaneous direct myocardial revascularization: safety and feasibility of high-density myocardial laser therapy and 1-month follow-up

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The Biosense DMR™ technology combines a novel 3-dimensional (3D) navigation and mapping system with a catheter capable of delivering laser energy. After 3D reconstruction of the left ventricular endocardial contour, the tip of the laser catheter is visualized in real-time to allow positioning in the ischemic target region. A single laser pulse of 2 J is delivered to the myocardium when endocardial contact of the catheter is stable for 3 consecutive beats. 27 pts with severe coronary artery disease were included in this study. All pts were "no option" pts with regard to PTCA or CABG suffering of angina CCS III and IV (LV EF 58 ± 11%). **32 ± 7** laser channels (inter-channel distance approx. 8 mm) were delivered per pt. Periprocedural complications: Pericardial effusion in 2 pts, non-sustained VT in 4 pts. Follow-up (34 ± 3 days) was obtained from 21 pts (17 m, 4 f; 59 ± 11 years). Treadmill exercise time increased from 351 to 402 sec ($p < 0.05$), angina decreased from CCS 3.3 pre- to CCS 2.0 post DMR ($p < 0.05$). SPECT showed improvement in 11 pts, no difference in 6 pts and worsening in 4 pts.

Conclusion: High-density delivery of myocardial laser channels is a safe and feasible method when a computer guided navigation system is used. One month after DMR there is a significant increase in treadmill exercise time and a decrease in angina.

P2826 Efficacy and safety of percutaneous transluminal myocardial revascularization with the holmiun laser fiberoptic system

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Purpose: To examine the safety and efficacy of performing Percutaneous Transluminal Myocardial Revascularization (PTMR) using the Eclipse laser system, the inmediate and midterm results of 53 patients who underwent the procedure at 4 different centers were analysed.

Methods: PTMR was performed in patients (p) with severe coronary artery disease unsuitable for surgical or percutaneous revascularization. Pre-procedure echocardiography was performed to assess myocardial wall thikness. The technique was performed via the femoral artery through a 9 French introducer. After the procedure, the patients underwent exercise test, when possible.

Results: Mean age was 64 ± 8 (71% male). Diabetes mellitus was present in 25 p (47%), hypertension in 27 (51%) and hipercholesterolemia in 34 (64%). All p were in class III or IV angina, 52 (98%) had multivessel disease, 28 (52%) had prior surgical and 23 (43%) previous percutaneous revascularization (PTCA). Mean left ventricular ejection fraction was 45 ± 9. In 4 p a combined PTMR and PTCA was performed. Procedural and fluoroscopy time was 52 ± 16 and 24 ± 12 minutes respectively. A total of 81 myocardial regions were treated (39 anterior, 29 latero-posterior and 17 inferior) producing an average of 14 ± 5 channels per procedure. There was no mortality or periprocedural myocardial infarction. Two patients had pericardial effusion (1 cardiac tamponade). At midterm follow up (6 ± 3 months) angina class improved in 44 (88%), there was no change in 5 (9%) and worsened in 1. Exercise test showed improved exercise tolerance in the 32 patients in whom it was performed. In 3 patients a repeated PTMR procedure was performed because or persistence of symptoms. No p has died or had suffered myocardial infarction at follow-up.

In conclusion: Percutaneous Transluminal Myocardial Revascularization is a safe and efficacious technique for reducing symptoms and improving exercise tolerance in patients unsuitable for conventional percutaneous or surgical revascularization.

P2827 Left ventricular electromechanical mapping for detection of myocardial viability in patients with impaired left ventricular function

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Aim: NOGA is a 3-dimensional left ventricular (LV) mapping sys-tem that uses low-intensity magnetic field energy to determine the localisation of sensor-tipped electrode catheters within the heart. We evaluated the ability of the system to distin-guish between irreversibly and reversibly dysfunctional myocar-dium in patients with impaired LV-function.

Methods: Unipolar voltage potentials and local endocardial shortening were measured in 13 patients (mean ± SD age 59 ± 12 years) with ischaemic cardiomyopathy (EF 32 ± 10%). Dysfunctional regions, identified by 2-D echocardiography, were characterised as irreversible when positron emission tomo-graphy (PET) revealed matched reduction of perfusion (13-N ammonia) and metabolism (18-FDG) and reversible when perfusion was reduced and metabolism preserved. For comparison with echocardiography and PET LV-mapping data were entered in a 9-segmental polar map.

Results: Out of 117 segments, 115 were assessable (table).

Segment characteristic	Unipolar voltage (mV)	Local Shortening (%)
Normal (n = 36)	11.5 ± 3.7	7.7 ± 3.3
Reversible (n = 30)	7.3 ± 3.1*	4.2 ± 2.5*
Irreversible (n = 49)	4.9 ± 2.2* **	2.9 ± 2.9*

*p < 0.01 vs. normal, **P < 0.01 vs. reversible. Mean ± SD.

Conclusion: LV electromechanical mapping detects electrical as well as mechanical impairment in irreversibly dysfunctional myocardium and impaired mechanical but preserved electrical activity in reversibly dysfunctional myocardium. LV mapping may enable detection of on-line myocardial viability in the catheterisation laboratory.

P2828 Radiofrequency percutaneous myocardial revascularization: a unique system for simultaneous radiofrequency percutaneous myocardial revascularization and gene therapy

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Background: Percutaneous myocardial revascularization (PMR) and transmyocardial revascularization (TMR) use laser energy to form channels in the myocardium and stimulate angiogenesis in swine models. Combining TMR and gene therapy has been shown to yields greater angiogenesis than TMR alone. Recent studies indicate that radiofrequency energy–which is less expensive to administer than laser energy–is an effective means of stimulating angiogenesis.

Methods: A 0.014 cm radiofrequency guidewire was passed through 6 French and 3 French catheters for percutaneous insertion in 3 swine under general anesthesia. A total of 30 channels (1 cm apart) were formed using radiofrequency energy in each animal. Automated ventriculography confirmed the presence of channels, and the animals were sacrificed.

Results: No animal suffered cardiac tamponade using this technique, and radiofrequency energy was easily applied through the 6 French system. The catheter was flexible, yielding access to all areas of the myocardium in the left ventricle. Successful injection through this hollow wire system indicates that gene therapy material could be delivered through it. At sacrifice, multiple sites of ecchymosis were confirmed on the endocardial and epicardial surfaces, but there was no evidence of inappropriate perforation.

Conclusions: Percutaneously applied radiofrequency energy delivered through a hollow guidewire successfully generates nontransmural channels in swine and is less expensive and easier to administer than laser energy. Further study is needed to confirm the system's ability to stimulate angiogenesis and its utility in delivering gene therapy.

P2829 Parameters influencing the clinical outcome after percutaneous myocardial laser revascularization

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Background: In the majority of patients with refractory angina pectoris due to end-stage coronary artery disease (CAD) percutaneous myocardial laser revascularization (PMR) leads to improvement of clinical symptoms and exercise capacity. The extent of improvement shows great variations. Clinical factors influencing the outcome after PMR have not yet been determined.

Methods: 45 patients (P) (mean age 64.1 ± 8.7 years; 38 men, 7 women) were treated with PMR. Clinical parameters (Canadian Cardiovascular Society [CCS] angina scale, use of additional nitroglycerin [semiquantitatively in 6 grades]) and results of non-invasive tests (bicycle exercise test, echocardiography) were analysed before and 3 months after PMR. Left ventricular function (LVF) was normal (ejection fraction [EF] > 60%) in 25 P. LVF was moderately reduced (EF 40–60%) in 14 P and severly reduced (EF < 40%) in 6 P.

Results:

Change in	EF > 60%	EF 40–60%	EF < 40%
CCS-class	−1.7 ± 0.9**	−1.7 ± 1.1**	−1.0 ± 0.9
Use of nitrates (grades)	−2.2 ± 1.8**	−2.1 ± 1.7**	−1.4 ± 1.7
Exercise capacity (s)	+73 ± 218	+193 ± 234*	−30 ± 222

*p < 0.005 vs baseline, **p < 0.001 vs baseline

The extent of CAD (1-, 2- or 3-vessel disease) and the number of laser channels created per region had no influence on clinical success.

Conclusion: Improvement of clinical symptoms after PMR was more pronounced in P with normal or only moderately reduced LVF compared to P with severely reduced LVF. Exercise capacity improved only in P with normal or moderately reduced LVF whereas it did not change in P with severely reduced LVF. Extent of CAD and number of laser channels seem to have no influence on clinical outcome after PMR.

P2830 Systolic function of lased myocardium improves after transcatheter laser therapy

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Direct transcatheter application of laser energy to the endocard of the left ventricle with a non-fluoroscopic guided device (Laser-Star™, NOGA™) is a novel method for the treatment of end-stage coronary artery disease. It can improve angina stability and exercise capacity. Improvement of myocardial perfusion has been shown with SPECT. It is not known whether myocardial function can improve after treatment.

26 consecutive patients, age 61.7 (± 7.8) years, 84.6% male, with no options for interventional or surgical treatment received direct myocardial revascularisation (DMR). Based on a nine-segment-approach 46 myocardial segments were lased. An average of 29.4 (± 6.9) Single 2J-laser-pulses were delivered to scintigraphic proven ischemic myocardium, when the catheter position was stable for 3 consecutive beats. Echocardiography after an adapted nine-segment model was performed at baseline and 30 days after treatment. Contractility was classified in normal, hypokinetic, akinetic and dyskinetic for each segment.

A total of 225 segments could be examined, 52 lased (L), 173 non-lased (NL). In the L-group there was an improvement in contractilty in 11/52 (21%) segments after 30 days compared with 9/173 (5.2%) in the NL-group ($p = 0.011$). Most segments in both groups (L = 36 (69%), NL = 154 (89%)) showed no change in contractility within 30 days and deterioration of contractility occurred in 5/52 (10%) (L) vs. 9/173 (5.2%) (NL) segments (n.s.).

Conclusions. Treatment with transcatheter applied laser energy significantly improves systolic function of lased myocardial segments in comparison to non-lased areas in the same patients. The underlying mechanism discussed is angioneogensis in the lased areas. Further insights in the improvement of perfusion and the return of viability could be gained by stress echocardiography

SURGICAL TREATMENT OF ATRIAL FIBRILLATION

P2831 Maze procedure combined with mitral valve replacement or repair – late results

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Chronic atrial fibrillation associated with mitral valve disease is an important cause of morbidity due to embolic events and haemodynamic compromise.

40 patients (all women, mean age 54.7 years) with acquired mitral valve disease and chronic atrial fibrillation were randomized to two groups: group A had mitral valve replacement in 18 pts (90%) or repair in 2 pts (10%) combined with maze procedure. Group B had mitral valve replacement (19 pts – 95%) or repair (1 pt – 5%) only. The cause of mitral valve disease was rheumatic in 80% of patients. 24 pts (60%) had mitral stenosis, 8 pts (20%) had mitral regurgitation, 8 pts (20%) had mixed lesion. 2 pts had history of peripheral emboli in upper or lower extremities. 1 pt had previous embolic stroke. There were no peri- or postoperative deaths. Early postoperatively, in group A, sinus conversion was obtained in 80% of pts. 3 patients (15%) had AF and one patient had a temporary complete A-V block. In group B only 4 pts (20%0 were in sinus rhythm. Significant reduction in the left atrial size was documented by echocardiography in group A only (59 mm preoperatively vs. 47 mm postoperatively). However, in 12-month follow-up only 25% of pts in group A versus 15% of pts in group B still stayed in the sinus rhythm. The others had atrial fibrillation.

In our experience, encouraging early results of maze procedure combined with MVR are not confirmed in late follow-up. Despite significant reduction in left atrial size most patients go back to atrial fibrillation

P2832 Development of a safe and effective surgical treatment strategy for the curative treatment of atrial fibrillation using minimally invasive techniques

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The Maze-operation is an effective but extensive and highly invasive procedure that requires long surgical bypass times with a considerable risk of complications. In an attempt to develop an effective but less aggressive therapeutic strategy, intraoperative radiofrequency (RF) ablation was performed in 11 pts. with chronic permanent AF during mitral valve surgery. Linear lesions (LL) in the left atrium were induced from the posterolateral mitral annulus to the left inferior pulmonary vein and continued via the upper left pulmonary and the upper right pulmonary vein to the lower right pulmonary vein. In 7 pts. access to the left atrium was achieved using a right atrial transseptal approach while in two pts. each the procedure was performed using a left atrial approach or a minimally invasive approach omitting thoracotomy. Induction of LL was achieved using a set of specially designed RF electrode probes (4–10 mm tip, temperature controlled; Sulzer Osypka Inc.). In 8 pts. RF energy was applied endocardially, while in 3 pts. endocardial and epicardial RF applications to the left atrium were performed. The efficiency of lesions induction was controlled by direct vision or using videoscopic techniques. All RF applications resulted in well delineated and contiguous atrial necrosis. Postoperatively, all pts. were in sinus rhythm. On days 2–5 following surgery 5/11 pts. developed a relapse of AF or atypical atrial flutter necessitating electrical cardioversion that was effective in all. Three of 7 pts. with a right atrial approach and 0/4 pts. with a left atrial approach or minimally invasive techniques required DDD-pacemaker implantation for sinus node dysfunction or AV-block. During follow-up (1–6 months) all but 1 pt. were in sinus rhythm or DDD-pacing.

Conclusions: The induction of contiguous left atrial lesion lines using intraoperative RF application seems to be safe and effective. The early experience with minimally invasive surgery shows that the technique is feasible and may develop to become an attractive therapeutic strategy to cure AF.

P2833 Long term follow-up of patients with mitral valve replacement and intraoperative radiofrequency ablation for curative treatment of atrial fibrillation

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Background: The original MAZE procedure has become the standard in the operative therapy in patients with chronic atrial fibrillation (AF). The efficiency of a continuous right and left atrial ablation line application using radiofrequency ablation for simplification of the operative procedure was analyzed in patients with mitral valve replacement.

Methods: In 10 patients (5 male and 5 female, age 45–74 years, mean 62 ± 10 years) suffering from mitral valve disease AF was documented for 18 ± 14 months, the left atrial diameter was between 47 and 68 mm (55 ± 6 mm). A continuous ablation line was performed through a right atrial transseptal approach starting at the posterior mitral valve annulus and incorporating all pulmonary veins. Electric isolation of the right atrial isthmus was performed using a new manual electrode.

Follow-up visits for rhythm stability are scheduled for 6, 12 and 24 months after the operation.

Results: There was no death in this series. No patient showed perioperative complications. Eight patients had sinus rhythm at the time of hospital discharge, three of them had a previous cardioversion. In 4 patients with high grade AV-block a dual chamber pacemaker was implanted. The first long term follow-up was carried out 206 ± 35 days after the operation. Seven patients still had sinus rhythm, one of them after an additional cardioversion. Three of the patients with sinus rhythm recieve a low dose Sotalol therapy, 3 low dose beta-blocker therapy. One patient with sinus rhythm does not recieve any antiarrhythmic drugs at all. Two patients were found with atrial fibrillation. One patient has moved with unknown address.

Conclusions: Electric isolation by an ablation line between the mitral annulus and the pulmonary veins and electric isolation of the right atrial isthmus can terminate chronic atrial fibrillation by interruption of the reentry circle and maintain sinus rhythm over a period of six months.

VALVE PROSTHESES

P2834 Haemodynamic performance of medtronic freestyle aortic root replacement as compared to homografts: a prospective randomised trial

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Homografts offer many advantages, particularly when inserted as a root. The Medtronic Freestyle is an unstented valve which can be inserted as a root, but its haemodynamic performance and ventricular response have not previously been well evaluated.

In order to assess the haemodynamic response and ventricular changes, we have conducted a prospective randomised trial comparing Homograft with Freestyle aortic root replacement.

Methods: Since August 1997, 54 patients have undergone aortic root replacement, 22 with Homograft and 32 with Medtronic Freestyle valves, 38 were male and 16 were female. Fifteen patients had concomittent CABG and 6 had had previous cardiac surgery. We have performed a preoperative transthoracic echocardiographic evaluation in all patients and again at 6 weeks, 6 months and 1 year postoperatively. Echocardiography has been performed up to 1 year postoperatively in 29 patients (9 Homograft and 20 Freestyle). Left ventricular diameters (LVD), posterior wall and interventricular septum thickness, left ventricular mass (LVM), fractional shortening, ejection fraction (EF) and peak and mean gradients across the valve were measured.

Results: No statistically significant differences were found between Homograft and Freestyle groups over time, postoperatively. After 1 year, preoperative LVM decreased from 342.8 ± 26.5 g to 263.5 ± 31.5 g in the Freestyle group, with a significant improvement after 6 months (235.8 ± 27.3 g, $p < 0.05$ vs preop). Left ventricular EF improved from 58 ± 4.3% to 63.9 ± 5.4% in the Freestyle group and both systolic and diastolic LVD reduced (42.3 ± 3 mm vs 40.1 ± 3.7 mm and 57.5 ± 2.8 mm vs 50.8 ± 3.4 mm, respectively). Mean preoperative aortic peak gradient was 47.7 ± 7.5 mmHg in the Homograft patients and 74.7 ± 6.4 mmHg in the Freestyle group which significantly improved to 9.6 ± 3.4 mmHg ($p < 0.05$) and 10.6 ± 5.1 mmHg ($p < 0.05$), respectively, after 1 year.

Conclusions: Our data show that haemodynamic performance of the Freestyle valve is comparable to that of the Homograft for periods up to 1 year with considerable regression of LV mass in patients who received Freestyle valves. This is an ongoing study.

P2835 Improvement of endothelial cell adhesion on biological prosthesis by preseeding with autologous fibroblasts

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Introduction: Endothelialization of biological prostheses, such as homografts or porcine aortic valves, may improve long-term durability by avoiding immune responses of the recipient. Purpose of our studies was to improve human endothelial cell seeding on such biological surfaces by preseeding of autologous fibroblasts.

Methods: In a first experiment pieces (4 cm^2) of cryopreserved aortic roots were seeded with endothelial cells (EC) for 24 hours. Groups 1–4 were preseeded with autologous fibroblasts using different times (8 or 16 h, 1 or 2 h stopping medium). The probes were then examined histologically and with the scanning electron microscope (SEM). In the second experiment complete human (n = 4) and porcine (n = 4) aortic roots were endothelialized (24 h) using a specially developed apparatus; 2 of each group were preseeded with fibroblasts (16 h). After a resting phase of 5 days they were perfused for one hour at a mean pressure of 70 mmHg. Specimen were taken after each culture step and after perfusion for examination (histologically and SEM).

Results: Fibroblasts formed a confluent cell layer after a seeding time of 16 hours. EC's could be seeded on these firboblasts and built a confluent cell layer. The same results were obtained by seeding on human aortic roots. Although porcine roots were pretreated with glycerol, obviously not all native cells were destroyed. This resulted in small defects of the cell layer. Fibroblast preseeded human aortic roots showed a nearby complete EC layer after perfusion; no interruptions of the fibroblast layer were seen. Aortic roots seeded only with EC's lost about 30% of their initial cell layer.

Conclusion: Preseeding with autologous fibroblasts improves endothelial cell adhesion of biological surfaces. For seeding on porcine valves a better preservation technique is necessary, that provides complete decellularization and therefore improves human cell seeding.

P2836 Cardiovascular tissue engineering: scaffold precoating with human autologous extracellular matrix for improved cell attachment

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Cell attachment to a scaffold is a precondition for the development of bioengineered valves and vascular substitutes. This is generally facilitated by the use of precoating factors, but they are heterologous and might be immunogenic. We used human autologous extracellular matrix (ECM) to precoat polyglycolyc acid (PGA) scaffolds, and compared the cell attachment with conventional precoating methods.

Methods: Tissue from the ascending aorta of a heart donor was cultured to obtain human myofibroblasts. Autologous ECM was extracted from the same aortic tissue. PGA scaffolds, measuring 1.0 × 1.0 × 0.3 cm, were precoated with autologous ECM, human serum, or poly-L-lysine; control group was pre-treated with phosphate buffered saline (PBS). Myofibroblasts (10^6 cells, passage 4) were seeded onto each scaffold and were allowed to attach for one hour. The number of cells attached to the meshes was determined using MTT-assay. Scanning electron microscopy was performed to document the extent of cell attachment.

Results: Compared to the control group, precoating with human serum, poly-L-lysine and ECM increased number of attached cells by 24%, 53% and 48%, respectively. Differences between precoating groups were significant ($p < 0.01$), except for ECM versus poly-L-lysine. Scanning electron microscopy also demonstrated the high degree of cell attachment to the PGA fibres on scaffolds precoated with ECM and poly-L-lysine.

Conclusion: Precoating polymeric scaffold with autologous human extracellular matrix is a very effective method of improving cell attachment in cardiovascular tissue engineering without the potential risk of immunologic reactions.

P2837 World wide performance of the Freestyle® stentless aortic bioprosthesis during a follow-up of five years

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Introduction: Stentless aortic xenografts do not require lifelong anticoagulation. However, the effectiveness of the valve during long term follow-up has not been proven. Therefore the hemodynamic performance of a new type stentless bioprosthesis, Freestyle®, implanted in the aortic position was evaluated in a prospective, nonrandomized multicenter clinical trial.

Methods: In 1100 pts a Freestyle® aortic xenograft 19–27 mm was implanted in 21 centers throughout the world. Implantation was performed using three different techniques (Subcoronary (SC), Root-Inclusion (RI), Full Root (FR)). Performance of the bioprosthesis was evaluated with 2D-echocardiography and Doppler-ultrasound 4 weeks. 3–6 months, and every year during a follow-up of 5 years after implantation.

Results: Mean aortic valve pressure gradients for the different techniques (SC, RI, FR) were 11.6 ± 6.7, 9.9 ± 7.5, 6.4 ± 4.4 mmHg respectively at 4 weeks after surgery and decreased to 7.7 ± 5.4, 7.7 ± 7.9, 5.5 ± 4.0 mmHg respectively after 3–6 months. The gradients remained at this low level throughout the follow-up of 5 years ($p < 0.0001$). Cardiac index for the different techniques was stable at 2.9 ± 0.9 (SC), 3.1 ± 0.9 (RI) and 2.5 ± 0.8 (FR) L/min/m^2 throughout the study period (n.s). Calculated effective orifice area (eoa) was 1.6 ± 0.6 (SC), 1.9 ± 0.7 (RI) and 1.9 ± 0.6 (FR) cm^2 after 4 weeks and remained so throughout follow-up (n.s). In 34% (SC), 19% (RI) and 13% (FR) of the patients valvular insufficiency grade 1 was observed and in 1% (SC), 1% (RI), 4% (FR) insufficiency grade 2. None of the pts had insufficiency grade 3 or 4.

Conclusion: Medium term hemodynamics of Freestyle® showed stable low gradients and excellent performance during a follow-up period of five years. Mechanics are superior to those reported from stented bioprostheses and mechanical valves.

P2838 Echocardiographic follow-up after mitral valve replacement with a cyopreserved homograft

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Cryopreserved homograft (CH) has been recently proposed as a new substitute for mitral valve replacement (MVR). However, one of the concerns is related to the structural evolution of the homograft. We report the results of transthoracic echocardiograhic (TTE) follow-up (FU) after MVR with a CH.

Between 1993 and 1998, 44 patients (pts) underwent MVR using a CH. Post-operative complications were 3 deaths and 1 repeat MVR. Of the 40 remaining pts, 25 had ≥1 year FU and FU TTE was available in 23 of them (92%).

The 23 patients who had FU TTE had a mean age of 39 ± 14 years [11–66], 12 pts (52%) were in NYHA class III/IV, and 19 (83%) in sinus rhythm. The indications for MVR were acute endocarditis in 8 pts and rheumatic disease in 15. Total CH was implanted in 9 pts and partial CH in 14. Associated procedures were aortic homograft in 1, tricuspid homograft in 1, tricuspid annuloplasty in 2, and aortic repair in 2. Post-operative valve area (VA) was 2.2 ± 0.4 cm^2 and 9 pts had grade 1/4 regurgitation.

Mean FU was 37 months [13–54]. No pt died and 2 underwent reoperation: 1 after 5 years because of endocarditis on CH and the other at 4 years for deterioration of aortic repair. All patients were in NYHA class I or II at last FU. FU TTE showed VA of 2.0 ± 0.3 cm^2 [1.4–2.6], with 2 pts having <1.5 cm^2. Mean gradient was 4.8 ± 2.6 mmHg. The degree of regurgitation was 1/4 in 8, while no pt had regurgitation > 2/4. Mean left ventricle end-diastolic diameter was 49 ± 4 mm and shortening fraction 36 ± 7%.

In conclusion: Mid-term TTE FU after MVR by a CH shows continuing good valve function in most pts. However, longer FU is necessary to detect deterioration.

P2839 Regression of left ventricular mass in patients with a small aortic root after the Ross operation as compared to patients who received a small-size mechanical aortic rosthesis

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In pts with small size aortic valve mechanical prostheses significant gradients are often found with Doppler echocardiography, which is not the case after the Ross operation. We compared regression of left ventricular mass (LVM) post valve replacement as an expression of the effect of these gradients on the LV.

Methods: We reviewed our population with size 19 and 21 mechanical prostheses (CM19 and CM21 group) and Ross pts with comparable preoperative aortic annulus (LVOT) dimension. Compared groups were matched for age, body surface area (BSA), pre-operative indexed LV size and mass, severity of aortic stenosis and regurgitation and of mitral regurgitation. Pts with > grade 2 post-operative aortic regurgitation during follow up (FU) were excluded. Gradients and left ventricular ejection time corrected for heart rate (LVETc) were measured in the mechanical prosthesis groups. LVM was compared preoperatively and during FU and was indexed (LVMi) since part of the population had increasing BSA during FU.

Results: No significant differences were noted between the groups in blood pressure and BSA pre-operatively and during FU. Gradients and LVETc were significantly higher in the CM19 than in the CM21 group. Regression of LVMi occurred in all groups and was most significant in the Ross pts and the CM21 group but not significant in the CM19 group during prolonged FU:

LVM index	Pre-op	6 mth p value	2 yr p value	4 yr p value
Ross (LVOT21) n = 23	128 ± 29	79 ± 14 <0.000001	80 ± 17 <0.000001	75± 19 <0.00001
CM 21 n = 34	137 ± 35	91 ± 23 <0.00001	90 ± 27 <0.000001	90 ± 26 <0.00001
Ross (LVOT 19) n = 14	112 ± 31	74 ± 16 <0.002	74 ± 13 <0.002	71 ± 8 <0.001
CM 19 n = 16	121 ± 36	94 ± 28 <0.05	99 ± 27 ns (0.1)	104 ± 27 ns (0.2)

Conclusion: Small mechanical prostheses frequently show high gradients and a small AVA especially when size 19 is used. Regression of LVMi in pts with a small aortic root is significantly more pronounced after the Ross operation as compared to pts who underwent valve replacement with a size 19, but not as compared to pts with a size 21 mechanical prosthesis. Lowest values of LVMi were seen in Ross pts.

P2840 Different characteristics of interstitial cells from human heart valves, pericardium and skin

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Heart valves consist of a matrix of collagen and elastic fibres containing interstitial cells (ICs) – fibroblasts (fibs), myofibroblasts and smooth muscle cells (SMCs) – covered by endothelial cells. Fibs can differentiate into myofibroblasts which are characterised by the presence of stress fibres containing the a-actin isoform present in SMCs. The aim of this study was to determine whether valve ICs were uniquely different from pericardium (peri) and skin ICs by determining their phenotype and investigating their intracellular Ca^{2+} ($[Ca^{2+}]_i$) response to vasoactive agents.

ICs cultured from human heart valves (n = 13), peri (n = 3) and skin (n = 4)were grown on glass coverslips and stained by immunofluorescence. $[Ca^{2+}]_i$ changes were evaluated by loading the cells with fura 2-AM, a calcium ratiometric dye and analysed using the IonVision system. ICs from skin expressed virtually no SM a-actin or SM myosin. 57 ± 9% (mean ± sem) of cells from valves and 24 ± 10% of cells from peri expressed SM a-actin and occasionally some cells (<4%) expressed SM myosin. ICs from peri and skin always expressed a fibroblast surface antigen, whereas expression was variable on valve ICs (80 ± 7%). Transient increases in $[Ca^{2+}]_i$ were induced when angiotensin II (Ang II), endothelin-1 (ET-1), 5-HT and U46619, the TXA2 mimetic, were added at 10^{-7} M (see table). The response of valve and peri ICs to Ang II and 5-HT were similar, however, pericardial cells were exquisitely sensitive to ET-1 and virtually unresponsive to U46619. Skin fibs were least responsive to all agents.

Table. Average increase in $[Ca^{2+}]$ ± sem (nM)

	ET-1	Ang II	5-HT	U46619
Valve	259 ± 36	397 ± 159	249 ± 47	192 ± 23
Peri	630 ± 218	391 ± 64	218 ± 53	41 ± 5
Skin	111 ± 34	138 ± 15	85 ± 46	163 ± 20

In conclusion, ICs from heart valves consist of a mixed population, the majority of which express SM a-actin and may be classified as myofibroblasts. Fewer cells from peri and no cells from skin expressed SM a-actin, suggesting that most of these cells were fibs. The heterogeneous $[Ca^{2+}]_i$ responses indicated that a number of receptor signalling pathways existed in all cell types. Evaluation of the nature of these events may help to elucidate the role of myofibroblasts in valve function.

P2841 105 Ross procedures: mid-term echocardiographic follow-up

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Pulmonary homograft function, pulmonary autograft in aortic position dimensions and function were assessed in a prospective echocardiographic study in mid term follow up.

Between March 92 and July 98, 105 patients (25 F and 80 M) underwent the Ross procedure; mean age at implant was 28.4 ± 10 years. Transvalvular gradients (G) and autograft size at three levels (annulus, sinuses and proximal ascending aorta) were measured in the postoperative period, at 6 months and annually.

Results: Perioperative mortality was 4.7%. One hundred patients had a mean 28.6 months echocardiographic follow up (range: 0.5 to 6.6 years), during which four non-cardiac deaths occurred. In these series, two patients underwent late reoperation (1 endocarditis, 1 proximal suture line dehiscence).

	Postoperative	Late	p
Peak G Ao (mmHg)	4.8 ± 2.9	5.1 ± 3	ns
PeakG Pulm (mmHg)	7.6 ± 5.8	12.5 ± 8	<0.0001
Annulus (mm)	24.7 ± 3	24.9 ± 3.4	ns
Sinuses (mm)	34.1 ± 4	36 ± 4.5	<0.0001
Prox. Aorta (mm)	29.1 ± 3.4	31 ± 4.5	<0.0001

There was no moderate nor severe regurgitation in the postoperative period. Two moderate pulmonary (2%) and 4 moderate aortic (4%) regurgitation developped during follow up.

Conclusion: The mid term follow up of Ross procedures shows 1) stability of autograft gradients and slight increase in peak pulmonary gradients (without moderate nor severe obstruction), 2) no severe regurgitation and 3) slight increase in autograft dimensions at sinuses and proximal aorta.

PHARMACOLOGY AND DRUG THERAPY

P2842 Reduction of myocardial infarct size with sCR1sLex, an alternatively glycosylated form of human soluble complement receptor type 1 (sCR1), possessing Sialyl Lewis X

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Introduction: There is evidence that the activation of the complement system and the expression of adhesion molecules in response to myocardial ischaemia may initiate a number of pathophysiologic responses that contribute to the progression of myocardial ischaemia and reperfusion injury. Certain animal disease models which have been shown to be complement dependent using the soluble human complement receptor type 1 (sCR1) and have also been shown to be selectin-dependent using the sLex tetrasaccharide. There is preclinical evidence that inhibition of the complement system or inhibition of PMN's leads to a reduction in tissue injury.

Objective: This study investigated the effects of soluble complement receptor type 1 (sCR1) or sCR1sLex, agents which function as a complement inhibitor or as a combined complement inhibitor and selectin adhesion molecule antagonist, respectively, on the infarct size and cardiac troponin T (cTnT) release caused by regional myocardial ischaemia and reperfusion in the rat.

Methods: Seventy-three, male Wistar rats (210–310 g) were anaesthetised, tracheotomised and ventilated. The jugular vein and carotid artery were cannulated to administer drugs and to measure mean arterial blood pressure, respectively. The chest was opened by a left-side thoracotomy and an atraumatic needle was placed around the left anterior descending coronary artery (LAD). After a stabilisation period of 30 min, the rats were subjected to 30 min occlusion of the LAD followed by 2 h of reperfusion. Haemodynamic parameters were continuously recorded and at the end of the experiments infarct size (with p-nitro-blue tetrazolium) and cTnT release were determined.

Results: The mean values for the AR ranged from 51 ± 3% to 54 ± 3% and, hence, were similar in all animal groups studied ($p > 0.05$). Infusion of sCR1 (1, 5 or 15 mg/kg, n = 5, 6 or 5) or sCR1sLex (1, 5 or 15 mg/kg, n = 5, 13 or 13) 5 min prior to LAD-reperfusion caused a reduction in infarct size from 61+2% (PBS-control, n = 10) to 46 ± 8%, 21 ± 10% and 31 ± 7% or 45 ± 7%, 35 ± 6% and 35 ± 4%, respectively. Infusion of sCR1 (15 mg/kg, n = 5) or sCR1sLex (15 mg/kg, n = 5) also reduces the myocardial TnT release from 80 ± 20 ng/ml (control) to 13 ± 7 or 4 ± 1 ng/ml, respectively.

Conclusions: Thus, sCR1 or sCRsLex significantly reduce infarct size and cardiac TnT release caused by 30 min of regional myocardial ischaemia and 2 h of reperfusion in the rat. The mechanims of the cardioprotective effects of sCR1 or sCR1sLex are not entirely clear, but may be due complement inhibition and/or prevention of the adhesion and activation of neutrophils.

P2843 Multiple cardiovascular disease risk factor reduction: a one-year weight loss intervention trial with orlistat

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The presence of multiple cardiovascular disease (CVD) risk factors within the same individual increases the overall risk of morbidity and mortality and such clustering of CVD/metabolic risk factors (high blood pressure, hypercholesterolemia, hyperinsulinemia) is far more prevalent in obese persons. The aim of the present analysis was to assess the impact of a one-year weight loss intervention on multiple CVD risk factors. The intervention consisted of a hypocaloric diet (500–800 kcal/day deficit) plus either orlistat 120 mg tid (n = 1508), a non-systemically acting gastrointestinal lipase inhibitor which reduces dietary fat absorption, or placebo (n = 1075). Data were derived by pooling 5 randomized, double-blind, placebo-controlled trials conducted in Europe and the US. Presence or absence of the following CVD risk factors were applied to categorize subjects based on these criteria: LDL-cholesterol: >3.362 mmol/L; diastolic blood pressure > 90 or systolic > 140 mmHg; fasting serum insulin > 90 pmol/L. At randomization, 70% of subjects in both groups had one or more of these risk factors. After 1 year, orlistat-treated patients had lost significantly more weight than placebo recipients (9.0 ± 0.2% vs 5.6 ± 0.3% of initial body weight, $p < 0.001$). A total of 27.2% of orlistat patients with 1 or more risk factor at baseline had no risk factors present at 1 year, (vs 13.9% of placebo-treated patients, $p < 0.01$). The number of risk factors present was reduced in 30.5% of orlistat patients vs 23.4% of placebo patients, and were increased in 27.4% of placebo patients vs 19.1% of orlistat patients. Thus, the greater weight loss in patients treated with orlistat plus hypocaloric diet compared with diet alone was associated with greater improvements in CVD risk status. Orlistat may be of benefit for the treatment of obese subjects at high risk of CVD.

P2844 BK_{Ca} channels mediate testosterone-induced coronary artery relaxation in vitro

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Testosterone (T) relaxes coronary arteries (CA) in vitro, an effect which appears to be mediated by potassium (K^+) channels. The lack of inhibition of testosterone-induced relaxation by glibenclamide suggests that the ATP-sensitive K^+ channel is not involved. We therefore investigated the possible role of calcium-sensitive K^+ (BK_{Ca}) channels in the mediation of T-induced CA relaxation in vitro. Epicardial CA rings from male and female rabbits were suspended in organ baths for measurement of changes in isometric tension. A concentration response curve to K^+ (10–80 mM) was performed, then repeated after a 20 min incubation in T (10 μM). Control curves in rings incubated in the specific BKCa channel inhibitor iberiotoxin (IbTx; 100 nM) were then constructed and repeated after co-incubation for 20 min with T. T-induced relaxation was then performed in the presence of IbTx. Response was measured as % contraction compared with control at the same concentration of K^+. Incubation in IbTx significantly reversed the attenuation of contraction by T to K^+ (table).

$[K^+]$	10 mM	20 mM	40 mM	80 mM
Control	8.1 ± 3.8	48.6 ± 7.2	91.3 ± 4.6	100 ± 0
T	3.0 ± 1.1	25.0 ± 3.3*	50.1 ± 6.8**	74.3 ± 9.2
IbTx	18.0 ± 10.4	67.1 ± 7.6	98.1 ± 1.9	100 ± 0
IbTx + T	22.9 ± 21.9	68.8 ± 14.3*	90.6 ± 12.8*	92.5 ± 13.0

(Values are mean % contraction ± SEM. *P < 0.05, **P < 0.01)

IbTx, in concentrations previously found to close BK_{Ca} channels, reversed the CA relaxing effects of T suggesting that the opening of BK_{Ca} channels is likely to contribute to T-induced relaxation in CA's.

P2845 $Endothelin_A$ receptor antagonism increases myocardial ischaemia during coronary angioplasty

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There exist conflicting results regarding the cardioprotective effects of endothelin (ET) receptor antagonists on myocardial infarct limitation in animals. In the present study we examined the effects of BQ-123 (15 patients), an ET_A receptor antagonist, on myocardial ischemia during angioplasty.

Methods: Thirty patients with stable angina were studied while undergoing angioplasty for a single artery lesion. According to the protocol, all patients underwent a minimum of 3 balloon inflations (BI) all of 120 s in duration. Between the 2nd and 3rd BI, an intracoronary (IC) infusion of either BQ-123 (15 patients) in saline or normal saline (15 controls) was infused at the rate of 3 ml/min (BQ-123 300 nmol/min) for 20 min. IC and surface ST-segment elevation in mV and pain score were measured at the end of the 3 BIs.

Results:

	(Mean ± SD)	1st BI	2nd BI	3rd BI
BQ-123	IC ST	1.22 ± 0.48	0.91 ± 0.56*	1.13 ± 0.62
	Surface ST	0.17 ± 0.18	0.14 ± 0.18	0.17 ± 0.21
	Pain score	51 ± 17	35 ± 13*	37 ± 15*
Controls	IC ST	1.26 ± 0.55	1.02 ± 0.55	0.77 ± 0.56*†
	Surface ST	0.20 ± 0.15	0.12 ± 0.09*	0.10 ± 0.07*†
	Pain score	54 ± 17	38 ± 15*	28 ± 10*†

*p < 0.05 vs 1st BI; †p < 0.05 vs BQ-123 group. Blood pressure and heart rate were similar during the 3 BIs in the 2 groups.

Conclusion: These findings indicate that ETA receptor antagonism increases myocardial ischemia during angioplasty.

P2846 Effects of phosphodiesterase-5 inhibition on myocardial ischaemia in patients with chronic stable angina in therapy with β-blockers

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Phosphodiesterase 5 inhibition (PD5I) has been suggested to be potentially hazardous and to increase the risk of cardiac events in pts with coronary artery disease (CAD). To verify whether PD5I with Sildenafil (S) affects exercise-induced myocardial ischemia in pts on beta-blockers we studied 14 pts with known CAD and positive exercise test (ET) in a randomized, double-blinded, placebo-controlled study.

Methods: All pts underwent off-therapy a baseline ET and were then started on Atenolol (A, 100 mg o.d.). After a run-in phase of 2 weeks, pts underwent a second ET and were randomized to receive either S (50 mg) or Placebo (P) given in a random order in 2 different days, 2 days apart. ET was repeated 2 hours after the administration of S or P.

Results: All pts had >1 mm ST↓ while off-therapy. Eight pts had a negative exercise test response after A, which was unaltered by the adjunct of either S or P. In the remainders, A significantly prolonged time to 1 mm ST↓ and exercise time. S and P did not reverse the beneficial effect of A upon exercise-induced myocardial ischemia.

	Baseline	A	A + S	A + P
1 mm ST↓				
HR (bpm)	123 ± 21	115 ± 12	116 ± 10	114 ± 16
SBP (mm Hg)	178 ± 24	182 ± 22	178 ± 24	184 ± 28
Time (sec)	412 ± 45	584 ± 42	592 ± 35	579 ± 52
Not Attained		8/14 (57%)	8/14 (57%)	8/14 (57%)
Peak Exercise				
HR (bpm)	131 ± 24	130 ± 18	132 ± 16	128 ± 22
SBP (mm Hg)	186 ± 26	184 ± 32	182 ± 28	186 ± 26
Time (sec)	523 ± 54	754 ± 42	762 ± 53	748 ± 39

In conclusion, phosphodiesterase 5 inhibition with S can be safely administered in pts with chronic stable angina whose symptoms and exercise test response are well controlled by beta-blocker therapy.

P2847 Calcium activated potassium channels regulate NO-mediated vasodilation through modulation of vascular superoxide anion production

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Recent in vitro data suggest, that endothelial large conductance calcium activated K^+ channels (BKCa) modulate the vascular response to nitric oxide (NO), but the in vivo implications of this interaction is not clear. This study investigates 1) the effect of BKCa modulation on nitroglycerin-derived NO-mediated vasorelaxation in isolated rat coronary arteries, the isolated perfused rat heart and consious unrestained rats and 2) characteristics of BKCa-mediated effects on NO-induced vasorelaxation. Administration of iberiotoxin (IbTX (10^{-7} M), a specific inhibitor of BKCa) reduced Emax of the nitroglycerin (NTG) concentration-relaxation curve in isolated coronary arteries from 89 ± 2% to 33 ± 2% ($p < 0.05$). Infusion of IbTX (0.1 mg/kg) reduced the in vivo hypotensive effect of NTG by 55% (before IbTX: 32 ± 3 mmHg, vs after IbTX: 15 ± 3 mmHg, $p < 0.05$). Additionally, the NTG-induced increase in coronary flow in the isolated perfused heart was reduced by 77 ± 6%, $p < 0.05$ after IbTX (10^{-7} M) infusion. Incubation with indomethacin, an inhibitor of prostaglandin synthesis, the endothelin receptor antagonist BQ-123 or an inhibitor of NO synthase did not affect the response to IbTX on isolated vessels, suggesting that the effect of IbTX is independent of a potential depolarization-induced vasoconstrictor release. In contrast, the inhibitory effect of IbTX on coronary blood flow changes was significantly ($p < 0.05$) counteracted by in vivo intravenous pretreatment with the superoxide scavenging agent PEG-SOD (30.000 units/kg). The results suggest, that blockade of endothelial BKCa in rats significantly reduce NO-induced effects in conscious animals, isolated coronary arteries and the isolated perfused heart. This effect probably occurs through BKCa-induced changes in the vascular membrane potential regulating superoxide anion production.

P2848 Major cardiovascular events following infusional 5-fluorouracil and cisplatin antineoplastic therapy

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Background: Antineoplastic therapy with infusional 5-Fluorouracil (5-FU) is known to have several potential life-threatening cardiovascular side effects. The aim of this prospective study is to verify the possible predictive power of some ECG-related variables in this setting.

Methods: Sixty-three consecutive patients (men 53, women 10) aged 60 ± 9 years, affected by head and neck squamous cell carcinoma, received totally 216 courses of chemotherapy with 5-FU (1000 mg/m²/day continuous infusion for 5 days) and Cisplatin (100 mg/m² i.v. at day 1). Clinical examination and 12-lead ECG were performed at baseline and at day 1–3–5 of each course of chemotherapy.

Results: Antineoplastic therapy caused a decrease of heart rate (from 72 ± 13 to 65 ± 10 bpm, $p < 0.001$) and an increase of both QT and QT_c intervals (from 382 ± 37 to 409 ± 41 ms, $p < 0.001$ and from 412 ± 21 to 424 ± 32, $p < 0.001$). During a mean follow-up of 289 days (range 7–980 days) 8 major cardiovascular events (3 in-hospital) were recorded: 3 acute ischemic heart events (1 myocardial infarction and 2 unstable angina episodes), 2 fatal strokes, 2 sudden deaths (1 in-hospital cardiac sudden death) and 1 acute heart failure. In the patient who died suddenly in the hospital, an ECG taken 2 hours before the event showed a maximum QT interval of 530 ms (QT_c = 560 ms) and a maximum QT interval dispersion of 40 ms.

Conclusion: Sudden death, acute ischemic heart events, fatal stroke and acute heart failure have been observed following chemotherapy with 5 day infusional 5-FU and Cisplatin with an overall prevalence of 12.7%. The role played by the QT interval increase and QT dispersion in relation to these events should be further explored.

P2849 Nitrate tolerance and cross-tolerance in human internal mammary artery and saphenous vein following low-dose nitroglycerine infusion

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The mechanism of nitrate tolerance in man remains uncertain. Hypotheses include impaired metabolism of nitroglycerine (NTG) to nitric oxide, inactivation of nitric oxide, and desensitization of guanylate cyclase. The present study investigated these hypotheses utilizing segments of internal mammary artery (IMA) and saphenous vein (SV) from patients undergoing coronary artery bypass grafting for stable angina.

Methods: Patients were randomized to either 24 hours intravenous NTG at 10 micrograms/minute (Tolerant group) or 24 hours nitrate-free (Control group) prior to harvest of the IMA and SV. Segments of the vessels were preconstricted with noradrenaline to 70–80% of maximum and then relaxed with one of the nitric oxide donors; NTG, sodium nitroprusside (SNP) or the endothelium-dependent nitric oxide generator A23187.

Results: See table.

Vascular responses

	IMA Control Log EC50 (M)	IMA Tolerant Log EC50 (M)	IMA Control Emax (%)	IMA Tolerant Emax (%)
NTG	−7.73 (0.14)	−7.02 (0.08)*	97 (2)	85 (2)*
SNP	−7.04 (0.12)	−6.98 (0.15)	98 (1)	95 (1)
A23187	−7.53 (0.15)	−7.40 (0.13)	79 (4)	67 (3)#
	SV Control Log EC50 (M)	**SV Tolerant Log EC50 (M)**	**SV Control Emax (%)**	**SV Tolerant Emax (%)**
NTG	−7.03 (0.14)	−6.52 (0.13)*	97 (1)	84 (5)*
SNP	−6.84 (0.16)	−6.87 (0.22)	98 (1)	96 (3)
A23187	−7.63 (0.09)	−7.36 (0.10)	39 (5)	37 (4)

*$P < 0.01$, # $P < 0.05$ Control vs Tolerant via unpaired T-test. n = 6–10 in each group. Data are expressed as mean with standard error in brackets.

Conclusions: Low-dose intravenous NTG causes significant nitrate tolerance within 24 hours in human IMA and SV, with minimal cross-tolerance to A23187 and no cross-tolerance to SNP. These data are consistent with impaired metabolism of NTG to nitric oxide as the primary mechanism of nitrate tolerance in man.

P2850 Direct cardio-depressive effect of Cyclosporine A in human and rabbit myocardium: measurements of contractile parameters, SR calcium-content, and myofilament responsiveness

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The immunosuppresive drug Cyclosporine A (CsA) is a key substance in pharmacological therapy following solid organ transplantation. CsA therapy is associated with severe side effects such as hypertony and renal complications, and cardiotoxicity. However, the mechanism underlying the direct cardio-depressive effects of CsA are largely unknown. In multicellular cardiac muscle preparations from rabbit hearts and from end-stage failing and non-failing human hearts we investigated the direct effects of CsA on contractile performance, sarcoplasmic reticulum (SR) Ca^{2+}-load, and on the actin-myosin matrix. In rabbit muscle preparations (n = 8) we observed a concentration dependent decrease in developed force to 50.2 ± 7.7% of control at 100 nmol/L with an EC50% of 1.9 ± 0.4 nmol/L. In muscle preparations (n = 6) from failing human hearts the maximal effect amounted to 55.6 ± 6.4% of control while EC50% was reached at 1.0 ± 0.3 nmol/L. These values are at and below the therapeutically applied plasma levels. Rapid cooling contractures revealed a decreased SR calcium load to 74.0 ± 7.4% in rabbit preparations (n = 8) and to 84.4 ± 6.5% in preparations from failing human hearts (n = 4). No direct effects were observed on the actin-myosin matrix: myofilament calcium sensitivity, cooperativity,and maximal force development of permeabilized preparations from the rabbit (n = 7) remained unchanged in the presence of CsA. Additionally, results obtained in muscle preparation from non-failing human hearts (n = 4) were similar to those obtained in rabbit muscles and preparations from failing human hearts. We conclude that CsA causes a direct, dose-dependent cardio-depressive effect at clinically relevant concentrations, most likely due to altered handling of Ca^{2+} by the SR.

P2851 Continuous treatment with pentaerythritol tetranitrate prevents the increase of LDL-oxidation in established atherosclerosis

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Recent investigations in rabbits have shown that continuous treatment with the nitric oxide (NO) donor pentaerythritol tetranitrate (PETN, 6 mg/kg/day) for 16 weeks does not induce typical nitrate tolerance, sightly decreases aortic superoxide production and prevents the development of impaired endothelium-dependent vasorelaxation (EDR) induced by a high cholesterol diet. We sought to determine if continuous treatment with PETN can prevent oxidation of low density lipoprotein in established atherosclerosis. Three groups of 10 New Zealand White rabbits were fed a chow containing 0.75% cholesterol for 16 weeks. One group (CHOL16) served as control and two groups were fed for another 16 weeks a cholesterol-chow without (CHOL32) or with 6 mg PETN/kg/day (PETN32). LDL was islolated from blood taken after 16 weeks and after 32 weeks in CHOL32 and PETN32. Oxidation of 150 μg LDL protein by 1.7 μM CuSO4 was continuously monitored at 234 nm and the time to onset of oxidation (lag-time) which directly corresponds to the LDL-oxidation resistance was measured. After 16 weeks of cholesterol feeding the lag time was 214 ± 9 min. A similar lag time was measured in PETN32 after 32 weeks (220 ± 21 min). In striking contrast, the lag-time after 32 weeks in CHOL32 was significantly reduced to 168 ± 24 min (P = 0.035). These results suggest that the decrease of LDL oxidation resistance induced by cholesterol feeding in established atherosclerosis can be prevented by continuous treatment with the NO-donor PETN. This effect of PETN was accompanied by a protective action on EDR. Isolated aortic rings of CHOL16 showed a typical impairment of EDR with a maximal relaxation at 1 μM acetylcholine of 22.2 ± 8.5%. In CHOL32-rings EDR was completely impaired, while EDR in PETN32 (23.3 ± 9.1%) was similar to that of CHOL16. We suggest that long-term continuous treatment with PETN might have favourable antioxidative effects in established atherosclerosis.

P2852 40 mg aspirin are not sufficient to inhibit platelet function under conditions of limited compliance

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Aspirin is the standard agent for prevention of atherothrombotic vessel occlusions. Because of the permanent platelet inhibition, daily administration of low-dose (30–50 mg) aspirin will cumulate in a sufficient (>90%) inhibition of platelet thromboxane A2 (TXA2) synthesis. However, elderly patients adhere to aspirin treatment only on 40–70% of days (Carney et al., Health Psychol 1995;14:88). Thus, an effective treatment concept, designed to prevent atherothrombotic events, should be able to compensate for "missed" aspirin doses. In order to simulate patient "non-compliance", we have conducted a study in healthy volunteers, comparing 40 mg with 100 mg aspirin administered every second day.

Methods: 20 healthy male volunteers aged 21 to 37 were enrolled in the study. The effects of aspirin (40 mg vs. 100 mg) on collagen (0.3–5 μg/ml)-induced TXA2 formation (radioimmunoassay) and platelet aggregation (turbidimetry) in citrated plasma were studied in a randomized, double-blind cross-over design (14 days treatment, 14 days wash out).

Results: Collagen-induced TXA2 formation was significantly ($p < 0.001$) inhibited by both aspirin dose regimes. However, in contrast to the 100 mg dose, which sufficiently (>90%) blocked platelet thromboxane formation, only a partial (60–70%) inhibition was seen with 40 mg aspirin ($p < 0.01$ 40 mg vs. 100 mg). This was paralleled by a significantly ($p < 0.001$) reduced inhibition of collagen-induced platelet aggregation by 40 mg aspirin as compared to the 100 mg dose.

Conclusion: Under conditions of limited patients' compliance, a reduction of aspirin doses below 100 mg/d might result in an impairment of its antithrombotic efficacy.

P2853 Stereoselective effects of (R)- and (S)-carvedilol

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Carvedilol is currently used as a racemic mixture, (R,S)-carvedilol, consisting of equal amounts of (R)-carvedilol, an alpha-blocker, and (S)-carvedilol, an alpha- and beta-blocker, which have never been clinically tested in their optically pure forms. We performed a randomized, double-blind, placebo-controlled, cross-over study in 12 healthy male volunteers. At intervals of 7 days, subjects received single oral doses of 25 mg (R,S)-carvedilol, 12.5 mg (R)-carvedilol, 12.5 mg (S)-carvedilol and placebo, respectively, at 8 a.m. as well as at 8 p.m. Exercise was performed at 12 a.m., and heart rate and blood pressure were measured before exercise, during the last minute of exercise, and after 15 min of recovery. Urine was collected between 10 p.m. and 6 a.m., and 6-sulfatoxy-melatonin (aMT6s, the main metabolite of melatonin which is almost completely eliminated in urine) was determined by RIA.

Compared to placebo, heart rate at exercise was reduced by (R,S)-carvedilol (−11%, $p < 0.001$) and (S)-carvedilol (−14%, $p < 0.001$) whereas (R)-carvedilol had no effect. Resting heart rate after 15 min of recovery was increased by (R)-carvedilol (+10%, $p < 0.01$) with no effect of (R,S)- and (S)-carvedilol at this time. None of the substances had any effect on diastolic blood pressure as well as on nocturnal excretion of aMT6s in urine.

Our results indicate that only (S)-carvedilol causes beta-blockade whereas (R)-carvedilol obviously increases sympathetic tone at rest. In contrast to other beta-blockers, none of the enantiomers of carvedilol appears to reduce nocturnal melatonin release. This unexpected result deserves further investigation

P2854 The Ca^{2+}-sensitizer EMD 57033 and CGP 48506 influence crossbridge interaction in human myocardium in a different mode of action

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Ca^{2+}-sensitizers may be beneficial in the treatment of heart failure as drugs without additional increase in intracellular free Ca^{2+} or energy cost.

Methods: The present study investigated the mode of action of the novel Ca^{2+}-sensitizers CGP 48506 (CGP) and EMD 57033 (EMD) on isometric force of contraction, the intracellular Ca^{2+}-transient (fura-2 method) and myosin-ATPase activity (ATPase) in left ventricular papillary muscle strips (PAP) and skinned fibers of PAP from human hearts (dilated cardiomyopathy, NYHA IV, heart transplants, n = 15).

Results: CGP (1–100 μM) and EMD (0.5–30 μM) increased force of contraction without changing the intracellular Ca^{2+}-transient. Both Ca^{2+}-sensitizers increased the sensitivity of the Ca^{2+}-induced force-generation (EC_{50} Ca^{2+} control: 1.52 μM, +CGP: 0.67 μM, +EMD: 0.96 μM). Only CGP, but not EMD, increased the Ca^{2+}-sensitivity of the ATPase (EC_{50} Ca^{2+} control: 1.08 μM, +CGP: 0.62 μM, +EMD: 0.99 μM). CGP did not change maximal Ca^{2+}-activated tension or ATPase, whereas EMD increased the maximal Ca^{2+}-activated force-gemeration but not maximal ATPase.

In conclusion, the Ca^{2+}-Sensitizers CGP 48506 and EMD 57033 enhance force via a different mode of action; only EMD 57033 increases maximal tension.

P2855 Effect of different oestrogen-progestin replacement therapy schemes upon exercise-induced myocardial ischaemia in female menopausal patients with coronary artery disease

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Although in hormone replacement schemes progestins are required to reduce the likelihood of uterine malignancies, little is known on their possible detrimental effect upon the cardiovascular system. The aim of this study was to evaluate the effects of estrogen replacement alone and 2 different estrogen-progestin replacement therapy schemes upon exercise induced myocardial ischemia

Methods: After a baseline exercise test, 14 female menopausal pts with CAD received conjugated equine estrogens (CEE) 0.625 mg alone for 30 days. Then, they underwent a second exercise test and were randomized to receive in a cross-over design medroxyprogesterone acetate (MPA) either in continuous combined therapy (2.5 mg/daily) for 28 days or in cyclical therapy (10 mg od from day 16 to day 28).

Results: CEE increased time to 1 mm ST↓ compared to baseline (352 ± 185 vs 265 ± 133 s, $p < 0.01$). After CEE alone, 2 pts with a previously positive exercise test showed a negative exercise test. In these 2 pts, the test remained negative during continuous combined MPA therapy while become positive during cyclical MPA. CEE + continuous combined MPA increased both time to 1 mm ST↓ and exercise time compared to baseline (386 ± 165 vs 265 ± 133 s, $p < 0.01$, and 545 ± 198 vs 465 ± 186 s, $p < 0.05$, respectively). No difference was found between baseline and CEE + cyclical MPA in time to 1 mm ST↓ (268 ± 164 vs 265 ± 133 s, NS) and exercise time (455 ± 223 vs 465 ± 186 s, NS). One patient developed unstable angina during cyclical MPA.

In conclusion, continuous combined therapy with CEE + MPA improves exercise-induced myocardial ischemia in female pts with CAD, while the beneficial effect of CEE is abolished by cyclical therapy with MPA.

P2856 The addition of vitronectin receptor antagonism to a platelet glycoprotein IIb/IIIa inhibitor confers an additional antiproliferative effect

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Abciximab, but not Tirofiban or Eptifibatide, has reduced restenosis in a large trial. Abciximab differs from these other highly specific IIb/IIIa inhibitors in having equal affinity for the vitronectin receptor (VNR). We investigated whether a small molecule G3580, inhibitory for both IIb/IIIa and VNR would inhibit smooth muscle cell proliferation *in-vitro,* compared to Lamifiban, a specific IIb/IIIa inhibitor.

Methods: Porcine aortic vascular smooth muscle cells were plated in DMEM with 20% porcine serum onto fibronectin, laminin, collagen type IV, vitronectin or uncoated plastic. 24 hours after plating, they were treated with 100 μM of G3580 100 μM Lamifiban or control, (doses shown not to detach adherent cells). Cell proliferation was assessed at 48 and 96 hours.

Results: G3580 but not Lamifiban significantly reduced proliferation on both uncoated plastic (Light Units (SEM) at 96 hrs; Control 22.5 (1.5) Lamifiban 19 (7.5) G3580 4.5 (0.5), $p < 0.05$) and vitronectin; (at 96 hrs; Control 26.5 (0.5) Lamifiban 27.5 (1.5) G3580 8.5 (0.5), $p < 0.05$). Neither compound affected proliferation of PVSMC on fibronectin, laminin, or collagen IV.

An anti-proliferative effect mediated via VNR antagonism may explain the anti-restenotic effect of Abciximab.

P2857 Thyroxine administration prevents the deleterious effect of dobutamine on postischaemic function

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Aim: The aim of the study was to investigate the inotropic effect of dobutamine (DOB) administration on postischaemic dysfunction, in the setting of global ischaemia and reperfusion, in normal (NORM) and hyperthyroid (THYR) hearts.

Methods: Cardiac hypertrophy was induced in rats by thyroxine administration, twice a day, for 14 days, subcutaneously. Isolated rat hearts were perfused in a Langendorff preparation. Normal hearts after an initial stabilization period were subjected to 20 min of global, zero flow ischaemia followed by 45 min reperfusion without DOB (GpA, n = 6) and with DOB (GpB, n = 8), (10 μg/kg/min). We have shown that this DOB dosage to exerts a positive inotropic myocardial response in hearts without ischaemia. THYR hearts were subjected to the same protocol without DOB (GpC, n = 10) and with DOB (GpD, n = 12). Postischaemic recoveries of left ventricular developed pressure (LVDP) were expressed as % of the initial value (LVDP%). Left ventricular end-diastolic pressure (LVEDP) was measured in mmHg at 45 min of reperfusion.

Results: In NORM hearts, LVDP% was higher in GpA compared with GpB, 45.4 (SEM 4.2) vs 19.1 (2.7), $p < 0.05$ and LVEDP was lower in GpA than in GpB, 65.5 (8.6) vs 96.7 (6.4), $p < 0.05$. In THYR LVDP% was lower in GpC compared with GpD, 59.4 (4.6)c vs 72.1 (2.9), $p < 0.05$ while LVEDP was not different between the two groups 36.5 (5.7) vs 50 (5.0) p = n.s

Conclusion: In NORM hearts thyroxine administration does not alter postischaemic dysfunction. However it prevents postischemic dysfunction caused by dobutamine. This effect may be due to calcium handling interrelationships affected by both hyperthyroidism and dobutamine.

P2858 Potentiation of halofantrine-induced QTC prolongation by mefloquine

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The antimalarial drug halofantrine can cause QT prolongation and torsade de pointes, and its effects may be greater in patients who have previously received mefloquine. To investigate possible interactions between these drugs, their effects have been determined in pentobarbitone-anaesthetized, female NZW rabbits prepared for measurement of arterial BP, limb lead ECG and epicardial and endocardial monophasic action potentials (MAP).

Mefloquine up to 10 mg kg^{-1} did not alter ECG intervals, heart rate (HR) or BP, but at 30 mg kg^{-1} caused profound reductions in BP. Halofantrine decreased HR and increased QTc. Prolongation of QTc by halofantrine was greater in rabbits which had received mefloquine 3 mg kg^{-1}. Halofantrine also caused Mobitz type I AV block and delays in repolarisation were seen on the MAPs. None of the rabbits had torsade de pointes.

Table 1. The effects of increasing doses of vehicle, halofantrine (HF), mefloquine (MQ), or halofantrine after 3 mg kg^{-1} mefloquine (HF + MQ).

	n	Dose		
		3 mg kg^{-1}	10 mg kg^{-1}	30 mg kg^{-1}
QTC interval (ms)				
Vehicle	6	305 ± 10	311 ± 14	311 ± 11
MQ	6	307 ± 19	317 ± 17	
HF	6	361 ± 26	410 ± 19*	410 ± 18**
HF + MQ	6	439 ± 18*†	452 ± 14*	461 ± 14**†
Halofantrine concentration (μM)				
HF	6	0.7 ± 0.1	3.2 ± 0.3	13.5 ± 1.7
HF + MQ	6	1.8 ± 0.3†	6.9 ± 1.7†	24.7 ± 4.3†

Values are mean ± s.e. mean. *$P < 0.05$, **$P < 0.01$ compared with vehicle, †$P < 0.05$ compared with HF, Kruskal-Wallis test.

Blood concentrations of halofantrine were approximately twice as high in the group that had received mefloquine. This indicates that mefloquine alters the distribution of halofantrine, thus providing an explanation for the ability of mefloquine to enhance halofantrine-induced QTc prolongation.

P2859 Different action of β-blockers on daytime and nighttime heart rate variability

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Beta-blockers (BB) have proven to be of beneficial effect in some heart diseases (HD) and arrhythmias, because of their correlations with autonomic nervous system. The present prospective study was undertaken to investigate the effects of BB on heart rate variability (HRV) according to the HD and the time.

Methods: we studied 60 patients (pts), aged 39 to 76 years (mean 56 ± 15). 40 of them survived a myocardial infarction, 12 to 24 months previously (group I-gr). 20 pts had did not have HD (gr II). 24 hour monitoring was performed at baseline and after 8 to 10 days of atenolol (100 mg/day, n = 35) or metoprolol (100 to 150 mg/day, n = 25) (BB). Measures of HRV in the time and frequency domains were calculated for the the entire 24 hours (h) and from 09:00 to 21:00 h (daytime) and 23:00 to 6:00 h (nighttime).

Results: the 24 h HRV analysis shows an improvement over control values in indices of parasympathetic tone, but the results were significant only for high-frequency power (HF) in groups I ($p < 0.01$) and II ($p < 0.05$). A decrease of the coefficient of variance (CV) was noted in gr II ($p < 0.05$). The analysis during the day and the night revealed a predominant action of BB during the night with HF increase from 64.5 ± 45 to 161 ± 111 ms^2 in gr I ($p < 0.001$) and from 99 ± 89 to 268 ± 348 ms^2 in gr II ($p < 0.02$). In gr II, daily HF power did not change after BB. The decrease of CV in gr II disappeared in the daily and nightly analysis.

Conclusion: beta-blockers enhance HRV indexes reflecting parasympathetic activity, mainly during the night in patients with and without ischemic heart disease. This effect could explain the beneficial effect of BB on general survival in patients with and without myocardial infarction.

P2860 Chronic transdermal 17β-oestradiol therapy lowers blood pressure in newly diagnosed hypertensive postmenopausal women

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Hypertension has been considered as a contraindication for estrogen replacement therapy based on the assumption that the effect of the hormones used in menopause were similar to those of estrogens contained in oral contraceptive pills.

Methods: In a double blinded placebo controlled trial, the effect of chronic therapy with estradiol-17β (E2) on 24-hr ambulatory blood pressure monitoring (ABPM) was evaluated in 12 postmenopausal women (age: 54 ± 2.4 yrs) with newly diagnosed mild hypertension (SBP < 180, DBP < 100 mm Hg). All had menopausal symptoms and none was on hormone replacement therapy or antihypertensive drugs.

Results: After a 2-week run-in period, pts were randomized to receive E2 transdermal patches (50 mcg/day) or matched placebo for 4 weeks, after which they were crossed to complementar treatment after a 2 week washout period. ABPM was performed at baseline, and at the end of each treatment period. E2 treatment significantly lowered 24 hour mean blood pressure as well as mean daytime and nightime blood pressure:

	Baseline	E2	Placebo
24 h SBP	162 ± 11	142 ± 9*§	166 ± 12
24 h DBP	94 ± 6	86 ± 6**§§	94 ± 7
Day SBP	173 ± 10	156 ± 10**§§	172 ± 12
Day DBP	96 ± 6	88 ± 7**§§	94 ± 7
Night SBP	138 ± 14	122 ± 12*§	135 ± 16
Night DBP	88 ± 9	76 ± 8*§	86 ± 10

*p < 0.05, **p < 0.01 E2 vs baseline; §p < 0.05, §§p < 0.01 E2 vs placebo

In conclusion, chronic estrogen replacement therapy lowers blood pressure in untreated newly diagnosed hypertensive menopausal women. This therapeutic option should be considered when early menopausal women with recent onset hypertension are evaluated.

P2861 A randomized comparison of the time course, magnitude and consistency of platelet inhibition by abciximab, tirofiban or eptifibatide

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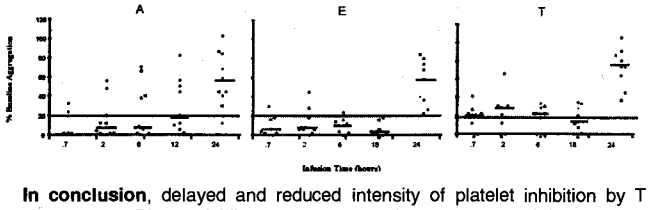
Platelet GP IIb/IIIa blockade reduces ischemic outcomes following percutaneous coronary intervention (PCI). No randomized comparative trials of GP IIb/IIIa blocking agents have been done.

Methods: We compared platelet function by standard light transmission aggregometry (LTA) with 20 μM ADP and rapid bedside assay (RPFA) during and following administration of either abciximab (A; 0.25 mg/kg bolus pushed, 0.125 mcg/kg/min to maximum 10 mcg/min over 12 hours), tirofiban (T; 0.4 mcg/kg/min bolus for 30 minutes, 0.1 mcg/kg/min infused over average 19.4 hours), or Eptifibatide (E; 180 mcg/kg bolus pushed, 2.0 mcg/kg/min infused over average 19.8 hours) on a randomized basis during PCI in 30 patients with unstable angina. No differences between therapies were observed for clinical outcomes or bleeding events.

Results: LTA for individuals and (–) medians are shown over time.



In conclusion, delayed and reduced intensity of platelet inhibition by T was observed. Platelet inhibition was similar during infusion of A or E. The more robust clinical outcomes reported from trials of A during PCI can not be explained by intensity of platelet inhibition during infusion alone. Randomized comparative clinical trials of these agents should be performed.

P2862 Increased superoxide concentration as a possible basis for platelet hyperaggregability and nitric oxide resistance in patients with ischaemic heart disease

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We have previously observed that platelets from patients with stable angina pectoris (SAP) exhibit increased aggregation in response to ADP and are hyporesponsive to the anti-aggregatory effects of sodium nitroprusside (SNP) and other nitric oxide (NO) donors, irrespective of prior nitrate therapy. We now investigated the possibility that the observed phenomenon of NO resistance in platelets is associated with increased concentrations of superoxide radical (O_2^-), which is known to inactivate NO.

Methods: In blood samples from normal subjects (n = 18) and patients with SAP (n = 22) or acute coronary syndromes (ACS, n = 16) we studied inhibitory effects of SNP (10 μM) on ADP (1 μM)-induced platelet aggregation (impedance aggregometry) in conjunction with an O_2^- assay (lucigenin-enhanced chemiluminescence). Specificity of the O_2^- detection was verified with superoxide dismutase in combination with catalase (SOD/Cat).

Results: Platelets from patients of both groups were more aggregable (p < 0.01) and less responsive to anti-aggregating effect of SNP (p < 0.01) than platelets from normal subjects. O_2^- contents (chemiluminescence signal, mV; mean ± s.e.m.) are summarised in the Table. Platelet responsiveness to SNP was inversely correlated with both basal (r = –0.83) and post-aggregation (r = –0.99) O_2^- content. Among patients with SAP, higher O_2^- levels were recorded in those with 3-vessel stenosis (p < 0.05) than in those with 2- or 1-vessel stenosis. SOD/Cat normalised responses to ADP (p < 0.01) and SNP (p < 0.01) in patients, with no effect in normals.

Table. Chemiluminescence signal

O_2^- content	Normals	SAP	ACS
Before aggregation	62 ± 8	125 ± 20*	280 ± 60** #
After aggregation	200 ± 50	660 ± 80**	830 ± 180**

(*p < 0.05 and **p < 0.01 vs Normals; #p < 0.05 for ACS vs SAP)

Conclusion: Increased O_2^- concentration in blood of patients with both SAP and ACS contributes towards platelet hyperaggregability and hypo-responsiveness to anti-aggregatory effects of NO donors.

P2863 Effects of Na^+/Ca^{2+} exchange inhibitor, KB-R7943, on reoxygenation-induced injury in guinea pig papillary muscles

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The precise mechanism of Ca^{2+} overload on reoxygenation remains poorly defined. A possible candidate is a Ca^{2+} influx via the reverse-mode of Na^+/Ca^{2+} exchange (NCX). In order to study the pathophysiological role of Ca^{2+} influx via NCX for reoxygenation injury, we studied the effects of a novel agent that is reported to selectively block Ca^{2+} influx by NCX, KB-R7943 (2-[2-[4-(4-nitrobenzyloxy)phenyl]ethyl]isothiourea methanesulfonate).

Methods: Papillary muscles were obtained from the right ventricles of guinea pig heart. We investigated the effects of KB-R7943 (1) on contracture induced by a low-sodium (21.9 mM) perfusion to examine whether KB-R7943 inhibits Ca^{2+} influx via NCX, (2) on the action potentials and contractile parameters, and (3) on the incidence of reoxygenation-induced arrhythmias and the recovery of developed tension after reoxygenation.

Results: KB-R7943 dose-dependently suppressed the contracture tension during a low-sodium perfusion (23 ± 8% at 10 μM vs. 56 ± 11% steady-state developed tension in control group, n = 6, p < 0.05). KB-R7943 did not change action potential and contractile parameters. KB-R7943 significantly decreased the incidence of arrhythmias (4 of 9 muscles vs. 9 of 9 control muscles, p < 0.05), and shortened the duration of arrhythmias (16 ± 11 sec vs. 72 ± 14 sec in control muscles, p < 0.05) during the reoxygenation period after 60 min substrate-free hypoxia. KB-R7943 significantly enhanced the recovery of developed tension at 30 min after reoxygenation (83 ± 4% vs.69 ± 3% in control muscles, n = 9) (p < 0.05).

Conclusion: It is likely that KB-R7943 selectively inhibits the reverse-mode of NCX, attenuates reoxygenation-induced arrhythmic activity, and prevents contractile dysfunction in guinea pig papillary muscles. These results suggest that Ca^{2+} influx via the reverse-mode of NCX may play a key role in the mechanism of Ca^{2+} overload on reoxygenation.

P2864 Determinants of platelet responsiveness to nitric oxide donors in the presence and absence of ischaemic heart disease

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Our recent investigations have demonstrated that platelets from patients with stable angina pectoris (SAP) are hyporesponsive to the anti-aggregatory effects of the nitric oxide (NO) donors nitroglycerine (NTG) and sodium nitroprusside (SNP). Furthermore, this phenomenon was associated with increased superoxide (O_2^-) concentrations. We have now examined determinants of inter-individual variability in platelet responsiveness to NO in patients with SAP, acute coronary syndromes (ACS) and in normal subjects.

Methods: Inhibitory effects of NTG (100 μM) and SNP (10 μM) on ADP (1 μM)-induced platelet aggregation (impedance aggregometry in whole blood) in SAP (n = 53), ACS (n = 120) and normals (n = 52) were compared using uni- and multi-variate analysis. Coronary risk factors, extent of fixed coronary artery disease (CAD) and current medication were examined as possible correlates of response.

Results: In patients with SAP and ACS, platelet aggregability was greater (ANOVA: $p < 0.01$) than in normals. Platelet responsiveness to anti-aggregatory effects of NTG and SNP was similarly impaired in SAP and ACS ($p < 0.01$ vs. normals in both cases). Furthermore, in patients with SAP, NO responsiveness decreased with increasing extent of CAD. Neither individual, nor combined coronary risk factors were correlated with NO responses. While prophylactic nitrates, aspirin, ACE inhibitors, statins or calcium antagonists did not affect platelet responses to NO donors, responses were significantly increased with concomitant perhexiline therapy ($p < 0.05$ for SAP and $p < 0.01$ for ACS), and reduced in the presence of beta-adrenoceptor antagonists ($p < 0.05$ for ACS).

Conclusion: Despite the association of platelet NO resistance with increased O_2^- concentrations, extent of NO resistance is not correlated with coronary risk factors. However pharmacotherapy may modulate platelet responsiveness to NO donors.

P2865 Nitrate tolerance: non-invasive assessment using brachial artery and mitral Doppler ultrasonography

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The efficacy of long-term nitrate therapy is limited by the development of tolerance. This phenomenon is often studied by invasive hemodynamic measurements. We describe a simple clinical method for detection of arterial and venous nitroglycerin (NTG) tolerance. Tolerance was induced by continuous transdermal NTG administration. Eleven healthy volunteers were randomised in a double-blind cross-over study to NTG-patch (10 mg/24 hours) and placebo-patch for 7 days separated by a wash-out period of 6 days. In both periods, the acute response to NTG spray 0.4 mg was determined at 0 h, 6 h, day 3 and day 7. Brachial artery diameter was measured by high-resolution ultrasonography and mitral flow E velocity (early peak filling) by Doppler echocardiography.

In the placebo period, NTG spray significantly increased brachial artery diameter (0 h, 6 h, day 3, day 7 in mm: 4.3 to 4.9; 4.2 to 4.9; 4.3 to 4.9 and 4.3 to 4.9). In the NTG-patch period, the brachial artery before NTG spray was significantly dilated at 6 h, but at day 3 and day 7 the diameter again significantly declined due to development of arterial NTG tolerance. Also, NTG spray did not significantly further dilate the artery at day 3 and day 7 (0 h, 6 h, day 3, day 7 in mm: 4.2 to 4.8; 5.0 to 5.1; 4.7 to 4.9 and 4.5 to 4.9). In the placebo period, NTG spray at all time points significantly reduced the mitral E velocity due to its venodilating effect (0 h, 6 h, day 3, day 7 in m/s: 0.86 to 0.71; 0.82 to 0.68; 0.81 to 0.75 and 0.86 to 0.74). In the NTG-patch period, the response to NTG spray on E velocity was completely blunted at 6 h, day 3 and day 7 (0 h, 6 h, day 3, day 7 in m/s: 0.85 to 0.76; 0.78 to 0.77; 0.86 to 0.83; 0.88 to 0.87).

Thus, using a simple non-invasive technique we have demonstrated the development of arterial and venous NTG tolerance. This method is useful for investigating the mechanisms underlying nitrate tolerance and for evaluation of pharmacological interventions directed against tolerance.

COST-EFFECTIVENESS DECISION MAKING AND SOCIETY

P2866 Reduction of hospital costs for patients with acute non-Q-wave myocardial infarction or unstable angina treated with enoxaparin compared to standard heparin

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Recently, enoxaparin has been approved for the treatment of unstable angina (UA) and non-Q-wave myocardial infarction (NQWMI) in Europe, the US, and other Western countries. Higher cost of daily treatment compared to unfractionated heparin (UFH) has been considered a limitation to the widespread use of this compound.

Methods: We analysed in-hospital costs for 256 patients included in the ESSENCE trial in South America. Patients were randomly assigned to either SQ enoxaparin or IV UFH for a minimum of 48 h and a maximum of 8 days. Data were collected from the initial hospitalisation and any re-hospitalisation at 30 days follow-up. Items analysed included daily hospital fees, enoxaparin and UFH costs, angiography and revascularization procedures, and professional fees.

Results: Mean duration of treatment was 82 h ± 48 h and 71 ± 46 h for UFH and enoxaparin, respectively (p = NS). Individual treatment cost was higher with enoxaparin ($ 93.75 ± 56.67 Vs 216.70 ± 141.24; p = 0.177). However, less urgent and total revascularization procedures were needed in the enoxaparin limb (12.6% Vs 20.2%), thus resulting in savings equivalent to $ 29.000/100 patients treated.

In conclusion: Higher costs of equivalent doses of enoxaparin compared to UFH are compensated by less revascularization procedures required by recurrent ischemia and infarction, resulting in reduced final costs.

P2867 A cost-effectiveness analysis of cardioverter-defibrillator implanted under local anaesthesia versus general anaesthesia

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Purpose: Implantable cardioverter-defibrillators (ICDs) with transvenous leads and downsized generators allow the use of simplified operative techniques. However, the efficacy and cost of these methods such as the implantation of ICDs under local anaesthesia remain to be evaluated.

Method: In 47 consecutive patients (pts) (mean age of 62 ± 12.5 years, mean ejection fraction of 34.3 ± 10.2%, coronary artery disease in 34 pts, cardiomyopathy in 13 pts and a history of ventricular tachyarrhythmias in all pts) an ICD was implanted. In 21 patients, implantation was performed under general anaesthesia, while in the remaining 26 under local anaesthesia with lidocaine with intravenous midazolam and propofol during defibrillation threshold (DFT) testing. A cost analysis was performed to determine if cost savings were associated with local vs. general anaesthesia.

Results:

	General anaesthesia	Local anaesthesia	Significance
Mean hospital stay (days)	7.05 ± 2.78	3.38 ± 1.3	p = 0.0120
Mean cost of implantation	1799 ± 645 Euro	1250.8 ± 528 Euro	p = 0.0000
Mean cost of hospital stay	1658.4 ± 653 Euro	804.2 ± 298 Euro	p = 0.0000
Mean time of implantation (min)	227 ± 50	173 ± 29	p = 0.0000

There was no operative or post-operative mortality and no major complications occurred except for one lead fracture and one case of acute pulmonary oedema, both in pts under GA.

Conclusions: This study demonstrates a reduction in the hospital charges and health care resource utilization, without any increase in the complication rate, operative and postoperative mortality, associated with ICD implantation when local rather than general anaesthetic technique is used.

P2868 Reduction in length of stay for acute myocardial infarction: lessons learned over 10 years in a defined geographic population

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Background: Hospital length of stay (LOS) for patients with acute MI has declined over the past two decades. The variability in the decline in LOS cannot be fully explained by new treatment strategies.

Methods: We identified a series of 849 patients admitted for acute MI to the Mayo Clinic Coronary Care Unit. We analyzed the impact of adjunct and reperfusion treatment on hospital LOS in acute MI, and the effect of time period on LOS. Three time periods were arbitrarily chosen: Period I (1988–1990); Period II (1991–1993); Period III (1994–1997).

Results: LOS significantly declined from 1988 until 1997 (10 to 5 days), $p < 0.01$. Adjunct and reperfusion therapy were associated with reductions in LOS by univariate analysis:

Use of	Change in LOS	p-value
Beta blocker	−2 days	<0.01
Aspirin	−2 days	<0.01
Lytic Agent	−1 day	<0.01
Primary PTCA	−1 day	<0.01

Weekday of admission and MI location did not affect LOS. Multivariate analysis suggested that the influence of time period was stronger than the influence of adjunct and reperfusion therapies, and was independent of other factors. The adjusted hazard ratios (HR) for reduced LOS was significant: HR Period II:Period I was 1.28 (95% CI 1.06–1.56) and HR Period III:Period I was 2.02 (95% CI 1.68–2.43). Overall mortality was 9.9%, and did not vary significantly from Period I to III ($p = 0.67$).

Conclusion: Our data demonstrate that clinical and non-clinical factors reduce LOS in acute MI. LOS was significantly reduced in patients who received adjunct and reperfusion therapy, but temporal period appeared to reduce LOS independent of the influence of treatment strategies. These data underscore the impact that non-clinical variables play on LOS in acute MI.

P2869 Impact of spironolactone on health-related quality of life in severe heart failure in the Randomized Aldactone Evaluation Study (RALES)

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Background: The Randomized ALdactone Evaluation Study (RALES) demonstrated that adding spironolactone, an aldosterone antagonist, to the current standard of care for heart failure significantly reduced all-cause mortality and cardiac mortality as compared to placebo. RALES involved more than 1600 patients with severe heart failure in 15 countries for an average of 24 months. While mortality was the primary outcome, the impact of spironolactone on self-reported health-related quality of life (HRQOL) was also assessed for a subsample of patients.

Methods: Subjects were randomized to receive either spironolactone 25 mg daily or placebo. HRQOL was assessed in a subsample of 88 subjects in 2 participating countries using the Medical Outcomes Trust Short-Form 36-item survey (SF-36). Assessments were made at baseline, 1, 2, 3, and 6 months after initiation of therapy. Change from baseline was assessed for the 8 dimensions of the SF-36, as well as the Physical (PCS) and Mental Composite Summary (MCS) scores of the SF-36.

Results: Sixty subjects (32 – spiro, 28 – placebo) had complete data for 6 months of follow-up. No significant differences were observed between active treatment and placebo in SF-36 scores at baseline. Statistically significant and clinically meaningful changes from baseline for all 8 SF-36 dimension scores in the spironolactone arm, compared to only 6 dimensions in the placebo arm, were observed at 3 and 6 months. At 3 months, the spironolactone group had significantly greater improvements in *Mental Health* (spiro = 19.9 ± 21.2 versus placebo 3.1 ± 20.9; $p = 0.004$) and *MCS* (spiro = 13.2 ± 11.8 versus placebo = 5.3 ± 11.6; $p = 0.016$) scores compared to the placebo group. The positive impact of spironolactone treatment on change from baseline *Mental Health* subscale scores continued to be statistically significant at 6 months (spiro = 17.5 ± 22.9 versus placebo = 4.5 ± 25.7; $p = 0.044$).

Conclusion: The addition of the aldosterone receptor blocking agent spironolactone to conventional heart failure therapy (ACE inhibitor, diuretic, ± digoxin) appears to positively impact self-reported HRQOL in subjects with severe heart failure. In particular, in this small sample of severe heart failure patients, the addition of spironolactone therapy appeared to have a strong, positive impact on mental health status, with no detrimental effect on physical health or functioning.

P2870 Outcome predicition by three different scoring systems (APACHE III, SAPSII, MPM_0) in 227 patients with acute cardiovascular disorders

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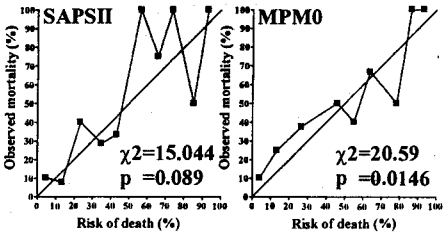
Aim of this prospective study was to compare three different scoring systems (APACHE III [APIII], SAPS II and $MPMII_0$) in terms of outcome prediction (hospital mortality) in patients with acute cardiovascular disorders admitted to a medical intensive care unit (ICU) and to assess the correspondence between the observed and the expected (O/E) mortalities for SAPS II and $MPMII_0$ (calibration).

Methods: APIII, SAPS II and $MPMII_0$ were determined for all consecutive patients (pts) 24 hours after admission. Hospital mortality was recorded. Discrimination power for mortality prediction was assessed by the Receiver Operating Characteristic (ROC). Calibration of the models for SAPS II and $MPMII_0$ was assessed by goodness of fit's (GOF) statistics and calibrations curves.

Results: Between 11/97 and 2/98 227 pts (164 male [72.2%], 63 ± 12 years) were admitted to our ICU (17 CPR, 29 heart failures, 76 infarction, 17 cardiogenic shock, 21 cardiomyopathies, 31 unstable angina, 2 mvocarditis, 3 aortic dissections, 31 rhythm disturbances). Hospital mortality was 16.7% (38/227 pts). Area under ROC curve (AUC) for AP III was 0.82 ± 0.04, for SAPS II 0.77 ± 0.05 and for $MPMII_0$ 0.76 ± 0.05.



Calibration curve for SAPS II and MPMII0. χ^2 = value of the GOF test; $p < 0.05$ significant difference between O/E mortality.

O/E mortality correlated well in SAPS ($r = 0.83$) and MPM II_0 ($r = 0.94$). O/E mortality ratio was 1.47 for SAPS II and 1.52 for MPM_0.

In conclusion: Discrimination power for mortality was reliable in all 3 scoring systems. SAPS II and $MPMII_0$ both underestimated mortality. Therefore, customization of both models should be performed for our population.

CARDIOVASCULAR NURSING – MISCELLANEOUS

P2871 Functional and psychosocial determinants of rehospitalisation in elderly cardiovascular patients

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Rehospitalisation is a prevalent problem in elderly cardiovascular patients and is associated with increased health care costs. Prevention of rehospitalisation is crucial in the care to the elderly. To identify patients at risk for rehospitalisation, this study examined the functional and psychosocial determinants of readmission in acute care hospitals in elderly cardiovascular patients.

Methods: This descriptive, longitudinal study included 128 hospitalised, frail elderly with cardiovascular disease (46% m.; 54% f.), with a mean age of 78 (SD = 8.2) years, in which a co-ordinated, multidisciplinary discharge planning and an intensive follow-up during 24 weeks was performed. Cardiovascular diseases comprised 15.7% hypertension, 9.4% ischemic heart disease, 2.4% disease of lung circulation, 39.4% other heart diseases, 52.0% cerebrovascular disease, 10.2% peripheral vascular and lymphatic disorders. Functional, depressive and cognitive status of patients were assessed using the ADL- and IADL-scale, Geriatric Depression Scale and Mini-Mental State Examination, respectively. Caregiver burden was evaluated by the Caregiver Burden Inventory. All patients and caregivers were monitored at 5 time-points during the study. Kaplan-Meier survival curves, log rank and the crude relative risk (RR) for each variable were computed.

Results: The cumulative probability for rehospitalisation 6, 12 and 24 weeks after discharge was 16%, 27% and 43%, respectively. Patients were predisposed for rehospitalisation if impaired cognition (log rank = 10.58; $p < 0.002$; RR = 3.45), increased caregiver burden (log rank = 3.89; $p < 0.05$; RR = 2.25), or dependence (through varying degrees) for clothing (log rank = 4.96; $p < 0.03$; RR = 2.75), for using the telephone (log rank = 8.13; $p < 0.005$; RR = 2.67) and for taking own medicines (log rank = 6.44; $p < 0.02$; RR = 8.38) was present.

Conclusion: Though multivariate analysis was not feasible due to limited sample size, this study indicated that rehospitalisation in frail elderly with cardiovascular morbidity is associated with cognitive decline, caregiver burden and selected functional parameters. These results allow health care workers to identify high-risk patients and to initiate appropriate interventions.

P2872 Morbidity and mortality in myocardial infarction complicated by nosocomial infection in a university coronary care unit in Brazil

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Background: The high incidence of invasive procedures in myocardial infarction (MI) could increase the risk for nosocomial infections on patients. Data about infection as a complication of MI is lacking.

Methods: We retrospectively analyzed prospectively collected data on 754 MI patients hospitalized in a 16-bed coronary care unit from January 1996 to December 1997. Demographic characteristics, infections and in-hospital case fatality rates were studied.

Results: Forty-two patients (5.5%) developed a nosocomial infection. The respiratory tract was involved in 21 episodes (41.4%) and the urinary tract in 13 (25.4%). A blood stream infection was detected in 13 (25.4%), cellulitis in 3 (5.8%), and peritonitis in one (1.9%). The table shows demographic data and in-hospital case-fatality rates in patients who developed or not a nosocomial infection. Female patients who died were significantly older than male (74.9 ± 9.0 and 66.9 ± 10.5 years respectively, $p < 0.001$). In-hospital case fatality rate was significantly greater in male patients who had infectious complications ($p < 0.001$).

Demographic data and in-hospital case-fatality rates

	Male (547)		Female (207)	
	Mean age (yrs)	Deaths	Mean age (yrs)	Deaths
Infected (42)	69.7 (46–83)	12 (41.4%)	68.1 (52–89)	4 (30.7%)
Non-infected (712)	60.9 (27.88)	48 (9.3%)	66.6 (30–91)	33 (17%)

Conclusions: On this population, nosocomial infection complicating an acute myocardial infarction had a great impact on mortality, mainly in male patients.

P2873 A prospective study of the complications on patients that underwent a continuous venous-venous haemofiltration in a cardiac intensive care unit

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A continuous hemofiltration is a very usefull technique in the I.C.U. The aim of this study is to analyze the actual situation and complications of the continuous venous-venous hemofiltration (CVVHD) in the cardiac ICU.

Material and Method: From November 1991 to July 1997 we had 67 patients in the I.C.U that underwent a CVVHD, but only 47 were studied. We analyzed descriptional and observational parameters in a prospective study from the medical records: hemodynamic, status, temperature, blood parameters, ultrafiltration and reposition levels, liquid balance, filter's duration, and symptomatology and other problems presented.

Results: Hypothermia was present in 41/47 (87.2%) of the patients, and 26 of them (53.3%) presented discomfort. The urea and creatinine clearance was insuficient in 18/47 of the patients (38.29%). Neurological problems appeared in 15/47 (31.9%). The duration of the filters is 13–18 hours. There are statystical differences between hypothermia and discomfort ($p = 0.03$), hypothermia and loading volume ($p = 0.02$), a major duration of the filter (48 h.) and lower creatinine clearance ($p = 0.045$).

The most important complications we found were hypothermia and acidosis due to the biological and the discomfortable situations.

Conclusions: The nurse's knowledge and a correct prophylaxis could avoid these complications. This brings us to the need to protocol this technique.

P2874 Can a coronary care-trained nurse expedite emergency department management of acute cardiac syndromes?

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A variety of options are currently under consideration for "fast tracking" patients (pts) who present to the Emergency Department (ED) with chest pain, possibly of cardiac origin, to definitive cardiac treatment (DCT). One possible strategy is the placement of coronary care-trained nurses (CCTN) as supernumerary personnel in ED's, but there is little data currently available to evaluate the potential efficacy of this approach.

We performed a pilot study in which an experienced senior CCTN was randomly assigned to work in a hospital ED for 16 hours per week; comparable hours over the same period without a CCTN in attendance were utilized for control data. The major endpoint assessed was time to DCT for pts with acute myocardial infarction (AMI).

During the assessment period, 893 pts were assessed as possible acute coronary syndromes (ACS). Mean assessment rates were 0.4 pts/hour with the CCTN (CCTN+) and 0.6 pts/hour with the CCTN absent (CCTN–). Times (mean ± standard deviation in minutes) to DCT for pts with ACS were:

Group (n)	CCTN+ (205)	CCTN– (688)
ALL ACS (91)	102 ± 85 (30)	117 ± 87 (61)
AMI (44)	80 ± 97 (15)	112 ± 102 (29)
AMI with thrombolytic/primary PTCA (19)	33 ± 27 (8)	54 ± 43 (11)

These pilot data therefore suggest that DCT may be expedited by assignment of senior coronary care-trained nurses to ED's. Larger controlled trials are necessary to evaluate whether those non-significant trends arise from Type II error and to determine therapeutic impact and cost:benefit implications of this strategy.

P2875 To sting or not to sting? A study into the warming of local anaesthetic prior to insertion

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Introduction: Cardiac catheterisation requires subcutaneous infiltration of local anaesthetic (lignocaine), around the right femoral arterial area. This aspect of the procedure is consistently described as the most unpleasant aspect of the procedure. The most frequent complaint noted was the stinging or a burning pain associated with subcutaneous infiltration.

Aim: To assess whether warmed lignocaine reduces local pain associated with coronary angiography.

Methods: A descriptive study of 42 patients undergoing routine cardiac catheterisation. The study was carried out over a two week period on alternate days. The patients were asked to report their pain to an observer and the responses noted on a Likert scale measuring 0–3. The lignocaine was warmed on the day and was not removed from the warmer until the doctor was ready.

Results: The average pain score (SD) in the warm group was 0.18 (0.64) v 0.84 (0.97) in the non warm group ($p < 0.0001$, t test). For discomfort of insertion 16/21 in the warm group had a pain score of 0 v 5/21 in the non warm group ($p < 0.006$ chi square) and for removal of femoral arterial sheaths 20/21 had a pain score of 0 v 12/21 in the non warm group ($p < 0.03$ chi square).

Conclusion: The simple procedure of warming lignocaine to 37°C reduces the pain of this invasive procedure. The study recommends this technique should be adopted.

PSYCHOLOGICAL ASPECTS OF CARDIOVASCULAR NURSING

P2876 Psychosocial variables in relation to prognosis in patients with stable angina pectoris: the APSIS study

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Psychosocial variables were studied in 767 out of 809 patients (236 women) with stable angina pectoris, who participated in the Angina Prognosis Study in Stockholm, (APSIS). The patients were <70 years at inclusion, and were treated with either metoprolol or verapamil during a median follow-up of 3.4 years. Overall outcome did not differ between treatments. Psychosocial relationships are presently analyzed.

Method: The patients were interviewed about previous life events, sleep disturbances, psychosomatic symptoms, type-A behaviour, job strain and overall life satisfaction at inclusion. Questions about how the patients usually felt and health related problems are reported.

Results: 36 patients suffered a cardiovascular death (CVD) of which 10 were sudden deaths (SD). Thirty patients suffered a non-fatal MI and 96 were submitted to revascularization due to incapacitating angina pectoris. CVD was related to problems with sex life ($p < 0.001$) and these patients also performed least daily physical activity of all patients ($p < 0.05$). SD was related to several physical symptoms ($p < 0.01$); The patients pushed themselves harder in competition ($p < 0.01$) and they felt most burned out ($p < 0.01$). Sexual problems were also more common ($p < 0.001$). Patients suffering a non-fatal MI described feelings of loneliness ($p < 0.05$) and being missunderstod ($p < 0.05$). Patients who underwent revascularization mostly had problems related to physical symptoms ($p < 0.01$) and feelings of not getting any better ($p < 0.05$).

Conclusion: Listening to patients with stable angina pectoris is of importance since the patients own reporting of psychosocial variables may carry prognostic information.

P2877 Pacemaker users quality of life from a nursing perspective

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Pacemaker users' quality of life (QoL) has been investigated in a number of studies in connection with which pacemaker system has been implanted, but not from a nursing perspective. QoL is difficult to define, but through the use of Orem's nursing perspective it was possible to focus on the entire individual. The purpose of the study was to describe pacemaker users' evaluations of their QoL in general, but also with respect to gender, age, civil status and occupation.

Method and Results: In total 182 patients (ages 26–93), 51% of whom were men, with pacemaker were randomly selected for interviews about their QoL in this cross-sectional study. The instrument used was Quality of Life Questionnaire. Data were grouped into an index in accordance with Orem's self-care theory, and it was shown by means of statistical analysis that the total QoL was good. A poorer QoL was found in regard to mental-physical health, the possibility of influencing one's own situation, and life style. Men, those who were co-habiting, and those <64 years of age assessed their QoL as higher.

Conclusion: By using Orem's self-care theory, information, choice of pacemaker system, support and education can be carried out in such a way that nursing care affects the entire QoL of the pacemaker users. It is of great importance to educate personnel who work in this area and to inform, advice and support the relatives, with the pacemaker users' self-care as the goal.

P2878 Patients with implantable cardioverter-defibrillator and their conceptions of the life situation: a phenomenographic analysis

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The implantable cardioverter-defibrillator (ICD) is today widely used for the treatment of sudden cardiac near death episodes as a result of malignant ventricular arrhythmia. After examining the literature, only four descriptive studies, all carried out in the USA, with a qualitative analysis based on the ICD-patients' own perspective of their life situation have been found. The aim of this study was to describe how patients living with an ICD-device in south-western Sweden conceive their life situation.

Methods: As the focus was on the patients' conceptions from a holistic perspective, phenomenographic analysis was employed on a strategic sample of 15 ICD-patients.

Results: Six categories emerged: feeling safety, feeling gratitude, feeling of being, having a network, feeling a belief in the future, and gaining awareness.

In conclusion, even if the findings cannot be generalised due to the descriptive research design, they can illuminate the beneficial as well as intrusive effects of such a device. They emphasise the need for different support groups for patients and families as well as further education for personnel in hospital and primary health care.

P2879 A qualitative enquiry into the impact of heart attack on women: implications for nursing policy and practice

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Purpose: There is a dearth of literature on the experience of women following heart attack, and therefore little evidence upon which to base practice. This study aimed to contribute to this meagre research base, thus providing guidance for practice and identifying issues for more focussed investigation. It addressed the following research question: What is the psychological experience of women in the period surrounding heart attack?

Methods: This was an exploratory study in which thirty women and men, recruited from two centres, were interviewed at two time points (three weeks and three months) following their heart attack. Interviews were semi-structured and audio-tape recorded. Audio-tapes were transcribed and then subjected to content analysis, both by hand using two blind raters, and by the computer programme NUD.IST.

Results: Womens heart attacks occurred in a different context in respect of family and other social roles and relationships. They demonstrated different personal characteristics to the men. Women frequently ignored, misattributed or otherwise excused symptoms, even when they were very serious, and this very often resulted in excessive delay in help seeking behaviour. They reported not having seen themselves as being at risk, and had beliefs about causation which may have differed with those of health professionals.

The emotional response was different in women, who often had to return to ongoing social stressors. Women often resumed their household chores too early whereas men felt pressured to return to work. Neither group was well informed about their illness or rehabilitation issues such as advisable health related behaviour. Practical issues also contributed womens more difficult rehabilitation, including the presence of co-morbidities and dependence on others for transport to rehabilitation classes.

Conclusions: Women underestimated personal risk and were slow to recognise symptoms. A larger study focussing specifically on womens illness representations is likely to be fruitful and of benefit to rehabilitation practice. Neither men nor women received adequate information and advice about activity levels, and this was often very much to their detriment. Advice needs to be given to all patients and tailored to their individual lifestyle. Alternatives need to be considered for those patients who are unable to travel to rehabilitation classes.

CARDIOVASCULAR NURSING AND HEART FAILURE

P2880 Conceptions of the life situation among female patients with congestive heart failure

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Congestive heart failure (CHF) is a significant health problem for women, particularly elderly women. Results from several studies suggest a better long-term prognosis for CHF women. However, the small number of women and lack of comparisons with men in these studies make any consistent interpretation of the results impossible. The aim of this study was to describe, from a nurse's perspective, how female patients with CHF conceive their life situation.

Method and Results: A qualitative method was used with a phenomenographic approach, as this approach examines aspects of the surroundings as they are conceived. Five categories emerged in the results: feeling content, feeling a sense of support, feeling a sense of limitation, feeling anxiety and feeling powerless. A sense of limitation regarding working capacity and being able to support those in their surroundings causes patients with CHF to experience anxiety due to feeling insecure about themselves and in relation to their surround-ings. This may cause a feeling of worthlessness in women with CHF both concerning their own capacity and the fact that they feel they are a burden to those around them.

Conclusion: Through nursing intervention, these patients must receive help to break this vicious circle of feeling limited and powerless. This can be done by encouraging them to verbalize their feelings and set realistic goals and expectations, and by increasing their knowledge and that of their families concerning CHF and its symptoms, with a focus on self-care and existing possibilities. These measures will make it easier for women with CHF to maintain a hopeful perspective and a sense of control, competence, and self-esteem. A comparative study of men using the same research design and variables have been published.

P2881 Patients with congestive heart failure and their conception of the sleep situation: a first preliminary analysis

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Background: Polysomnografic studies have shown that patients with congestive heart failure (CHF) and Cheynes-Stokes respiration often have shorter total sleep time and a disturbed sleep structure with frequent arousals and sleep stage changes.

Aim: To describe, from a nurse's perspective, how patients with CHF conceive their sleep situation with focus on influencing factors and the handling of these factors.

Method: A qualitative design using a phenomenographic approach was employed. Conceptions were collected through semi-structured interviews with 20 CHF patients. The informants were selected strategically based on gender, age, civil status, education, NYHA-classification etiology and duration of heart failure. There were 13 men (38–83 years) and 7 women (45–85 years).

Results: In the preliminary analysis three categories emerged. The first category, the sleep situation, described how the patients conceived the sleep situation in accordance to reality and desire. The second category, consequences of the sleep situation, described how the patients were physically, emotionally and socio-culturally influenced by the sleep situation. The third category, coping with the sleep situation, described the patients intellectual and behavioural coping mechanisms.

Conclusion: The CHF patients described a desire for a peaceful and continuous sleep, but experienced a frequently interrupted sleep that gave both emotional and physical effects. The awakenings were often connected with dyspnea and anxiety that resulted in difficulties regaining the sleep. The following daytime sleepiness gave a feeling of further limitation in working capacity and led to that the patients participated less in social activities. The final analysis will give a deeper understanding of CHF patients conceptions of their sleep situation. This knowledge can help the nurses to support the patient in a better way to cope with this situation.

P2882 Can patients benefit from a clinical heart failure trial which proves to be negative? The patients' perspective

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Background: Clinical trials, the gold standard for the evaluation of new therapeutic strategies, may prove that a drug is beneficial, harmful or ineffective. The perspective of the pts participating in a trial of a drug which proves to be ineffective has not been studied.

Patients and Methods: Study group consisted of 42 consecutive pts participating in 3 heart failure trials shown to be ineffective (neutral effect) with regard to primary trial end-point (MACH-1 trial of mibefradil, REACH-1 trial of bosentan and CASCO trial of calcium sensitizer). 20 pts received active drug and 22 placebo. At end of the follow-up period, an anonymous self-completed questionnaire was administered and analyzed.

Results: Although all studies showed a neutral effect on primary study endpoint, 59% pts (68% placebo group, 48% active group, NS) reported moderate or marked subjective improvement after participating in the trial. The major reason for improvement was attributed by the patient to increased confidence (33/42 pts) and better clinical follow-up (8/42 pts). Degree of improvement was not related to whether they received placebo or active drug, although pts receiving active drug tended to report less improvement (see Table).

Subjective Patient Improvement

	Little or none	Moderate	Marked
Total	17 (41%)	16 (39%)	8 (20%)
Placebo	7 (32%)	9 (41%)	6 (27%)
Active drug	10 (52%)*	7 (37%)*	2 (11%)*

Degree of improvement reported by patient (*p = NS, active vs placebo)

Conclusions: In 3 clinical heart failure trials with drug which proved to be ineffective: 1. Half to two-thirds of pts participating in the trial reported subjective clinical benefit. 2. Clinical benefit was not related to whether on active drug or placebo, in keeping with known neutral result of the trial. 3. The higher than expected "placebo effect" should be taken into account in planning future clinical trials.

P2883 Patient-initiated calls to a heart failure nurse?

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Specialised Heart Failure (HF) outpatient clinics and HF nurses are rather new developments in the Netherlands. In addition to patient education, one of the components of the specialised HF care is the telephone access to a HF nurse. Insight in the reason of patient initiated calls and the related nursing interventions can be helpful to further improve care, guide education of patients and of the nurses. The **objective** of this study was to describe the number and underlying reasons for a telephone call of patients to the HF nurse and to describe the nursing interventions needed.

Method: Data from the registration of the outpatient clinic HF nurse were analysed. Patients had a mean age of 73, 56% was male.

Results: During 1998, 223 patients visited the clinic, resulting in 960 clinic visits. In addition 64 patients received a nurse initiated telephone call to check on weight or medication. Of the 223 patients from the clinic, 78 patients called to the HF nurse, resulting in 274 telephone calls. The number of calls ranged from 1 to 14. Most important reasons for calling were weight change (30%) medication (15%) change in HF clinic visits (11%) and dyspnea (9%). Noticeable was the amount of calls with questions in regard to preparation for clinical tests (e.g. colonscopy) (7%). Most important interventions of the HF nurse were information, education and medication change (after consultation with the cardiologist).

Conclusion: Telephone access to a HF is a useful component of specialised HF nurse care.

INTERVENTIONAL CARDIOLOGY IN CARDIOVASCULAR NURSING

P2884 Local anaesthetic infiltration by registered nurses prior to femoral arterial sheath removal

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Vasovagal episodes occur during arterial sheath removal and compression of the femoral artery. The resultant hypotension can lead to potentially life threatening complications such as coronary occlusion. Vasovagal episodes appear to occur more frequently when sheath removal is some hours after the procedure, when the local anaesthetic has worn off, as is the case following percutaneous coronary interventions.

We hypothesized that the incidence of vasovagal episodes may be reduced with infiltration of local anaesthetic prior to sheath removal.

At our institution, Registered Nurses (RN) routinely remove arterial sheaths, often out of hours, when limited medical cover is available. We therefore trained RNs to administer lignocaine (1%) up to 5 mls around the sheath prior to its removal.

All patients had a femoral approach using a size 7 french catheter. The sheaths were left in situ varying from 2 hours to 14 hours (overnight). In 100 patients lignocaine was infiltrated in each quadrant approximately 1–2 cms from sheath, 3 to 5 minutes prior to sheath removal.

A vagovagal reaction was classified as symptomatic bradycardia, hypotension and light headedness which required treatment with atropine or atropine with haemaccel.

Results: The preliminary results from the 200 patients are presented below:

	Lignocaine	Control
Patients	100	100
Vasovagal Reaction	1	6 (p = 0.059)

There was no apparent difference in other complications between the two groups, in particular, no excess bleeding.

In our study, local anaesthetic infiltration by trained registered nurses reduced the incidence of vasovagal reactions. We recommend consideration of local anaesthetic administration to the sheath site prior to removal of femoral arterial sheaths for percutaneous interventions. This can be safely performed by trained Registered Nurses.

P2885 How soon can patients safely mobilise following a diagnostic cardiac catheter?

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Patients undergoing a diagnostic cardiac catheter are usually mobilised four hours after the procedure. A desire to increase the number of patients undergoing day case procedures in order to reduce waiting lists has led to interest in the use of devices to seal femoral artery punctures – however, these devices are costly. If patients can safely mobilise shortly after haemostasis has been achieved by manual compression, this could lead to more rapid discharge without the need for such devices.

In our tertiary referral centre approximately 2300 cardiac catheters are undertaken per annum. This audit is part of a larger audit of haemostasis techniques following cardiac catheterisation which is currently in progress. The records of 50 consecutive patients undergoing manual compression following sheath removal after day case cardiac catheterisation were studied. Details of the time to mobilisation, the time to discharge and any complications were obtained.

All of the 50 patients studied underwent day case left heart catheterisation using 6 French femoral artery sheaths. Manual compression was performed after sheath removal in all cases. Of the 50 patients, 37 (74%) were mobilised after 30 minutes following manual compression and 48 (96%) were mobilised within 60 minutes. The remaining two patients were not mobilised until 95 and 100 minutes because of sedation they had received during the procedure. Two patients experienced minor oozing from the puncture site after mobilisation, both of whom responded to further manual compression. All 50 patients studied were discharged home within 150 minutes.

Rapid mobilisation of patients following manual compression after sheath removal is associated with a low rate of bleeding complications and may obviate the need for femoral puncture closure devices following routine day case diagnostic cardiac catheterisation.

P2886 Safe early ambulation and short femoral compression times after diagnostic left heart catheterisation using 4-F catheters

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Background: Early mobilisation following left heart catheterisation (LHC) results in an increased incidence of groin haematoma. 7F femoral arterial sheaths for diagnostic LHC usually requires approximately 10 minutes of femoral compression and patients are advised to stay in bed for 4 hours after sheath removal. 4-F femoral arterial sheaths cause a smaller arterial puncture and may therfore result in shorter compression and immobilisation times following sheath removal. We therefore assessed compression times at sheath removal and the incidence of haematoma with only 2 hours of bed rest.

Methods: We prospectively studied 70 patients (67 Males) undergoing diagnostic LHC using the 4-F (Quick Care 4F Infiniti TM, Cordis) sheaths and catheters. Post procedure, the groin was manually compressed for 2 mins and if oozing noted, the groin was compressed for further 1 min intervals until no oozing was observed. Patients sat up 1 hr post compression and mobilised 1 hour later.

Results: Mean groin compression time and (SD) required to stop oozing from the femoral arterial site was 3.17 (0.68) minutes. No groin haematoma was observed 4 hours after the procedure and prior to discharge.

Conclusion: 4-French diagnostic LHC resulted in a shorter femoral compression time than is traditionally required. Also, patients are able to safely mobilize after only 2 hours of bed rest.

P2887 Real life experience with arterial sealing devices: is manual pressure obsolete?

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Background: Multiple randomized trials have reported that the use of arterial sealing devices after diagnostic catheterization or coronary interventions is associated with lower complication rates and earlier ambulation compared with manual pressure. We prospectively evaluated whether these advantages exist in the clinical setting of unselected patients and multiple operators.

Method: One hundred and ninety two patients having interventional or diagnostic catheterization by twenty-five different physicians were prospectively analyzed. Clinical characteristics, complication rates and ambulation delay in patients with sealing devices or manual pressure were compared.

Results: In the manual pressure (n = 40), Angioseal (n = 86) and Perclose (n = 65) groups, coronary interventions were performed in 86%, 75% and 78% of cases respectively. Sheath sizes were 6F in 15%, 14% and 31% of cases respectively and 8F in 60%, 80% and 55%; GpIIbIIIa inhibitors were used in 31%, 26% and 31%. The success rate for local hemostasis with manual pressure was 90.5%, with Angioseal 86% and with Perclose 78%. (p = ns) Complications were seen in 15%, 26% and 26% respectively (p = ns): Hematoma in 7.5%, 17% and 12% (p = ns) and major bleeding in 2.5%, 3.5% and 1.5% (p = ns). Ambulation times are presented in the table below.

Ambulation Time	Manual Pressure	Angioseal	Perclose
0–2 hours	0%	5%	8%
2–6 hours	0%	27%	26%
6–12 hours	20%	26%	20%
>12 hours	70%	31%	23%

Global $p < 0.001$.

Conclusions: In a real life setting of unselected patients and multiple operators, sealing devices did not demonstrate clear advantage over manual pressure on successful hemostasis and complication rates. Early ambulation occurred in patients treated with the sealing devices. However, the majority of them began ambulating after six hours. The impact of closure devices, closure device learning curves and sub-optimal compliance with early ambulation protocols requires further investigation.

P2888 Is early ambulation 4 hours after coronary angiography with 7-F catheters safe?

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Early ambulation after coronary angiography has been advocated with small diameter catheters. This however results in poorer image quality and entails greater operator experience.

Aim: To evaluate whether shorter bed rest (4 hours (hrs)) after coronary angiography using 7 F sheaths and catheters increases femoral complication rate when compared to conventional 8 hr bed rest. In particular, whether it increases the risk of bleeding after ambulation of the patient (pt) – late rebleeding.

Methods: 345 consecutive pts undergoing coronary angiography using 7 F sheaths and catheters were randomized to 4 hr (172 pts) and 8 hr (173 pts) bed rest after the procedure. Pts were examined on an out-pt basis within 4 days of the procedure by physicians blind to the randomized allocation. Both groups had comparable pt characteristics.

Results:

	4 hrs	8 hrs	Significance
No complications	115 (67%)	127 (73%)	NS
Small haematoma (<5 cm)	31 (18%)	24 (14%)	NS
Medium haematoma (5–10 cm)	22 (13%)	16 (9%)	NS
Big haematoma (>10 cm)	1 (0.6%)	4 (2%)	NS
Early rebleeding (during bed rest time)	4 (2%)	4 (2%)	NS
Late rebleeding (after ambulation)	2 (1.2%)	0	NS
Pseudo-aneurysm	1 (0.6%)	0	NS

In the 4 hr group 3 pts with rebleeding and the pt with a pseudo-aneurysm had a haematoma. Late rebleeding occurred immediately on ambulation in both pts. Recompression and a further 4 hr bed rest was resorted to without further complications. In the 8 hr group 2 pts with early rebleeding had a haematoma.

Conclusion: 4 hr bed rest after coronary angiography using 7 F sheaths and catheters is safe and does not confer an added risk of femoral complications. Late rebleeding is rare, occurs immediately on ambulation and is easily managed.

P2889 Is a tourniquet necessary for reaching haemostasis after PTCA via the radial artery?

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The aim of this trial is to determine if hemostasis can be safely achieved using only a pressure bandage for 6–8 hours following a PTCA or angiography via the radial artery using a 6 french introducer. In the past we noticed that application of pressure bandage with a tourniquet was painful and uncomfortable for the patient. The tourniquet also causes venous congestion.

Method: We studied the safety of obtaining hemostasis using only a pressure bandage without tourniquet. We studied 100 patients after PTCA or angiography via the radial artery using a 6 french, 23-cm introducer. The introducer was removed immediately after the procedure and a tight pressure bandage was applied. The endpoints were incidence of major and minor bleeding complications.

Results: 4 Out of 100 patients had minor bleeding which required no further action. 12 patients had bleeding immediately after the application of pressure bandage, one patient received re-application of pressure bandage with success and the 11 other patients required application of tourniquet to achieve hemostasis.

Conclusion: Hemostasis can effectively be obtained with a pressure bandage only. If bleedings occurs, it is usually immediately following application of the pressure bandage, any consequences are minor. We are presently researching a smaller pressure bandage to achieve better compression and to reduce the number of bleedings. The results will be available during my presentation.

P2890 Blood flow volume increase in cranial and abdominal arteries during eecp

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We report result of the study of enhanced external counterpulsation (EECP), a non-invasive therapy for patients with coronary artery disease and chronic angina pectoris. The investigation was conducted to test hypothese increase of blood flow volume to cranial and abdominal region during EECP. The study was an experimental, pre-test post-test design. We enrolled 25 patients, of whom 15 have carotid-atherosclerotic (A) plaque and 10 non-atherosclerotic (NA) subjects. Eighty nine percent were males We used ultrasound to measure blood flow volume. Observed vessels were Abdominal Aorta, Communes Carotid Artery, Internal Carotid Artery, Vertebral Artery. Baseline characteristics were obtained before EECP. Second mesurements were performed forty five minutes during EECP. Comparison of baseline and during EECP measurements represents effect of EECP on the observed variables. Data were analyzed using student t test for paired samples. Results in non atherosclerotic subjects:

Flow	Before EECP mm^3	During EECP mm^3	p
Abdominal aorta	3670 ± 854.3	5410 ± 730.9	3.3×10^{-5}
Communes carotid artery	702.5 ± 144.1	798.9 ± 174.3	0.001
Internal carotid artery	441 ± 88.2	512 ± 124.1	0.020
Vertebral artery	133.6 ± 36.3	148.7 ± 42.0	0.0078

In atrherosclerotic subjects, abdominal aorta did not always apllicable to be measured, because of abdominal wall thickness. The result were:

Flow	Before EECP mm^3	During EECP mm^3	p
Communes carotid artery	570.1 ± 109.7	737.4 ± 130.4	3.7×10^{-5}
Internal carotid artery	321.5 ± 79.5	415.6 ± 159.2	0.0046
Vertebral artery	158.3 ± 67.2	196.3 ± 65.3	0.0041

In conclusion, during EECP blood flow volume was increased in all observed arteries both in Non Atherosclerotic and Atherosclerotic subjects during EECP.

P2891 Once-daily treatments with usual doses of the loop diuretic torasemide do not reduce serum zinc concentration

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Hypozincaemia may cause hypogeusia, and thus increase salt intake, and it may also retard healing. Thiazides are usually regarded as the only diuretics that raise zinciuresis. However, we recently found that serum zinc (Zn) concentration, measured in blood drawn 3, 12 and 24 h after dosing, was lower on the seventh than on the first day of once-daily treatment with furosemide 40 mg in healthy adults. The aim of the present study was to evaluate the response of zincaemia to the loop diuretic torasemide (T).

Methods: Sixteen healthy subjects in a metabolic unit took once-daily oral doses of placebo, T 2.5 mg, T 5 mg, and T 10 mg, at 08.00 hours, over 4 separate single-treatment periods of 7 days each. A crossover, individually randomized and double-blind design was folowed. The renal instantaneous fractional excretion (FE) of Zn was evaluated by the standard procedure.

Results: None of the T treatments changed mean 24-h zinciuresis on day 1 nor on day 7. Mean zincaemia was not changed by T (mean ± SD):

Day	Once-daily treatment	Instantaneous FE of Zn (%) Hours after dosing		Serum Zn (μmol/litre) Hours after dosing		
		1.5	24	1.5	6	24
1	Placebo	0.46 ± 0.20	0.30 ± 0.09	15 ± 2	12 ± 2	15 ± 2
	T 2.5 mg	0.54 ± 0.32	0.31 ± 0.13	15 ± 2	13 ± 2	14 ± 2
	T 5 mg	0.54 ± 0.25	0.28 ± 0.13	16 ± 2	13 ± 2	15 ± 2
	T 10 mg	0.73 ± 0.38‡	0.25 ± 0.07‡	15 ± 2	12 ± 2	15 ± 2
7	Placebo	0.50 ± 0.30	0.35 ± 0.12	14 ± 2	12 ± 2	15 ± 2
	T 2.5 mg	0.54 ± 0.21	0.31 ± 0.12	14 ± 3	13 ± 2	16 ± 2
	T 5 mg	0.52 ± 0.25	0.35 ± 0.23	14 ± 2	12 ± 2	15 ± 2
	T 10 mg	0.59 ± 0.20	0.31 ± 0.11	15 ± 2	13 ± 2	15 ± 1

‡$p < 0.05$ compared with placebo.

In conclusion, T 2.5 and T 5 mg did not affect the renal tubular handling of Zn. T 10 mg tended to decrease Zn reabsorption from the preurine early after dosing on day 1, but a late-after-dosing rebound in this phenomenon avoided a net 24-h urinary Zn loss.

VARIOUS ASPECTS OF VALVULAR HEART DISEASE

P2892 Impairment of diastolic function in asymptomatic patients with severe aortic regurgitation and poor exercise tolerance

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Asymptomatic patients with severe aortic regurgitation (AR) may have subclinical LV dysfunction, shown by a fall in EF on exercise by >5% with an absolute value of <50%, but simpler echo parameters would be helpful.

Methods: We assessed global and regional diastolic function as a possible marker of subclinical LV dysfunction, applicable at rest, in 21 asymptomatic patients (NYHA class ≤ 2a) with severe AR (jet area/LVOT area > 44%). EF was measured at baseline and peak exercise (Weber protocol). Global diastolic function was assessed by PW Doppler of the transmitral flow; peak early (E) and atrial velocities (A) were measured, and E/A ratio was calculated. Regional diastolic function was assessed using tissue Doppler echocardiography (TDE) of the mitral annular motion for the long-axis, and of the LV posterior wall for the short-axis. From the spectral traces we measured peak velocities during early filling (E_{DMI}) and atrial contraction (A_{DMI}). E_{DMI}/A_{DMI} ratio was calculated.

Results: In 11 patients, EF increased or did not change on exercise (from 55 ± 5% to 58 ± 4%, $p < 0.05$); in 10 patients it decreased by >5% (from 54 ± 4% to 42 ± 5%, $p < 0.001$), all these patients also having an EF on exercise <50%. At rest, there were no significant differences between the groups in EF, LV diameter indices, or end-systolic wall stress. 70% of the patients with poor exercise response had global diastolic dysfunction, with an E/A ratio < 1, in comparison with 36% of the patients with good exercise responses ($0.05 < p < 0.10$). All 21 patients had normal short-axis diastolic function, but 80% of the patients with poor exercise responses had long-axis diastolic dysfunction (E_{DMI}/A_{DMI} ratio < 1) in comparison with only 9% of the patients with good exercise responses ($p < 0.01$). Sensitivity and specificity to predict a poor exercise response of global E/A ratio < 1 were 70% and 64%, compared with 80% and 91% for an E_{DMI}/A_{DMI} ratio < 1 for long-axis function.

Conclusion: Diastolic function is impaired in asymptomatic patients with severe AR and poor exercise response. Long-axis diastolic dysfunction measured by TDE may provide a simple and reliable parameter of subclinical LV dysfunction in this group of patients.

P2893 Relationship between the rest parameters of the mitral valve and exercise capacity

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Purpose: Interventional therapy to the mitral valve aim to provide the patient with a better exercise capacity. It is therefore crucial to detect the exercise capacity before deciding on the time of intervention. In this study, we aimed to demonstrate whether the rest parameters of the mitral valve relate to the restricted exercise capacity.

Methods: 46 patients (30 female) were enrolled to study. Patients with moderate/severe mitral insufficiency, moderate/severe aortic stenosis or insufficiency, lung disease, systolic or diastolic left ventricle dysfunction, chronic illness, and those who are unable to exercise were excluded. As for the mitral parameters; mitral valve resistance (MVr), planimetric valve area (MVApl), mitral valve area calculated with the continuity equation (MVAce), pressure half time of early diastolic filling (PHT), and transmitral mean pressure gradient (MPG) were obtained. The parameters were calculated as follows: MVr = MPG × DFP × 1.333/SV, MVAce = SV/VTIm, SV = Dao2 × 0.785 × VTIao. Abbreviations in the above formulas are Dao = aortic annulus diameter on the parasternal long-axis view, VTIao = time-velocity integral at the level of aortic annulus on the apical 5 chamber view, VTIm = time-velocity integral of PW Doppler tracing taken just distal to the mitral valve leaflets, DFP = diastolic filling period. All patients went thorough on exercise test due to the Bruce protocol. The MET value achieved was calculated as: ob-METs = 1.11 + 0.016(exercise time), predicted MET as: pre-METs = 16.6 − 0.16(age), and exercise capacity was derived as: (ob-METs/pre-METs) × 100. The relation between parameters of the mitral valve and exercise capacity was evaluated with the linear regression analysis.

Results: In our series of patients we found mean MVr 57.4 ± 33 dyn sec cm^{-5}, MVApl 1.41 ± 0.39 cm^2, MVAce 1.48 ± 0.40 cm^2, PHT 168 ± 54 msec, MPG 8.55 ± 5.14 mmHg, ob-METs 7.9 ± 2.2 METs, exercise capacity 82 ± 26%, rate of maximal heart rate achievement was 99 ± 13%. There' s statistically insignificant, low degree correlation between MVr, MVApl, MVAce, PHT, MPG and exercise capacity (correlation coefficients −0.39, 0.27, 0.33, −0.33, and −0.39 respectively).

Conclusion: In patients with mitral stenosis, the rest parameters showed no statistically significant relation with the exercise capacity, and this findings indicates that the decision on the time of intervention cannot be made depending on these parameters.

P2894 The role of cardiac rhythm on early and late outcome of percutaneous mitral balloon valvulotomy in rheumatic mitral stenosis

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Previous studies have suggested that, being on sinus rhytm prior to percutaneous mitral balloon valvulotomy (MBV) is one of the determinants of favourable early and late outcome of MBV procedure. In this study we investigated the effect of baseline cardiac rhythm on the early (1st year) and late (5 years) restenosis rates of the patients (pts) with rheumatic mitral stenosis who underwent MBV. Restenosis is defined as 50% reduction of the increase in mitral valve area (MVA) obtained by MBV and/or MVA < 1.5 cm^2. The study group consisted of 224 pts with MVA < 1.5 cm^2 and echo score < 9. There were 184 pts in group A with sinus rhythm and 40 pts in group B with chronic atrial fibrillation. All pts underwent pre- and post MBV echocardiographic and hemodynamic evaluation at cardiac catheterization. Follow-up echocardiographic studies were done up to 5 years. In group A pts were younger (34.4 ± 9.1 vs 42.9 ± 10.5 years, $p < 0.001$) and there were more women (91.3% vs 65%, $p < 0.001$). Pre-MBV left atrial size, pulmonary artery pressure and diastolic mitral gradient were similar in both groups. In group A left atrial size was smaller and MVA was larger compared to group B (4.6 ± 0.5 vs 5.2 ± 0.7 cm and 1.08 ± 0.25 vs 0.99 ± 0.23 cm^2 consecutively) ($p < 0.001$ and $p = 0.03$ respectively). Post-MBV MVA was not different between the groups (2.19 ± 1.79 vs 1.85 ± 0.19 cm^2). At 1st and 5th year follow-up MVA was 1.87 ± 0.24 (184 pts) and 1.69 ± 0.25 cm^2 (134 pts) in group A, and 1.78 ± 0.67 (38 pts) and 1.61 ± 0.23 cm^2 (34 pts) in group B ($p = 0.03$ and $p > 0.05$ respectively). In group A 1st and 5th year restenosis rates were 1.1% (184 pts) and 26.9% and 0% and 23.5% in group B, and the differences were not significant. Cumulative restenosis rates at 5 year follow-up were 26.9% in group A and 23.5% in group B, and the difference was not significant. In conclusion, the early and late outcome of MBV in pts with severe mitral stenosis is not different with chronic atrial fibrillation compared to sinus rhytm prior to the procedure despite the unfavourable baseline characteristics of atrial fibrillation pts.

P2895 Percutaneous balloon mitral commissurotomy as a treatment for mitral valve restenosis after open or closed surgical commissurotomy, report of 35 cases

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Percutaneous mitral commissurotomy (PMC) using Inoue balloon has been shown to be a promising method of treatment for both primary mitral valve (MV) stenosis and MV restenosis after surgical commissurotomy (SC).

Methods and results: between Jan. 1992 and Jan. 1999, 425 patients (pts) underwent PMC in two medical centers. There were 63 (14.8%) males and 362 (85.2%) females with mean age of 30 years (20 to 60 yrs). 35 (8.75%) pts had underwent previous open (20%) or closed (80%) surgical commissurotomy 5 to 17 years before (mean 8 yrs). All these pts were symptomatic with III-IV NYHA class. 25 pts had atrial fibillation. Their echocardiographic MV stenosis score was between 7 to 14. 20% had mildly calcified mitral valves. 3 pts had organized clot in their left auricle.

Technical success (MV area > 1.5 cm^2) was achieved in all the 35 pts. PMC resulted in decrease of the mean MV peak gradient from 25 mmHg to 5 mmHg. The mean MV area increased from 1 cm^2 to 1.8 cm^2. Mean pulmonary artery pressure decreased from 50 mmHg to 30 mmHg. Mitral regurgitation (grade 1+ to 2+) developed in 4 (11%) pts and one pt required MV replacement after 6 months. All procedures were completed successfully without death, cardiac tamponade, stroke or emergency surgery.

Conclusion: PMC with Inoue balloon is an effective and safe technique for treatment of MV restenosis after open or closed surgical commissurotomy.

P2896 Non-invasive prediction of coronary artery disease in patients with valvular aortic stenosis by use of electron-beam computed tomography

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Background: Preoperative coronary angiography is usually recommended for patients with aortic valve stenosis requiring valve surgery. The coronary artery calcium deposit detected with electron beam computed tomography (EBT) is a marker for coronary artery disease (CAD), but no data are available in patients with aortic valve stenosis. The aim of this study was to assess the capability of noninvasive measurement of coronary calcium deposit using EBT as a tool in the diagnosis of CAD in the patients with severe aortic valve stenosis.

Methods: Thirty-five patients (22 males and 13 females, mean age 64.5 ± 8.4 years) with aortic valve stenosis (maximal instantaneous ventriculo-aortic gradient greater than 50 mmHg) were included. Seven patients had significant CAD (>50% luminal stenosis in coronary arteries) (CAD-group) and 28 patients had no significant CAD (non CAD group) on coronary angiogram. Agatston total coronary artery calcium deposit scores (TCS) were calculated by use of EBT. TCS were compared between CAD-group and non CAD group.

Results:

	CAD group	Non CAD group	
Age (years)	66.0 ± 7.3	64.1 ± 8.7	n.s.
Sex (male/female)	6/1	16/12	n.s.
TCS	1428 ± 1240	102 ± 279	p < 0.001

TCS values > 500 had a sensitivity of 86%, a specificity of 96% and an accuracy of 94% for predicting CAD.

Conclusion: TCS using EBT can be useful for the noninvasive prediction of CAD in patients with aortic valve stenosis.

P2897 Structural features of the left ventricular outflow tract in physiological aortic valve regurgitation

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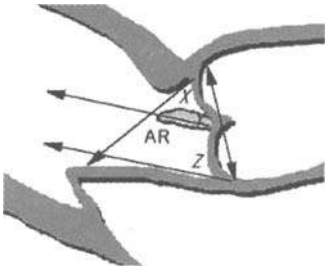
Since the advent of the color Doppler echocardiography, a small degree of aortic regurgitation(AR) has been detected with relative frequency in clinically normal elder heart. This study aimed at clearing the mechanism and quantitative definition of this physiological regurgitation.

Methods: 299 Japanese patients were selected from consecutive 906 patients underwent echocardiography from Jan. 1, 1996 to Dec. 31, 1998 at NTT Nagasaki hospital.In all the patients,the M,B mode echocardiogram was normal.AR was detected and AR jet area,length and width were measured by color Doppler echocardiography.The dimension of aortic annulus and the angles of anterior(X) and posterior portion of left ventricular outflow tract(Z) to aortic annulus and angle of AR jet(Y) to aortic annulus were measured in long axis diastolic view (figure).



Results: The incidence of AR was 24.4%. AR jet angle was 83 ± 17° (range 129 to 51),area was 34 ± 25 mm^2 (range 106 to 6),length was 13 ± 7 mm (range 36 to 4) and width was 3.5 ± 1.3 mm (range 6.2 to 0.7). AR-positive group was significantly elder than AR negative group(68 ± 13 vs. 59 ± 16 years p < 0.0001). Body mass index (BMI) and the angle of X were significantly smaller in AR-positive group than in AR-negative group(21.9 ± 2.8 vs. 22.8 ± 3.4 P = 0.03. 80 ± 13 vs.85 ± 11 P = 0.008). There was no significant difference in the angle of Z between two groups (76 ± 10 vs.76 ± 11).In AR-positive group, except for obesity (BMI was more than 26.4), angle of X was significantly directly correlated with thickness of interventricular septum, (r = 0.26 p = 0.03) and inversely correlated with diameter of aortic annulus(r = −0.27 p < 0.03).

Conclusion: Slight obstruction of anterior portion of left ventricular outflow tract was associated with physiological aortic valve regurgitation.

P2898 The relationship between spontaneous echocontrast and microembolic signals established with transcranial Doppler ultrasonography

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The purpose of this study was to search microembolic signals established with transcranial doppler ultrasonography (TCD) in patients with mitral stenosis (MS) and spontaneous echocontrast (SEC).

Methods: Fourty seven patients with MS were included into the study (30 women, 17 men, mean age: 41 ± 12). Exclusion criterions were thromboembolic events, multiple valve disease, and previous cardiac operation. All patients underwent transthoracic and then transesophageal echocardiography. Transcranial doppler records were recorded for 30 minutes from bilateral middle cerebral arteries as transtemporally with depth of 40–50 mm (Multy-doppler X4 TCD, with 2 MHz probe). During recording, signals shorter than 300 msec and higher than 9 dB were evaluated as the embolic signals. The patients were divided into two groups according to having SEC. There was no significant difference in the medical treatment of both groups. Findings were shown on the table. P < 0.05 was accepted as statistically significant

	SEC(+) n: 29	SEC(−) n: 18	P
MVA (cm^2)	1.28 ± 0.26	1.49 ± 0.4	0.03
MG (mmHg)	11.6 ± 5.5	12 ± 5	0.8
MR ≥ 2 degree (%)	17	55	0.01
AF (%)	65	27	0.02
Having Embolic signal (%)	63	27	0.03
Mean Embolic Signal (Count)	7 ± 4	3 ± 2	0.04
Mean Embolic Signal (dB)	17 ± 6	11 ± 4	0.04

MVA: Mitral valve area, MG: Mitral gradient, MR: Mitral Regurgitation, AF: Atrial fibrillation.

Conclusion: increased microembolic signals were detected with TCD in patients with mitral stenosis who were SEC positive. This finding supports the relationship between SEC and thromboembolic events.

P2899 Does mitral regurgitation prevent left atrial spontaneous echo contrast and thrombus formation and effect LA and LAA function in patients combined with mitral stenosis?

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It is well documented that in pts with rheumatic mitral valve disease, severe mitral regurgitation(MR) prevents spontaneous echo contrast(SEC) and thrombus(THR) formation in left atrium (LA) and left atrial appendage(LAA). However in pts with moderate to severe mitral stenosis(MS) the effect of concomitant mild to severe MR on incidence of LA-LAA SEC-THR and LA-LAA functions is not evaluated. This study aimed to investigate the effect of mild, moderate and severe MR on LA-LAA functions and SEC-THR formation in pts with MS. 256 pts (167 F, 98 M, mean age: 37 ± 15, 95 pts with no, 84 pts with mild, 45 pts with moderate, 32 pts with severe MR, 117 pts with sinus rhythm-SR, 139 pts with atrial fibrillation-AF) with MS (mitral valve area < 1.5 cm^2) who underwent TEE evaluation were taken into study. Midportion of LA flow velocity (both evaluated with horizontal and vertical planes, at the regions of free of MR jet) and flow velocities and ejection fraction of LAA were determined. Degree of MR was graded as (A)with no or mild,(B)moderate, (C)severe. Data were compared with regard to cardiac rhythm among the three groups.

In pts with SR, LA diameter and LA-LAA flow velocities of Group B (5.2 ± 0.6 cm, 0.33 ± 0.11, 0.35 ± 0.14 m/sec) and C (5.4 ± 0.2 cm, 0.35 ± 0.12, 0.37 ± 0.13 m/sec) were greater than Group A (4.5 ± 0.5 cm, 0.19 ± 0.12, 0.20 ± 0.13 m/sec) (p < 0.05). Incidence of LA-LAA SEC-THR of Group A (45.7%, 10.8%) were also greater than Group B (0%, 0%) and C (0%, 0%) (p < 0.05). In pts with AF diameter of LA in Group A (5.5 ± 1.6 cm) was lower than the other two groups (5.5 ± 1, 6.3 ± 1.3, 6.1 ± 0.8 cm Group B,C respectively, p < 0.05) and flow velocity of LA-LAA in Group C (0.18 ± 0.2, 0.19 ± 0.1 m/sec) was greater than the other two groups (0.05 ± 0.08, 0.07 ± 0.01; 0.06 ± 0.1, 0.08 ± 0.09 m/sec, respectively Group A,B) (p < 0.05). Incidence of LA-LAA SEC-THR in Group C (13%, 5.8%) was lower than the other two groups (86%, 49%; 75%, 28%, Group A, B respectively) (p < 0.01). Age,sex, peak and mean mitral gradient, mitral valve area were not different in both SR and AF in all groups(p > 0.05).

In conclusion, pts with moderate to severe MR protects against for LA-LAA SEC and THR formation as well as LA-LAA dysfunction in SR in pts with MS. However in pts with AF, mild to moderate MR does not protects against LA-LAA SEC and THR formation and does not preserve LA-LAA function, which all may be related to embolic events.

P2900 Surgical repair for severe mitral regurgation deteriorates the left atrium and left atrial appendage function

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Protective effect of significant mitral regurgitation (MR) for left atrium (LA) against spontaneous echo contrast (SEC) and thrombus (THR) formation is well evaluated. However, the effect of surgical repair of mitral valve for MR on LA and left atrial appendage (LAA) functions has not been study. Ninetyfour patients with severe MR (49 F, 35 M, mean age: 38 ± 14, 44 pts in sinus rhythm-SR, 50 pts in atrial fibrillation-AF) were included in the study. Each patient was evaluated with multiplane TEE preoperatively and within the first week after surgery. Mid portion of LA flow velocity (both with horizontal and vertical planes, at the regions free of MR jet) and flow velocites and ejection fraction of LAA were determined. Pre- and postopetative data were compared with regard to cardiac rhythm (SR and AF) and patients with unaltered rhythm postoperatively were included in the study. Patients with postoperative moderate to severe MR or pts with obstructive THR of the mitral valve were excluded from the study.

Left atrial diameter was found to be greater in patients with AF (5.3 ± 1.1 cm) than in pts with SR (4.7 ± 0.6 cm) postoperatively ($p < 0.001$). Mitral valve area, maximal and mean mitral gradient did not differ significantly between the two groups in postoperative state. Although none of the patients in SR had SEC (%0;0/44) or THR (%0;0/44) preoperatively, 4 patients (%9) showed evidence of SEC while none of the patients showed evidence of THR postoperatively ($p > 0.05$). Among patients with AF,%2 had SEC and%2 had THR preoperatively while%58 (29/50) had SEC and%26 (13/50) had THR postoperatively ($p < 0.001$).

In patients with SR, LA flow velocities (0.44 ± 0.12 vs 0.30 ± 0.12 m/sec) decreased and LAA functions (0.48 ± 0.15 vs 0.38 ± 0.13 m/sec, 48% ± 14 vs 36% ± 15) deteriorated significantly after the operation (preop vs postop, $p < 0.05$). In patients with AF postoprative LA flow velocities (0.37 ± 0.14 vs 0.20 ± 0.12 m/sec) were also decreased, and LAA functions (0.36 ± 0.13 vs 0.20 ± 0.12 m/sec, 34% ± 13 vs 22% ± 11) deteriorated significantly as compared to the preoperative state (preop vs postop, $p < 0.05$).

We conclude that in patients with MR in SR the surgical repair of MR deteriorates LA-LAA functions mildly in patients with AF surgical repair of severe MR deteriorates LA-LAA functions markedly and LA-LAA SEC and THR may develop consequently.

P2901 Prevalence of bicuspid aortic valve in children: a population study

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Bicuspid aortic valve (BAV) is estimated to be one of the most frequent form of congenital heart disease. Acquired stenosis due to calcification is a common complication and causes of death in young patients are infective endocarditis and dissecting aneurysm of the ascending aorta. Clinical and necroscopic observation suggest that BAV affect 1% to 2% of the general population. Data are not available in healthy people. The prevalence of BAV is assesed in a sample of 817 school-going children from a rural area of Veneto Region. 400 male and 417 female, 10 years old, all asymptomatic, were screnned by means of physical examination, 12 leads ECG and two-dimensional echocardiograf (2D echo). Four (3 M and 1 F) out of 817 (0.5%) were found to have a BAV, 1 of whom with mild incompetence. Among non-BAV: 3 (0.3%) had a dysplastic valve with a small left coronary cusp, 1 a rheumatic valve disease, 9 (1%) showed mild aortic incompetence. Aortic root size was increased in all BAV, particularly at sinus of Valsalva level (BAV mean 25.7 mm, 2 mmSD vs non-BAV mean 22.2 mm, 2.4 mm SD; $p = 0.02$). In conclusion, a low prevalence of BAV (0.5%) was found in school children population. BAV was strictly associated with aortic root enlargement. In these patients a 2D echo follow-up is mandatory.

VALVULAR HEART DISEASE – VARIOUS TOPICS

P2902 Effects of left atrial compliance on the pulmonary artery pressure in patients with pure mitral stenosis and sinus rhythm

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Background: Large left atrial(LA) V wave can be observed in pts with pure mitral stenosis(MS) because of decreased LA compliance. Few data are available regarding the relation between the magnitude of LA V wave and the peak pulmonary artery pressure(PAP) in MS. We hypothesized that PAP may be higher in pts with decreased LA compliance and large V wave.

Methods: We analyzed the right heart and transseptal catheterization data in 112 pts (16 male, 96 female, aged 39.1 years) of pure MS with sinus rhythm. Peak systolic, diastolic and mean pulmonary artery pressures were measured from the right heart catheterization. The magnitude of LA a, x and V wave was measured from transseptal catheterization. Two-dimensional and Doppler echocardiography were also performed to measure the left atrial size, mitral valve area (MVA), mean mitral gradient(MG) and valvular regurgitation. Multiple regression analysis was performed to identify the most important factor in the determination of PAP.

Results: Large V wave, defined if peak V wave height exceeded mean LA pressure by 10 mmHg or more, was observed in 44(39%) of 112 pts. Increased peak PAP (>50 mmHg) was observed in 35(31%) pts. Univariate analysis showed that factors associated with increased PAP were smaller MVA, higher MG, higher mean LA pressure and higher LA V wave; among them, LA V wave and ($p = 0.000$) and MG ($p = 0.001$) were significant independent factors for PAP in multivariate analysis.

Conclusion: In pts with pure MS with sinus rhythm, the magnitude of LA V wave is strongly associated with PAP and this finding may suggest that LA compliance is the most important factor determining PAP in pure MS.

P2903 Transoesophageal echo with three-dimensional reconstruction reveals organic tricuspid valve disease in patients with severe valve regurgitation and apparently normal cusp morphology

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Severe tricuspid regurgitation (TR) is well recognised as a long term complication of rheumatic mitral valve replacement (MVR), impairing the functional results of surgery. However, its exact basis remains unclear and its management is unsatisfactory. We therefore studied 22 patients, 17 female, age 67 ± 10 yrs, 8 ± 2 years after MVR by transoesophageal echo (TOE) with 3 D reconstruction. All had normal mitral prosthesis function but 15 had impaired exercise tolerance and marked fluid retention. In them transthoracic echo-Doppler showed enlarged right atrium (RA) and right ventricle (RV), a mean RV-RA pressure drop of 15 ± 4 mmHg and apparently normal cusp anatomy. TOE and 3D reconstruction, however, demonstrated abnormal cusp anatomy in all patients, with restricted cusp motion in 10, cusp shortening and thickening in the remainder, and dilatation of tricuspid ring suggesting rheumatic involvement. Although diastolic transtricuspid velocities were increased in all patients due to increased stroke volume (peak 1.0 m/s), significant tricuspid stenosis was present in 2 patients (mean gradient 4 and 3 mmHg). Histopathology confirmed leaflets vascularisation and extensive fibrosis in 2 patients who underwent tricuspid valve replacement.

Conclusion: Rheumatic cusp involvement contributes to severe tricuspid regurgitation occurring long term after mitral valve replacement, although overt stenosis is uncommon. Knowledge of the structural basis of this condition may thus improve its long term management.

P2904 Changes in echocardiographic left ventricular performance following mitral valve repair or replacement for pure mitral regurgitation

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Mitral Valve (MV) repair compared with replacement has been associated with lower mortality and better Left ventricular (LV) function. Aim of this study was to compare the effects of MV repair or replacement on postoperative LV performance in pure mitral regurgitation (MR).

Methods: We retrospectively analyzed 106 consecutive patients who underwent surgery for pure MR: 78 MV repair (Group A) and 28 MV replacement (group B). All patients underwent 2D echocardiographic study (ECHO) preoperatively and 1 year after surgery in order to obtain LV function parameters. Group A and B were devided on the basis of preoperative LVEF >= 60% (subgroup A1 and B1) or <60% (A2 and B2) and LVedD >= 65 mm (A3 and B3) or <65 mm (A4 and B4). Baseline ECHO parameters were substancially homogeneous within each subgroup (A1 vs B1, ...).

Results are reported in the following table.

Subgroups	LVEF %			LVedD (mm)		
	Preoper.	Postoper.	P	Preoper.	Postoper.	P
A1	68.1 ± 4.8	58.2 ± 7.1	0.001	59.1 ± 7.1	50.6 ± 6.1	0.001
B1	68.5 ± 4.7	56.8 ± 10.4	0.01	61.2 ± 7.3	54.1 ± 6.3	0.001
A2	55.7 ± 2.8	49.7 ± 14	ns	62.4 ± 6.3	52 ± 2.9	0.001
B2	53.4 ± 2.8	41.1 ± 8.7	0.01	65.8 ± 12.4	63.5 ± 9.6	ns
A3	65 ± 10	54.8 ± 10	0.05	69.4 ± 4.6	54.8 ± 10	0.001
B3	58.6 ± 10.6	45.1 ± 10.3	0.05	70.8 ± 7.3	63.1 ± 8.8	ns
A4	65.7 ± 6.3	58.1 ± 7.5	0.001	56.1 ± 5.6	49.1 ± 5.5	0.001
B4	65.5 ± 6.1	57.1 ± 8.2	0.001	56.6 ± 4.9	53.7 ± 7.2	ns

In pts with LVEF > 60% or LVedD < 65 mm, postoperative parameters are favourable independently of the type of surgery. If preoperative LVEF is <60% or LVedD > 65 mm, postoperative changes are still favourable after repair, while after replacement LV dimensions remain high with a significant decrease in LVEF.

Conclusions: These data suggest that in pts with significant MR, surgery should not be delayed, even if replacement is expected, as in pts with LVEF < 60% or LVedD > 65 mm favourable results can usually be obtained only with MV repair.

P2905 Valvular heart disease is associated with Chinese herbs and appetite suppressants intake

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Chinese herbs nephropathy (CHN), described in 1993 in women under slimming regimen, has been attributed to inadvertent replacement of *Stephania tetrandra* (ST) by *Aristolochia fang chi*. Cases of aortic regurgitation (AR) were reported in these patients. However, factors such as aging and metabolic or hemodynamic disturbances of end-stage renal disease could contribute to valvular abnormalities.

Methods: We assessed the prevalence of Doppler-detected valvular regurgitation in 40 CHN women with terminal renal failure (currently dialysed or transplanted) and in 32 age-matched control women with nephropathy of other origin (CTRL). Total cumulative doses of ST and appetite suppressants were reviewed and compared in CHN patients with and without valvular heart disease, defined as ≥ mild AR and/or ≥ moderate mitral or tricuspid regurgitation.

Results: 21 out of 40 CHN patients presented AR as compared to 6 out of 32 CTRL (P < 0.01). One CHN patient underwent aortic valve replacement in 1995 for recent onset of severe AR. All remaining AR were mild or moderate. There were no significant differences between CHN and CTRL with regard to mitral and tricuspid regurgitations. The mean (±SD) total cumulative doses of ST and fenfluramine (FEN) were higher in patients with (n = 23) compared to patients without (n = 17) valvular regurgitation (ST: 225 ± 17 vs 164 ± 19 g, P = 0.023; FEN: 19.0 ± 2.6 vs 10.9 ± 1.8 g, P = 0.020).

In conclusion, transplanted and dialysed CHN patients present an increased prevalence of valvular regurgitation, which is associated with a higher intake of ST and FEN. The respective role of these substances remain to be determined.

P2906 Is human myocardial Na^+/Ca^{2+} exchanger transcription altered according to the level of myocardial adaptation to chronic volume or pressure overload in patients with valvular heart disease

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A significant upregulation of Na^+Ca^{2+} exchanger (EXCH) gene expression was found in explanted hearts from patients with end-stage heart failure. As a change of the EXCH expression is one of the signs of disturbed myocardial calcium homeostasis, we investigated in patients with chronic valvular heart disease whether and in case at which level of myocardial adaptation to chronic pressure and/or volume overload the EXCH transcription is altered.

Methods: To determine the EXCH mRNA copy number in small biopsy samples, we established a quantitative PCR method using an internal RNA standard. Endomyocardial biopsy from the interventricular septum (IVS) of 11 patients (P) with aortic stenosis (AS), 5 P with aortic regurgitation (AR) and 6 P with primary mitral regurgitation (MR) were examined. The patients' left ventricular pump function was assessed by cardiac catheterization: Cardiac index (CI) varied between 1.8 and 4.5 l/min/m^2 and left ventricular ejection fraction (EF) between 34 and 70%. In addition, endomyocardial tissue (IVS) from explanted hearts of 13 P with end-stage heart failure were examined. As controls served endomyocardial tissue (IVS) from 4 P, in whom cardiac disease could be excluded.

The average level of EXCH mRNA in controls (2.2 ± 1.3 amol/ng total RNA) was not different from those in P with AS (1.8 ± 1.4 amol/ng total RNA) or in P with AR/MR (2.0 ± 1.5 amol/ng total RNA). The EXCH transcription showed no alterations parallel to the severity of valvular dysfunction nor to the impairment of left ventricular (LV) pump function. However, patients with end-stage heart failure (CI 2.4 plus EF < 30%) had a fourfold increase in EXCH mRNA level (8.9 ± 1.9 amol/ng total RNA).

LV pump function	CI (l/min/m^2)			EF (%)	
	>3.5	3.5-2.4	<2.4	>50	≤50
EXCH (amol/ng total RNA)	1.4 ± 1.1	2.5 ± 1.8	1.8 ± 1.0	1.9 ± 1.8	1.9 ± 0.9

In conclusion, an alteration of the EXCH transcription in humans seems to occur only after manifestation of end-stage heart failure and seems to indicate an irreversible myocardial damage. The EXCH transcription is therefore no marker to detect the exhaustion of myocardial adaptation to chronic overload.

P2907 Transseptal left heart catheterization: modification to the technique using venous puncture only

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Background: Transseptal left heart catheterization (TSC) is the key to successful balloon mitral valvotomy (BMV). Different fluoroscopic projections are used for TSC. It is usually done in the postero-anterior or right anterior oblique view using femoral arterial and venous punctures. Arterial puncture is used primarily for direct blood pressure monitoring, diagnostic purposes and to guide some operators during atrial septal puncture.

Methods: We performed TSC using femoral venous puncture only in 92 adult patients with tight mitral stenosis referred for BMV. Standard Mullin's dilator and Brockenbrough needle were used in all patients. Positioning of the Mullin's dilator with the Brockenbrough needle in the innominate vein was done using standard steps over a straight guide wire in the postero-anterior view. Interatrial septal puncture was done under fluoroscopic guidance only in the non magnified mode in the lateral view (90°) with the curve of the Brockenbrough needle directed straight towards the patient's left side. Puffs of concenterated dye are injected during needle withdrawal over the interatrial septum to verify interatrial septal bulge. Before transseptal puncture mild septal staining is done by injection of 1 ml of concentrated dye at the puncture site. The preferred puncture site is at the horizontal level of the body of the 8th thoracic vertebra. In this lateral view the aorta is anterior to the left atrium and away from the interatrial septum. After transseptal puncture by the needle tip, puffs of concentrated dye are injected into the left atrium to confirm correct needle position. Prior to mullin's dilator advancement and before I.V heparin injection, the brockenbrough needle is connected to pressure monitor to record left atrial pressure and to confirm proper needle site.

Results: TSC was successful in all patients. No complications occurred apart from transient vagal reaction in one patient.

Conclusion: The use of (90°) lateral view with the curve of the Brockenbrough needle straight at the level of the body of the 8th thoracic vertebra, appears to allow safe interatrial septal puncture. Only a single right femoral venous puncture is needed for this technique.

P2908 Effects of balloon mitral valvuloplasty on left atrial energetics

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Total mechanical energy of the left atrium (LA) can be quantified by a specific area in the pressure-area (P-A) diagram that is bounded by the end-systolic and end-diastolic P-A relations and the systolic P-A trajectory. In mitral stenosis (MS), LA afterload is increased because resistance is increased at the mitral valve.

Methods: We studied the effects of acute alterations in LA afterload on LA energetics caused by dilatation of the stenotic mitral valve by means of retrograde nontransseptal balloon mitral valvuloplasty (RNBMV). RNBMV is a technique developed in our institution for dilating stenotic mitral valves without any damage to the interatrial septum. LA pressure-area relations were obtained in 8 patients with mitral stenosis who were in sinus rhythm before and after RNBMV as well as in 8 controls (C). LA pressure was recorded by a catheter-tip micromanometer introduced retrogradely into the LA. LA area was simultaneously recorded using acoustic quantification. The total mechanical energy was quantified by the systolic P-A area (PAA). The PAA consists of two smaller areas: one is the area for external work (EW), determined by the LA A loop, and the other is the area for mechanical potential energy (PE) between the end-systolic and end-diastolic P-A relation curves. Furthermore, LA contractile efficiency (Ef) was determined as the ratio of EW/PAA.

Results:

	Controls	$MS_{pre\ RNBMV}$	$MS_{after\ RNBMV}$
PAA, mmHgcm^2	11.8 ± 1.7	23.9 ± 2.7***	13.7 ± 2.8***
EW, mmHgcm^2	7.5 ± 1.8	5.5 ± 0.8**	8.6 ± 2.3**
PE, mmHgcm^2	4.3 ± 0.5	18.5 ± 2.2***	5.2 ± 0.6***
Ef, mmHgcm^2	0.63 ± 0.07	0.23 ± 0.02***	0.62 ± 0.05***

$^{**}p < 0.01$, $^{***}p < 0.001$ controls vs $MS_{preRNBMV}$ and $MS_{preRNBMV}$ vs $MS_{afterRNBMV}$.

Conclusions: The mechanical efficiency of LA reduces in MS while following RNBMV, there is a significant increase. This efficiency varies as a function of afterload.

P2909 Increased platelet activation and endothelial dysfunction in patients following percutaneous balloon mitral valvuloplasty

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Immediately following percutaneous balloon mitral valvuloplasty (PBMVP), patients have a 3% risk of systemic thromboembolism. This may be due to increase in coagulopathy, platelet activation and endothelial dysfunction. To investigate this we measured indices of platelet activation (soluble P-selectin, sP-sel, ELISA), endothelial dysfunction (von Willebrand factor, vWf, ELISA) and coagulation (fibrinogen, modified Clauss) in 16 patients (15 females; mean age 59 years ± 10) admitted for PBMVP and 16 healthy age and sex matched controls. Peripheral venous blood samples were obtained prior to PBMVP, immediately following PBMVP and 24 after PBMVP. Arterial blood samples were obtained prior to and post-PBMVP.

Results, analysed using Wilcoxon sign test and expressed as mean (standard deviation) are:

Index	Pre-PBMVP	Post-PBMVP	24 hours
sP-sel (ng/ml)	73.4 (37)	92.8 (35)*	121.1 (51)*
vWf (IU/dL)	148.8 (24)	150.9 (34)	161.0 (15)*
Fibrinogen (g/l)	4.2 (0.8)	3.9 (0.9)	4.1 (0.9)

$^{*}P < 0.05$

Following PBMVP there was a significant increase in venous sP-sel levels immediately post-procedure and at 24 hours afterwards and arterial levels correspondingly increased post-PBMVP (p = 0.01). There was a significant increase in mean venous, but not arterial levels of vWf at 24 hours post-PBMVP. There was no significant changes in mean venous or arterial fibrinogen levels following PBMVP.

Conclusions: The increased levels of sP-sel immediately post-procedure ant at 24 hours, in association with increased vWf levels at 24 hours after PBMVP, is in keeping with increase in platelet activation and endothelial dysfunction following PBMVP. These changes may contribute to the increased risk of thromboembolism following PBMVP and suggest the need for adequate antiplatelet therapy and anticoagulant therapy following PBMVP.

GRADING OF VALVULAR STENOSIS

P2910 Reliability of different indexes of aortic stenosis severity in low flow states

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Background. New indexes of aortic stenosis (AS) severity have been recently introduced in addition to the transvalvular gradient and to the traditional "flow-corrected" indexes (continuity equation valve area; aortic valve resistance). These indexes can be defined as "function-corrected" (fractional shortening-velocity ratio = fractional shortening/4V max^2; ejection fraction-velocity ratio = ejection fraction/4V max^2) and "pressure-corrected" (stroke work loss = mean gradient/mean gradient + systolic blood pressure). Little information however is available about the reliability of each of these indexes for identifying patients with severe AS in low flow states.

Methods. We analyzed 161 patients with AS (96 males, 65 females, aged 68 ± 9 years) and low cardiac output (thermodiluition cardiac index < 2.5 l/m^2). All pts underwent cardiac catheterization and Doppler-echocardiography within 48 hours one of the other. Hemodynamic Gorlin valve area was used as gold standard. Echocardiographic indexes were measured by an investigator unaware of hemodynamic findings.

Results. Mean Gorlin valve area was 0.7 ± 0.3 cm2; cardiac catherization allowed to identify 129 patients with severe AS (Gorlin valve area ≤ 0.8 cm^2) and 32 with mild-to-moderate AS (area > 0.8 cm^2). Respective values of sensitivity and specificity are reported for each echocardiographic index (using previously suggested cut-off values of severity).

	Cut-off value	Sensitivity	Specificity
Mean Doppler Gradient	≥50 mmHg	55%	100%
Continuity Equation	≤0.8 cm^2	83%	90%
Mean Aortic Valve Resistance	>240 d s cm^{-5}	77%	97%
Percent Stroke Work Loss	≥23%	84%	84%
Ejection Fraction-Velocity Ratio	≤0.8	87%	88%
Fract. Shortening-Velocity Ratio	≤0.5	88%	78%

Conclusion. Our study confirms the inadequate sensitivity of Doppler gradient alone in the assessment of AS severity in patients with decreased cardiac output. The simple "function-corrected" and "pressure-corrected" indexes (in particular ejection fraction-velocity ratio and percent stroke work loss) provide a good diagnostic accuracy as well as "flow-corrected" indexes.

P2911 Non invasive assessment of pure mitral stenosis: role of dobutamine stress echocardiography (DSE) and cardiopulmonary test (CPX)

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Patients with mitral stenosis may present severe symptoms although basal echocardiographic data show only moderate mitral stenosis.

The aim of this study was to correlate the functional impairment (as evaluated by CPX) with DSE data in patients with pure moderate mitral stenosis.

Twenty-three consecutive symptomatic patients (21 women, mean age 50 ± 12 years, NYHA class 2.3 ± 0.5) with pure moderate mitral stenosis [mitral valve area (MVA): 1.4 ± 0.2 cm^2, mean valvular gradient (MVG): 8 ± 2 mm Hg] were evaluated. Eleven patients had atrial fibrillation.

CPX data included maximum oxygen uptake (max VO_2), max VO_2 % of predicted maximal oxygen uptake [ratio Wassermann (RW)].

DSE was performed increasing dobutamine by 5 mg/kg/min every 3 minutes until either maximal heart rate or symptoms occurred. MVG, MVA, pulmonary artery pressure (PAP) and cardiac output (CO) at rest and at peak stress were obtained.

Results: according to CPX data patients were divided in two groups: group A with impaired cardiopulmonary fitness (12 patients, RW = 0.61 ± 6, max VO_2 = 15 ± 3 ml/kg/min) and group B with normal cardiopulmonary results (11 patients, RW = 0.99 ± 17, max VO_2 = 19 ml/kg/min). Baseline clinical and echocardiographic data were similar in the two groups. At peak stress, PAP was significantly higher in group A (72 ± 2.1 versus 43 ± 7.2, p = 0.005) than group B, while MVG (15 ± 6.6 versus 15 ± 3.9) and CO (5.8 ± 1.1 versus 7.3 ± 2.2, p:0.06) increased in a similar manner in the two groups.

Conclusions: CPX and DSE are useful for assessment of mitral stenosis in patients with discrepancy between symptoms and baseline echocardiographic data. Patients with moderate mitral stenosis and impaired functional capacity show a disproportionate increase of PAP compared to the change of MVG, during stress. A pulmonary mechanism may be responsible of the poor functional capacity in these patients.

P2912 Aortic valve area and resistance in the evaluation of aortic stenosis: a dobutamine echocardiographic study

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In the evaluation of aortic stenosis (AS), Aortic Valve Area (AVA) and Resistance (AVR) have been suggested to be less flow-dependent than gradients, but presently few data are available. Aim of the study was to compare AVR to AVA for assessment of AS and normal LV function, at baseline and after dobutamine echo (DOB). We studied 15 pts with calcified AS, in sinus rhythm, without other valvular or coronary heart disease. Etiology was rheumatic (4) or degenerative (14 pts). Age was 68 ± 11 years. A standard DOB protocol was used. AVA was calculated with different echo methods: 1) Gorlin formula, 2) Continuity equation ($(Cross\ sectional\ area_{LVOT} * (V_x^{LVOT}/V_x^{aorta}))$, using for V_x either, V_{max}, V_{mean} or Flow Integral from LVOT; Stroke Work Loss (SWL) was also computed.

Results are summarized:

	Ao area V_{max}	Ao area V_{mean}	Ao area FVI	Ao area Gorlin	AVR	SWL %
Baseline	0.88 ± 0.3	0.82 ± 0.2	0.89 ± 0.3	0.93 ± 0.3	234 ± 115	23.1 ± 7.1
DOB	0.87 ± 0.3	0.84 ± 0.3	0.88 ± 0.3	0.91 ± 0.3	299 ± 139	30.6 ± 7.4
Change	−1.4 ± 14%	+6.4 ± 22%	−3.9 ± 23%	−2.2 ± 25%	+28 ± 44%	+37 ± 30%
p	ns	ns	ns	ns	<0.05	<0.001

No patient experienced major symptoms or arrhythmias during DOB. A good inverse linear correlation was found between G_{max} and V_{max}-calculated AVA (r = −0.80) at baseline. After DOB, AVA calculated with either method remained unchanged. However, relatively large interindividual variations were found. During DOB, 3 pts (21%) developed a significant intraventricular (IV) pressure gradient (mean 35 mmHg) that prevented calculation of AVA in two. In these subjects, LVOT flow at baseline was slightly higher (mean 108.3 cm/sec) than in the remaining pts (mean 74 cm/sec). Among the different methods, V_{max}-calculated area was the most flow-independent and showed the least interindividual variations while SWL and AVR were significantly flow dependent. AVR has been previously found to be the most flow-independent measure of AS severity in subjects with low-flow, low-gradient critical AS. In our pts with normal LV function, AVR increased significantly more than AVA. In conclusion, DOB proved to be a useful test for assessing AS even in pts with normal LV function. In comparison to AVR and SWL, V_{max}-calculated AVA was the most flow-independent parameter. Development of IV pressure gradients was a frequent and often misleading finding. DOB could unmask latent intraventricular gradients as a potential cause of misinterpretations of measurements of AVA.

P2913 Plasma N-terminal proBNP and cardiotrophin-1 in aortic stenosis

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Echocardiography with doppler examination of the aortic valve provides a very accurate assessment of the transvalvular gradient across the valve and is used to monitor progression of disease. Plasma BNP has been shown to correlate with end-systolic wall stress in patients with aortic stenosis (AS). We hypothesized that plasma N-Terminal proBNP (NT) and a newly identified cytokine Cardiotrophin-1 (CT-1) are elevated in patients with AS and correlate to the trans-valvular pressure gradient (TVPG).

Method: We compared plasma NT and CT-1 in15 AS patients (5 males, mean age 79 years [range 60–94], mean TPG 39.3 mm Hg [20–100]) with 10 echocardiographic normal controls (mean age 55.9 years [40–79]). None of the patients had Left ventricular systolic dysfunction (i.e. wall motion index < 1.4) or significant mitral regurgitation. Two competitive immunoluminometric assays using a methyl acridinium ester to label the peptides and an in-house polyclonal antibody to amino acids 65–76 of the prepro BNP sequence and 105–120 of the CT-1 sequence were developed. Results are expressed as medians [ranges] and comparisons were by the Mann-Whitney test.

Results: NT levels were elevated in AS patients when compared to the controls (242.9 fmol/ml [79.2–541.8] Vs 144 fmol/ml [73.7- 206.3], p = 0.001 Vs controls]. Also CT-1 levels were elevated in AS patients when compared to the controls (53.9 fmol/ml [33–86.3] Vs. 25.3 fmol/ml [7.6–37.2], p = 0.0001 Vs controls). Both NT and CT-1 levels correlated to the TVPG (r = 0.63 & r = 0.68, p = 0.01 & p = 0.005, respectively). Furthermore NT and CT-1 levels in the AS patients were weakly correlated (r = 0.49, p = 0.06). On best subset analysis the strongest correlate with TVPG was CT-1 (R2 = 42.8). The addition of NT improved diagnostic accuracy (R2 = 51.1).

Conclusion: These results suggest NT and CT-1 levels increase in proportion to the TVPG and could potentially be used to monitor progression of disease. These markers may be used to better identify the optimum time for surgery in AS.

P2914 Differences between Doppler and catheter gradients in aortic valve stenosis: related factors

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In the assessment of aortic valve stenosis, discrepancies between Doppler (D) and catheterization (©) gradients have been reported. The aim of the study was to investigate the frequency and possible related factors in the overestimation by D of mean aortic gradient obtained at ©.

Methods: We examined 75 consecutive patients (p) with aortic valve stenosis in sinus rythm. Mean age was 69 ± 10 years and D was performed 1 hour prior to ©. Relevant overestimation (RO) was defined if D mean gradient exceeded >10 mmHg that one obtained in catheter pull-back from left ventricle to the aortic root.

Results: Pearson correlation coefficient between D and © in those 75 pts was 0.90. RO was founded in 19 p (25%) and main results in univariate analysis were:

	RO n = 19	NO n = 56	p
Female sex	12 (63%)	23 (41%)	0.09
Height < 160 cm	7 (75%)	8 (46%)	0.04
Hemoglobin (hg), g/dl	12.5 ± 1.4	13.9 ± 1.3	0.003
Aortic root diameter, cm	2.9 ± 0.3	3.2 ± 0.3	0.004
Aortic root (A) < 3 cm	17 (81%)	21 (38%)	0.0001
Valve regurgitation (VR) > 2+	6 (32%)	6 (11%)	0.04
Mean D gradient, mmHg	80 ± 24	61 ± 23	0.004
D Heart rate, beats per min.	77 ± 12	72 ± 11	0.06

No other significant differences were seen attending to different clinical and echocardiographic variables including medications and selected acoustic window. Entered in a multiple logistic regression analysis, only A < 3 cm (OR 22) and VR > 2+ (OR: 9.7) were identified as independent predictors of RO. In this model, RO was predicted with 59% sensibility and 96% specificity.

In conclusion, in the setting of adult aortic valve stenosis, echocardiographic and clinical variables, mainly an aortic root diameter below 3 cm, may be useful to predict relevant discrepancies between Doppler and catheter gradients.

P2915 Aortic stenosis: role of contrast Doppler echocardiography

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Objective: The aim of this study is to compare the severity of aortic stenoses assessed by conventional and contrast Doppler echocardiography, with the "gold-standard" of cardiac catheterization.

Methods: We evaluated 21 consecutive patients referred to catheterization study for aortic stenosis, 12 men and 11 women, aged 39 to 94 years old (68 ± 14). All were submitted to conventional Doppler echocardiography, contrast Doppler echocardiography with Levovist® and catheterization study. Doppler measurements included: peak aortic velocity (V2) and velocity time integrated (VTI2), left ventricular outflow tract velocity (V1) and VTI (VTI1), peak aortic gradient (MxGr), mean aortic gradient (MnGr), aortic valve area. Catheterization measurements: peak and mean aortic gradients (C-MxGr and C-MnGr).

Results: Compared with conventional Doppler measurements, the use of contrast yielded: 1. Aortic flow – increased V2 (p < 0.001), MxGr (p < 0.001), MnGr (p < 0.01), VTI2 (p < 0.01). 2. Left ventricle outflow tract flow – increased V1 and VTI1, without statistic significance. 3. No statistic difference between aortic valve areas.

Doppler measurements vs. catheterization data: A positive significant correlation was found between C-MxGr and MxGr without contrast (r = 0.73, p < 0.001) and a stronger one between C-MxGr and MxGr with contrast (r = 0.89, p < 0.001). MxGr with contrast was higher (p < 0.01) than the C-MxGr (81.5 ± 27 vs. 70.5 ± 32).

Conclusion: In the evaluation of aortic stenosis, Doppler echocardiography has an excellent correlation with catheterization study. The use of contrast is a reliable method for the evaluation of aortic stenosis, having a better correlation with hemodynamic study than the conventional Doppler.

INFECTIVE ENDOCARDITIS

P2916 Embolization after adequate antibiotic treatment in infective endocarditis

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Aim and Methods: Assess embolization of patients (P) with infective endocarditis (IE) once an adequate antibiotic treatment has been initiated based upon prospective clinical follow-up.

The study group consisted of 143 episodes (ep) of left sided endocarditis (138 P, 92 men, mean age 56 ± 14 years) studied by transesophageal echocardiography (TEE). According to Duke criteria, 132 ep had definitive and 11 probable IE. These P were clinically followed (mean time follow-up was 144 days). Forty nine ep were on prosthetic valves and in 43 ep the P was on anticoagulants. Characteristics of the vegetations were analyzed by TEE.

Results: There were 27 embolic events in 22 ep (15.4%, group I). Thirteen of these embolic (48%) involved the central nervous system. Seventy five percent of these emboli occurred during first two weeks after TEE and adequate antibiotic treatment The remaining 121 ep did not embolize (group II). There were no significant differences between microorganisms of group I and II (*staphylococcus aureus:* 20 in 4 gI and 16 gII, *staphylococcus coagulase negative:* 21 in 4 gI and 17 gII. No significant differences among the infected valves were found. Anticoagulation was present in 18% in gI and 32% in gII (p = NS), and atrial fibrillation was detected in 22% in gI and 25% in gII (p = NS). Previous emboli was not a risk factor for embolization after treatment (8 gI and 29 gII, p = NS). TEE showed no differences in vegetation detection rate (91% gI and 86% gII). Comparing the vegetation size by TEE there were no statistical differences between both groups: ≤9 mm (16.7% gI and 29.2% gII), 10–20 mm (61.1% gI and 53.9% gII), ≥21 mm (22.2% gI and 16.9% gII). Surgery (41% gI and 54% gII, p = NS) and in-hospital mortality (41% gI and 31.5% gII, p = NS) was not different for both groups.

Conclusion: 1. Embolization after adequate antimicrobial therapy is frequent and most emboli occur during the first 2 weeks of treatment. 2. Vegetation size does not predict systemic embolism. 3. Embolic events do not appear to be predicted neither by the type of microorganism nor the clinical profile.

P2917 Active infective endocarditis. Prognosis of patients with initial medical treatment

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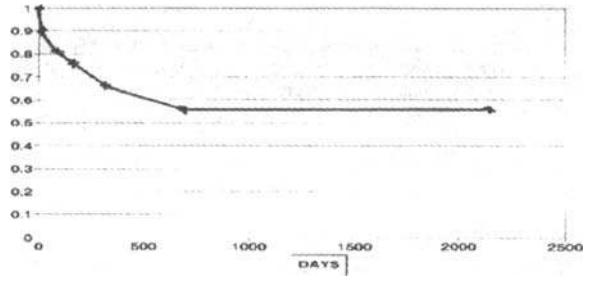
Background: Infective endocarditis is fatal if untreated. Despite microbiological cure, actuarial curves after admission show a significant number of late surgery or death.

Objective: To analyze the prognosis of patients with Active Infective Endocarditis (AIE) non requiring surgery during hospitalization.

Material and Methods: From June 1992 to January 1999, 129 patients (p) were included. During hospitalization, 83 p required surgery. Of the remaining 46 p treated medically, 44 were contacted during the follow-up interval [mean of 648 days (2–2145)]. Survival free of events (surgery or death) was performed by the Kaplan-Meier method.

Results: Mean age was 52.3 ± 17 years; male sex 67%. AIE affected native valves in 47.8% and prosthetic valves in 52.1%. In 15 cases Staphylococci were involved, Streptococci in 22, other in 3 and hemocultures were negative in 4. The echocardiogram showed vegetations in 68%. Emboli were present in 10 p (22.7%). During follow-up 10 p died (22.7%) and 7 required valvular surgery (15.9%). One patient is in NYHA FC IV and the remaining 26 in NYHA FC I.



Survival curve free of events.

Conclusions: In this group of p with AIE non requiring surgery during hospitalization: 1) Survival free of events at mid term follow-up was 56%. 2) Most of the events occurred early after microbiological cure. 3) 96% of survival patients are in NYHA FC I.

P2918 Time-related occurrence of neurological complications in patients with infective endocarditis submitted to surgical treatment

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Neurological complications of infective endocarditis modulate decisions regarding cardiac surgery. We studied the time-related occurrence of neurological complications and surgery in patients with infective endocarditis.

Methods: we studied 144 (24.9%) patients with 145 episodes of infective endocarditis with 161 neurological complications, among 579 patients with 641 episodes of endocarditis. The ages ranged from 2 months to 83 (33.5 ± 17.5) years; 89 (61.4%) episodes occurred in men and 56 (38.6%) in women. Mortality was higher in patients with neurological complications (44.1% vs. 19.1%; $p < 0.01$).

Results: In 95 (65.5%) episodes, patients were submitted to medical and in 50 (34.5%) to surgical treatment. Neurological complications were pre-operative in 38 (76%) episodes and post-operative in 12 (24%). Neurological complications preceded surgery from 2 to 132 (39.4 ± 32.9) days; after operation neurological complications occurred up to 16 (4.3 ± 4.9) post-operative days. Post-operative neurological complications were: neurological disability, toxic psychosis and meningitis in 1 episode each; seizure in 2 episodes; cerebral embolism, cerebral haemorrhage and stroke in 3 episodes each. Forty-nine (51%) patients submitted to medical treatment and 15 (30%) operated upon died ($p < 0.05$).

Conclusion: neurological complications of patients submitted to surgical treatment of endocarditis were more frequently pre-operative. The post-operative neurological complications occurred early after surgery. Mortality was higher in patients with neurological complications submitted to medical treatment than in those operated upon.

P2919 Unexpectedly high incidence of embolic events with the St. Jude Silzone valve

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Background: The incidence of thromboembolism (TE) following heart valve replacement is determined by patient-related factors, anticoagulant control and possible thrombogenicity. In a prospective study designed primarily to investigate patient-related factors, patients with both St. Jude Silzone (SZV) valves (silver-coated sewing ring) and standard St. Jude Medical valves (SJM) were included. Because of an unexpectedly high incidence of TE in patients with SZV, a comparison was made between SZV and SJM in this study.

Methods: We compared 51 patients (21 M) who had an SZV implanted between October 1997 and July 1998 with 118 patients (59 M) who had an SJM implanted between June 1995 and October 1997. All patients were anticoagulated with Warfarin to a mean INR of 2.5 for aortic, and of 3.0 for mitral and double valve replacement.

Results: Patients in the SZV group were younger (mean age [SD] 61[10] vs. 65[9] years, p = 0.01); they had 32 (63%) aortic, 13 (25%) mitral, and 6 (12%) double valve replacements, and 9 had CABG (42%). The SJM group had 72 (61%), 35 (30%), and 11 (8%) replacements respectively, and 36 (46%) CABG (ns). The proportions with atrial fibrillation, heart failure, hypertension, diabetes mellitus, previous stroke and smoking were similar. Follow-up was 98% in the SZV group and 96% in the SJM group, totalling 31 (mean 0.6; range 0.03–1.1 years) and 244 patient years (mean 2.1, range 0.03–3.6 years) respectively. The linearised rate of stroke/RIND/peripheral embolism was higher in patients with SZV (Table).

Linearised rates (%/year) of endpoints

Endpoints	SZV	SJM
Death	12.9	4.5
Stroke/RIND/embolism	22.6	0.8
TIA	22.6	9.4
Endocarditis	3.2	0.0

SZV – St. Jude Silzone valve; SJM – standard St. Jude valve; RIND – reversible ischaemic neurologic deficit; TIA – transient ischaemic attack.

Conclusions: The incidence of major embolic events after implantation of the St. Jude Silzone valve is significantly much higher than that of the St. Jude Medical valve, raising concern about the thromboresistance of the silver-coated ring. These findings need to be investigated in other studies.

P2920 Analysis of the interval between preoperative neurologic events and valve operations in patients with acute infective endocarditis

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Background: In patients with acute infective endocarditis and complicating cerebrovascular events due to embolization the duration of the interval between neurologic event (NE) and the valve operation (VO) is still discussed controversially. An interval of more than three weeks is supposed to be essential to prevent the impairment of the neurologic status by the use of extracorporal circulation. In the following we present our experience and results after valve replacement (VR) for acute endocarditis in patients with preoperative NE with particular concern of the interval between the NE and VO.

Methods: From 5/95 to 1/99, 88 patients (54 ± 13 years, range 20–82 y.) underwent VR or valve reconstruction for acute left heart valve endocarditis at our institution (64 patients with aortic VR, 13 patients with mitral VR, 7 patients with double VR, 3 homograft implantations and 1 mitral valve reconstruction). In 20 patients (23%) a preoperative NE required delayed VO. The interval between NE and VO ranged between 2 days and 22 days, respectively, with a mean of 9 ± 3 days.

Results: The overall perioperative survival of patients without preoperative NE was 94%, in patients with preoperative NE 90%, respectively. A new NE occurred in two patients without preoperative NE. In patients with preoperative NE no impairment of the neurologic status occurred.

Conclusions: The data demonstrate that valve operations in patients with acute infective endocarditis and preoperative NE can be performed safely within an interval of 9 days with good clinical results. In conclusion, decision making for the time of operation should be based mainly on the risk of further embolization.

P2921 A rapid molecular assay for the detection of antibiotic resistant organisms in infective endocarditis

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The cornerstone in the treatment of infective endocarditis (IE) has been traditionally based on the culturable anitibiotic susceptibility assay. However, this method may be unreliable with culturable agents of IE, in that it may be difficult to ascertain the modal action of resistance to a given antibiotic, as this may only be determined genotypically. In addition, as it is not possible to evaluate phenotypically the susceptibility of non-culturable causal agents of infective endocarditis (IE), genotypic detection of antimicrobial gene resistance loci employing molecular techniques offers both the opportunity to examine the susceptibility of the causative agent to antibiotics, as well as to reduce the time required for institution of definitive therapy. The aim of this study was to develop a rapid molecular assay for the detection of such resistance loci in organisms causing IE. As the majority of agents responsible for IE are Gram-positive, the following antimicrobial classes were examined: aminoglycosides, glycopeptides and B-lactams, targetting the aacA-aphD, aphA3, aadC for the aminoglycosides; vanA, van B, van C-1, van C-2 for the glycopeptides and mecA for the B-lactams. Three patients with IE due to Staphylococci (1 MRSA, 1 S. aureus & 1 CNS) were examined with respect to methicillin resistance, both by conventional and molecular means. Identical resistance profiles were obtained by both methods, however the molecular detection was completed within four hours, as opposed to the three days required for conventional workup. As it is not possible to evaluate phenotypically the susceptibility of non-culturable causal agents of IE, genotypic detection of antimicrobial gene resistance loci employing molecular techniques offers both the opportunity to examine the susceptibility of the causative agent to antibiotics, as well as to reduce the time required for institution of definitive therapy. In conclusion, rapid detection may reduce the use of inappropriate agents or enable the use of combinations of antibiotics, other than those that would normally be prescribed empirically for IE., viz. a combination of a b-lactam e.g. penicillin G and an aminoglycoside e.g. gentamycin. Detection of antibiotic gene resistance loci by molecular-based technologies,namely polymerase chain reaction (PCR) will allow for a more directed antibiotic therapy and may also provide opportunities for early identification of resistant organisms. This work was funded by the British Society for Antimicrobial Chemotherapy and the British Heart Foundation.

P2922 Brucella infective endocarditis: successful combination of medical and surgical treatment

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Brucella endocarditis is an under-diagnosed complication of human brucellosis, associated with high morbidity and mortality. We report the successful treatment of seven consecutive cases of Brucella infective endocarditis, based on high suspicion of the disease.

Methods: Seven patients with infective Brucella endocarditis were treated over the last 20 years. The native aortic valve was involved in 4 cases, the native mitral valve in two and the native aortic and mitral valves simultaneously in one. The early suspicion of Brucella infective endocarditis relied on reported professional contact with sheep and goats and clinical features. The standard tube agglutination titter on admission was >1:320 in all cases and blood cultures were positive in 1 patient. Valve cultures were positive in 1 patient. They both grew Brucella mellitensis. All patients were successfully treated with a combination of aggressive medical and early surgical therapy. Medical treatment included preoperative administration of co-trimoxazole, doxycycline and streptomycin. During the postoperative and follow-up period all patients received co-trimoxazole and doxycycline. All affected valves were replaced within one week from admission. There were neither operative deaths nor recurrence of infection. One patient died two years after the operation due to a massive cerebrovascular accident.

Conclusion: Brucella endocarditis is a rare entity. Its optimum management should be a combination of aggressive medical treatment and early surgical intervention. High degree of suspicion in areas with high incidence of the disease leads to early treatment, which may provide the best results.

P2923 Infective endocarditis in HIV infection

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Infective endocarditis (IE) is one of the HIV infection related cardiac diseases. It is uncertain whether advanced disease (AIDS) is characterized by a higher incidence of IE. The present study aimed at assessing if HIV infection represents an independent risk factor for IE.

Subjects and methods: all the HIV infected patients referred to the echocardiographic laboratory because of IE suspicion between 1992 and 1998 were considered (n = 68). The echocardiographic study was performed with HP Sonos 1000, 2000, 2500 or 5500. Diagnosis of IE was based on Duke University criteria, and patients were followed up for at least 6 months.

Results: diagnosis of IE was confirmed in 22 (IE+) out of 68 patients. In the remaining 46 patients (IE-) an alternative diagnosis was made and/or follow up was negative. Among the 22 EI+ patients 1)21 were drug abusers and 1 was affected by mitro-aortic disease, 2)12 were affected by AIDS, 10 asymptomatic HIV carriers. EI+ and EI− patients did not differ by mean age and sex distribution, while drug dipendence was more frequent in EI+ group. Echocardiogram was positive for IE in 17/22 patients, consistent with IE in 5/22. Positive blood cultures were found in 19/22 patients (S. Aureus in 12 cases). Tricuspid valve was involved in 15 cases, aortic valve in 5, mitral valve in 4. A left heart valvular involvment was shown in 7/12 AIDS patients and only in 2/10 HIV carriers. Two patients died in hospital (both were affected by AIDS). Four patients were submitted to cardiac surgery (1 AIDS patient). Long term mortality was mainly due to non-cardiac disease and was higher in IE- patients (11% vs 28%).

Conclusions: in our series IE was related to known predisposing factors; AIDS was not an adjunctive risk factor for IE, but in these patients left heart involvment and in-hospital mortality were more frequent; medical and, in selected cases, surgical treatment was effective.

P2924 Expression of E-selectin and VCAM-1 on aortic heart valves

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Shear stress causes endothelial cells (EC) to undergo functional alteration. While the expression of adhesion molecules by EC of large vessels has been widely studied, to our knowledge there are no such studies on EC of heart valves. As heart valves – like large vessels – are exposed to extreme shear stress we characterised immunohistochemically the expression of the adhesion molecules E-selectin and VCAM-1 (vascular cell adhesion molecule-1) on degenerated aortic valves and aortic valves with acute endocarditis. This knowledge might be important for the understanding of etiologic aspects of (recurrent) local inflammations but also for the development of new bioprosthetic heart valves.

Methods: 18 degenerated aortic valves (with no microscopical signs of inflammation) and 6 aortic valves with acute endocarditis were stained immunohistochemically with antibodies against E-selectin and VCAM-1. The FVIII-related antigen – constitutively expressed in EC – was used as an identification marker for the control staining reaction for EC. All valves were excised during prosthetic valve operation.

Results: There was a positive staining of the EC of all 6 aortic valves with antibodies against E-selectin and VCAM-1. The EC on 12 of the degenerated valves showed a positive reaction for E-selectin. 14 degenerated valves showed a positive staining of the EC with antibodies against VCAM-1.

In conclusion there is an expression of E-selectin and VCAM-1 not only on aortic valves with acute endocarditis (as expected) but also on degenerated aortic valves with no morphological evidence of inflammation. These findings might explain why patients with degenerated aortic valves are susceptible to recurrent endocarditis. Further investigations will show if the expression of E-selectin and VCAM-1 has to be regarded as pathogenetic similarity to the expression of these molecules in atherosclerosis.

PROSTHETIC VALVES – VARIOUS ASPECTS

P2925 Influence of left ventricular mass in the haemodynamic profile of bileaflet mechanical aortic protheses assessed by Doppler echocardiography

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Purpose: to evaluate the influence of left ventricular (LV) mass (LVM) in the hemodynamic profile of different sized bileaflet mechanical aortic protheses (BMAP), assessed by Dopppler echocardiography.

Methods: we studied 52 patients (pt) with normofunctional BMAP, sinus rhythm, 23.5 ± 8.4 months after surgery, divided in two groups (Gr) according to the size of the implanted protheses (P) – gr I: P 19 or 21 mm – 26 pt, 8 men, 61 ± 10 years, 14 with Carbomedics (CM) and 12 with St.Jude Medical (SJ) P; gr II: P 23 or 25 mm – 26 pt, 19 men ($p < 0.05$ vs gr I), 57 ± 13 years (NS), 13 CM and 13 SJ P (NS).

We analysed, at rest: maximal (Gmax) and mean (Gmean) transprothesic pressure gradients, P area (PA), P resistance (PRes), and PRes index (PResI). Gradients were calculated using the Bernoulli equation, PA using the continuity equation, PRes as 1333.Gmean.SEP/SV (SEP = systolic ejection period; SV = stroke volume), and PResI as PRes.BSA (BSA = body surface area). LVM was calculated using the ASE/Devereux method and LVM index (LVMI) as LVM/BSA.

Results: functional class, ejection fraction and time after surgery were comparable for the two Gr. There were no differences between CM and SJ P.

Gr I vs. GR II – Gmax: 21 ± 7 vs 19 ± 7 mmHg (NS); Gmean: 11 ± 3 vs 8 ± 4 mmHg (NS); PA: 1.3 ± 0.2 vs 1.8 ± 0.4 cm^2 ($p < 0.001$); PResI: 123 ± 22 vs 95 ± 29 dynes s cm^{-5} m^2 ($p < 0.001$); LVMI:158 ± 50 vs 176 ± 47 g.m-2 (NS).

In Gr I, but not in Gr II, we found a significant correlation between LVMI and PResI ($r = 0.65$). LVMI was independent from other analysed variables. Gr I PResI median was 119 – for pts with PResI < 115 (40th percentile) LVMI = 128 ± 27 and for those with PResI > 124 (60th percentile) LVMI = 184 ± 66 ($p = 0.03$).

Conclusions: PResI correlates with LVMI in pts with smaller sized BMAP. This is perhaps related to the influence of LVM in LV outlet flow dynamics, particularly in pts with smaller LV outflow tracts. The way LVM contributes to the magnitude of protheses resistance concept deserves further investigation.

P2926 Benefit of exercise training in patients with valve protheses and chronic heart failure

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In patients with chronic heart failure, exercise training improves ventilation and exercise capacity, but training programme has some particularities in patients with valvular disease. We studied the efficiency of exercise training in patients with valve protheses.

We evaluated 46 patients with mechanic valves (18 mitral, 23 aortic, 5 mitral and aortic; 29 males, 17 females; 54 ± 7 years old) 2 months after replacement of heart valves, with similar clinical features: left ventricular ejection fraction < 40%, NYHA class II-III, in relatively stable condition. In random order 23 patients underwent 12 weeks of conditioning by exercising (Group A) and 23 patients underwent 12 weeks of activity restriction (Group B). 4 patients in Group A and 2 patients in Group B did not complet the study. All patients performed six-minute walk test and cardiopulmonary exercise test before and after 12 week period. Exercise training protocol consisted of "interval training" (120 s work/60 s recovery) using mixed isometric and isotonic exercises at a maximum heart rate corresponding to 80% of maximum oxygen uptake (or at level 15 – hard – according to the Borg scale) 30–45 minutes, 3 times a week. Symptomes from daily activities were assessed by "Minnesota Living with Heart Failure Questionnaire" (score 0–105) and by the dyspnea-fatigue index (DFI) (score 0–12).

	6-min walk (m)	VO_2 max (ml/kg/min)	Minnesota	DFI
Baseline				
Group A	338 ± 36	14.8 ± 1.6	64 ± 12	6.5 ± 1.9
Group B	327 ± 38	13.9 ± 2.3	59 ± 16	6.3 ± 1.4
p value	NS	NS	NS	NS
Final evaluation				
Group A	405 ± 31	18.2 ± 2.3	36 ± 18	9.2 ± 1.4
Group B	342 ± 26	15.2 ± 2.1	54 ± 14	6.9 ± 2.1
p value	<0.01	<0.01	<0.001	<0.05

No major medical incidents occurred during the training programme. Patients with aortic protheses had a greater exercise performance than patients with mitral protheses. We noticed a good correlation between maximal oxygen uptake and distance ambulated during six-minute walk test ($r = 0.71$, $p < 0.001$).

In conclusion, exercise training is of great importance for the increase of effort capacity and quality of life in patients with valve protheses and chronic heart failure.

P2927 Medium-term left ventricular mass index and systolic function after stentless aortic valve replacement

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Background: The haemodynamic benefits of stentless aortic valve replacement (AVR) to the early improvement of left ventricular (LV) function is increasingly recognised. The medium term results, however, remain to be fully defined.

Methods: 140 patients (80 males, age at AVR: 72 ± 6 yr, 40% with Co-CABG) undergoing AVR using a Freestyle stentless valve (valve size 23 ± 2 mm) and with sinus cardiac rhythm were studied from 0.5 month to up to 4 years afterwards. LV ejection fraction (LVEF, %), mass index (LVMI, g/m^2), and mean pressure gradient of stentless valve (mPG, mmHg) were determined by echocardiography. Systemic blood pulse pressure (PBP, mmHg) was also measured.

Results: A total of 540 echoes were analysed, data were shown in mean ± SD.

	0.5 mth	6 mths	1 year	2 years	3 years	4 years
PBP	63 ± 20	63 ± 20	71 ± 25*	77 ± 22*	83 ± 23*	83 ± 26*
LV EF	56 ± 17	61 ± 14	63 ± 14*	64 ± 13*	64 ± 12*	65 ± 14*
LV MI	141 ± 60	116 ± 38*	109 ± 40*	110 ± 41*	114 ± 43*	116 ± 36*
mPG	8.4 ± 5.1	5.2 ± 3.1*	5.4 ± 3.6*	5.9 ± 3.8*	6.3 ± 4.3*	6.4 ± 4.5*

*: different from that of 0.5 mth by 95% CI.

In conclusion: The regression of LV MI and improvement of LV EF were achieved within 6–12 months after AVR, and both then remain stable up to 4 years even though pulse pressure had gone up significantly. Such a sustainable LV rehabilitations in elderly AVR patients may partially be attributed to a very low mPG of the stentless valve.

P2928 Magnetic resonance imaging after prosthetic heart valve replacement, safety and potential hazards

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Because of its potential diagnostic usefulness, nuclear magnetic resonance imaging (MRI) is performed in increased numbers of examinations in patients after cardiac valve replacement. Therefore, the purpose of the present study was to determine potential hazards in NMR imaging by the effects of strength static magnetic fields or radiofrequency pulses for prosthetic heart valves and the patient himself.

Seventeen different common prosthetic heart valves (12 technical valves and 5 tissue valves) were evaluated using an 1.5Tesla high field MRI-System (Siemens Magnetom Vision) in a well established model. The heart valves were suspended by a 35 cm suture. Deflection force was monitored by visual inspection looking for angular deviation and rotation about the suture line. Heat production was measured by submerging each valve in 40 ml of 1/1-electrolyt solution. in plastic containers. The containers were set in a Styrofoam block to isolate and separate each other. In the 1.5T-magnet, the block was imagined twice using a turbo spin echo (TSE) with repetition time (TR) of 5200 ms, echo time (TE) of 138 ms, flip of 180 degree, swap PA and LR and total imaging time of 10 minutes and 30 seconds. To determine heat production, the temperature of each electrolyt solution in the containers was measured just before and immediately after MR-imaging using a digital thermometer.

The examinated cardiac valve prostheses demonstrated no significant deflection in the 1.5 Tesla magnet. This means, that no significant force was exerted on the heart valve prostheses. No significant temperature increase was observed after MR-imaging.

In summary, the presented study demonstrated for the examinated valves no additional hazards to patients undergoing magnetic resonance imaging after cardiac valve replacement. There is no evidence contraindicating MR-imaging for patients with one of the examined prosthetic valves.

P2929 Low molecular weight heparin versus unfractionated heparin after mechanical heart valve replacement

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Low Molecular Weight Heparins(LMWH) are widely prescribed in Cardiology but almost no data are available on LMWH anticoagulation of patients with mechanical valve prostheses.

Methods: we performed a retrospective analysis of anticoagulation in the postoperative period after heart valve replacement with mechanical prostheses. Anticoagulation with either unfractionated heparin (UH) or LMWH was left to physician preference with a recent increase of LMWH use. Subcutaneous UH (500 UI/kg/day, 3 times daily) was adjusted according to aPTT and enoxaparin (100 UI/kg/12 hours) was controlled with antiXa activity. Oral anticoagulation was started before hospital discharge.

Results: 198 patients were treated (106 with UH vs 92 with LMWH) after aortic (75%), mitral (14%) or double (11%) valve replacement. There were no differences between the 2 treatment groups according to age (57 yrs), sex (69% men), weight, atrial fibrillation (19%), heart failure (11%), prior ischemic stroke (3%), renal failure, echocardiographic left atrial size and left ventricular function, and models of prostheses. There were more diabetes ($p = 0.017$) and more coronary disease ($p = 0.0006$)in the LMWH group. The mean duration of LMWH treatment was 13.2 ± 0.8 days (mean ± esm)with a mean antiXa activity of 0.8 ± 0.05 U. There were no death, no prostheses thrombosis and no thrombocytopenia in the whole population. One ischemic stroke occurred (UH group). There were 4 major bleedings (2 in each treatment group).

In conclusion, LMWH anticoagulation appears feasible after mechanical heart valve implantation. However, time has come now for large randomized trials evaluating this new strategy of anticoagulation in patients with mechanical prostheses.

P2930 Plasma brain natriuretic peptide levels correlate with clinical and cellular markers of cardiac function in patients undergoing surgery for mitral valve incompetence

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The poor outcome in patients undergoing surgery for chronic mitral regurgitation (MR) is partly due to previously undetected left ventricular (LV) impairment. Plasma BNP may be useful as a screening tool for asymptomatic LV dysfunction. We investigated the functional and cellular correlates of BNP concentrations in patients undergoing mitral valve repair/replacement (MVR).

Methods: Fourteen patients with chronic non-rheumatic isolated MR had pre-operative BNP measurement and myocardial oxygen consumption (MVO_2) assessment. MVO_2 was expressed both as an absolute value and as a percentage of predicted (%P). At the time of operation, an epicardial biopsy was taken and ventricular myocytes enzymatically isolated. These were then superfused and electrically stimulated at 37°C (1 Hz, 2 mM Ca^{2+} or 0.2 Hz, maximum Ca^{2+}) and contraction monitored.

Results: Patients were aged 38–76 (mean 60.1 ± 2.8) and NYHA: 0/I 9, II/III 5. BNP levels were raised in 13 patients, mean 23.2 ± 6.2 pmol/L,(2.5–54.8) Normal range = 1.6–4.7 pmol/L. MVO_2 levels ranged 13.4–44.4 ml/kg/min (24.5 ± 2.8) with%P 51–137 (85.8 ± 9.0). BNP inversely correlated both to MVO_2 ($p < 0.01$, $r^2 = 0.45$), and%P ($p < 0.02$, $r2 = 0.40$). Contractile myocytes were obtained in 11 patients. Time-to-50% or 90% relaxation (R50, R90) was slowed compared to previous control patients at both 2 mM and max Ca^{2+} and BNP was significantly correlated with R50 ($p < 0.03$, $r2 = 0.50$) and R90 ($p < 0.01$, $r2 = 0.60$) at max Ca^{2+}.

Conclusion: BNP correlated significantly with both clinical (MVO_2) and cellular markers of reduced LV function (impairment of relaxation in isolated myocytes). BNP may therefore be a useful indicator of LV function in patients with MR and may have important implications for the timing of surgery in the future.

VALVULAR HEART DISEASE – EPIDEMIOLOGY AND PROGNOSIS

P2931 The natural history of asymptomatic severe aortic stenosis

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Recent studies have reported a rapid progression and poor outcome of asymptomatic severe aortic stenosis (AS) independent of age, sex, and other risk factors. These findings raised the question of recommending early elective surgery in these patients. To evaluate whether such an approach is justified and to identify predictors of outcome, we followed 128 asymptomatic or mildly symptomatic pts (69 F, 59 M; age 59 ± 19 yrs) with severe AS who had an echocardiographic examination in 1994. The AV-Vel. was 4.5 ± 0.6 m/s. By August 98 follow-up was 98.4% complete. 22 patients underwent surgery within 90 days although remaining asymptomatic based on the decision of their primary care physician. The remaining 106 patients had a Kaplan-Meier event-free survival, with end points defined as death (n = 8) or aortic valve surgery (n = 67), of 67 ± 4% at 1 yr, 59 ± 4% at 2 yrs, and 32 ± 4% at 4 yrs. CAD, diabetes, mitral annulus calcification were not independent factors of outcome. Outcome was not significantly related to sex, hypercholesteremia, or hypertension. However, age was a highly significant predictor of outcome: for pts 50 yrs old or younger, event-free survival was 94 ± 4% at 1 yr, 85 ± 6% at 2 yrs, and 63 ± 9% at 4 yrs compared with 73 ± 5%, 59 ± 5%, and 23 ± 5%, respectively, for pts older than 50 yrs ($p < 0.0001$). Even after 10 yrs, 52% of the pts younger than 50 years were followed for 5 to 10 years without developing symptoms. 8 patients died, of whom 6 had a cardiac death. 5 of these patients had developed significant symptoms (3 refused surgery, 1 died on the waiting list and 1 had an end-stage cancer). 1 sudden death occurred. Thus, this study confirms that, in pts with hemodynamically significant AS, it is safe to delay surgery until symptoms develop. In particular, pts younger than 50 years may remain free of symptoms or adverse events for many years. Considering that aortic valve replacement does not represent a cure in this disease, the recommendation of early elective surgery does not appear to be justified in these pts.

P2932 Persistent left ventricular hypertrophy after aortic valve replacement for isolated aortic stenosis: implications on morbidity and mortality

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Background: In longstanding aortic stenosis [AS], left ventricular hypertrophy [LVH] is a common compensatory response of the left ventricle to increased wall stress. LVH itself increases the stiffness of the myocardium and impairs its relaxation, leading to diastolic dysfunction. After aortic valve replacement [AVR], regression of LVH is expected. The impact of persistent LVH after AVR on morbidity and mortality has not been assessed.

Methods: We retrospectively collected clinical, angiographic and echocardiographic data about patients undergoing AVR for isolated AS. For inclusion, echocardiographic measurement of left ventricular muscle mass had to be performed *at least six month after AVR*. As endpoints, all-cause mortality, cardiac-related morbidity (dyspnea NYHA IV, angina pectoris CCS IV, myocardial infarction, pulmonary embolism, valve replacement, major haemorrhage) and their combination were assessed. Patients were classified into three categories (without LVH [No-H], with persistent LVH [P-H] and with a muscle mass above the 75th sex-specific percentile [MAX-H]).

Results: Of 212 patients (141 men, 71 women), 99 patients (62 men, 37 women) had persistent LVH. During 1967 years of follow-up, 36 deaths (26 men, 10 women) occurred. In *univariate analysis* P-H and MAX-H were associated with increased dyspnea on exertion, angina pectoris and decreased quality of life, assessed by a questionnaire (all $p < 0.05$) and only MAX-H had a significant effect on mortality ($p = 0.01$). A multivariate Cox proportional hazards model (for survival) and multivariate logistic regression (for morbidity) showed (NS: $p > 0.1$, **bold:** $p < 0.05$):

	All-cause mortality	Cardiac-related morbidity	Combined Endpoint
P-H	NS	2.21 (0.90–5.41)	NS
MAX-H	NS	2.08 (0.88–4.86)	2.29 (0.98–5.36)
Age at AVR	*1.85 (1.39–2.47)*	NS	NS
Coronary artery disease	*3.36 (1.31–8.62)*	*2.34 (1.12–5.06)*	2.08 (0.98–4.40)
Current smoking	*4.81 (1.73–13.4)*	NS	NS
	Hazard Ratio (CI)	Odds Ratio (CI)	Odds Ratio (CI)

Conclusions: Persistent LVH itself has no independent effect on survival after AVR, but by impairing diastolic function, it is likely to account for cardiac-related morbidity (dyspnea on exertion, angina pectoris, history of myocardial infarction).

P2933 Aortic stenosis: parameters determining short- and medium-term prognosis after surgery

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We reviewed the population of patients (pts) referred to this centre for pure aortic stenosis who had aortic valve replacement (AVR) between 1989 and 1998, aiming to determine which clinical parameters influence perioperative evolution and post-discharge prognosis. The evaluated parameters were: age, gender, complaints of dyspnoea (NYHA class > 2), angina or syncope, presence of diabetes mellitus, left ventricular shortening fraction (LVSF) and peak (Pgrad) and mean (Mgrad) transvalvular gradients determined by echocardiography, presence of coronary artery disease (CAD) on angiography, prosthesis implanted and the complexity of the surgical procedure (concomitant bypass grafting (AVR+CABG) or aortic annulus widening (AoAW)). Population: 305 pts (44% female, 56% male), aged 23 to 85 y (65.1 ± 10.7 y). At the time of surgery 44.7% of pts referred dyspnoea (NYHA class 3 or 4), 29.8% angina and 26% syncope. Average gradients were Pgrad = 91.8 ± 27.3 and Mgrad = 60.5 ± 19 mmHg and LVSF = 35.1 ± 10.6%. Significant CAD was detected in 29.3% of pts and 7.8% had diabetes. 5%(16) were operated on as emmergencies due to refractory angina or heart failure (HF).

Results: types of prostheses implanted were: mechanical (42%); biological (36.4%), homografts (16%) and Ross procedures (5.6%); AVR+CABG in 25.5% of pts and AOAW in 3.6% cases (10 female/1 male). Peri-operative mortality (POPM) was 6.6%. The only factor that influenced POPM was age ≥ 75 y ($p < 0.01$), NYHA class >2 reached marginal significance ($p = 0.06$). Mean in-hospital stay (IHS) was 13.5 ± 11.9 days (IHS ≤1 day was excluded). Duration of IHS was more prolonged for pts ≥ 75 y ($p = 0.01$), diabetics ($p = 0.03$), LVSF ≤ 25% ($p < 0.01$) and AVR+CABG ($p = 0.03$). Mean follow-up for discharged pts was: 3.05 ± 2.69 y (0.044 to 9.875 y) with 7.86% total mortality (information was obtained in 98% of the population). Less than 1% of pts were re-operated on and 2.3% were admitted for suspected infective endocarditis. Mechanical prostheses presented a longer survival than biologicals ($p = 0.01$, after correction for age).

Conclusion: parameters (HF, LVSF, Pgrad/Mgrad, CAD/CABG) traditionally associated with severity and prognosis of aortic stenosis did not influence peri-operative mortality nor medium-term prognosis, bearing their weight in the duration of IHS. Age was a very important prognostic determinant both in and out of hospital. Mechanical prostheses have a better long-term prognosis.

P2934 Complex ventricular arrhythmias and cardiac death in mitral valve prolapse: results of a ten-year prospective follow-up

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Major complications in Mitral Valve Prolapse (MVP) can be predicted by some clinical and echocardiographic parameters. While palpitations are common in these patients (p) the prevalence of arrhythmias has been variously reported and their prognostic role still needs to be clarified.

Methods: 104 consecutive p with MVP (diagnosed using strict M-Mode and 2D echocardiographic criteria) underwent a 24-hour Holter monitoring at enrollment and were prospectively followed-up for a mean of 127 ± 61 months. Mean age was 38 ± 18 years, 51(49%) were males. Complex atrial and ventricular arrhythmias were present in 6 p (6%) and in 22 p (22%), respectively.

Results: During the follow-up 22 MVP-related major complications occurred in 20 p (17:mitral surgery; 5:cardiac death) (2.0 per 100 patient/years). Cardiac deaths were: sudden (2), due to pulmonary oedema (2) and to cerebral embolism (1). At the univariate analysis overall complications resulted significantly associated with age ($p = 0.007$), male gender ($p < 0.05$, OR = 3.0), presence of a moderate-to-severe mitral regurgitation ($p = 0.002$, OR = 8.6), left atrial ($p < 0.001$) and left ventricular ($p < 0.001$) enlargement; only left chamber enlargement resulted independently correlated at a multiple logistic regression. Cumulated complex arrhythmias showed a weak correlation ($p = 0.05$; OR = 2.8) with overall complications; significance was higher if death only was tested ($p = 0.018$, OR = 12.3). At multiple logistic regression they resulted as the unique independent predictor for death (cumulated complex arrhythmias: $p = 0.049$; complex ventricular arrhythmias: $p = 0.038$).

Conclusions: This prospective ten-year follow-up confirm the previously reported association between some clinical/echocardiographic parameters and overall complications in MVP and seems to confere to complex ventricular arrhythmias a potential role in detecting p at risk of cardiac death.

P2935 Patients with rheumatic mitral stenosis in sinus rhythm show a prothrombotic state and fibrinolytical disfunction

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Patients with chronic atrial fibrillation have a hypercoagulable state with impaired fibrinolytic function. The aim of our study was to analize if patients with rheumatic mitral stenosis in sinus rhythm have also these abnormalities in the hemostatic markers.

Methods: Tissue type plasminogen activator (tPA), its inhibitor (PAI-1) levels as fibrinolytic markers, and D-dimer (D-D) and modified antithombin III (ATM) levels, as prothrombotic markers, were measured in 24 patients with mitral stenosis in sinus rhythm (SR) and were compared with those found in plasma of 18 patients with rheumatic atrial fibrillation (AF) and 20 healthy subjects. None of them had received anticoagulation therapy. Transthoracic echocardiography was made. Results are expressed as median and 25th–75th percentiles. Statistical analysis was performed by non parametric tests

Results: There were no differences in the severity of mitral stenosis or left atrial diameter between patients in SR or AF.

	SR	AF	Controls
tPA (ng/ml)	2.30 (2.04–2.72)	1.78 (1.43–2.78)	2.92 (1.41–4.80)
PAI-1 (ng/ml)	28.5 (15.5–53.0)	45.9 (24.4–58.9)	7.3 (5.6–9.2)*
DD (ng/ml)	517.8 (272.2–861.9)	550.6 (292.9–737.9)	12.5 (7.2–31.5)*
ATM (ng/ml)	12.1 (8.0–27.2)	30.0 (21.3–152.3)	10.1 (8.2–12.6)*

*$p < 0.05$ between controls and SR or AF groups

Even in those patients of SR group without dilated left atria (diameter ≤ 45 mm), 10 patients, showed an increase in the PAI-1, DD and ATM levels ($p < 0.05$). These increases take more relevant in patients with dilated left atria.

Conclusions: Patients with mitral stenosis in sinus rhythm show also a prothrombotic state and high plasma levels of PAI-1 as those patients in atrial fibrillation, even without left atrial dilatation.

P2936 The "benign mitral leaflet syndrome": how benign is it, and is surgery warranted?

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Background: Patients with mitral regurgitation and absent or minimal symptoms are considered at low risk. The benefit of early surgery in this syndrome has never been directly confirmed.

Methods: To address this issue, we analyzed 340 consecutive patients in NYHA class I or II with MR due to flail leaflets diagnosed between 1980 and 1994 and considered as surgical candidates.

Results: At 10 years the incidence of death or heart failure was overall 52 ± 4%. After the Echo diagnosis of flail, 68 patients (20%) underwent mitral valve surgery within 3 months (Early_S group, 61 ± 13 years, 75% Males), and 272 were conservatively managed (Cons group, 66 ± 12 years, 75% Male). Early_S group at 10 years experienced a lower incidence of death or heart failure than the Cons group (33 ± 10 vs 56 ± 4%, P = 0.004). Moreover, multivariate analysis adjusting for age and ejection fraction and baseline predictors of death and heart failure showed early surgery to be independently associated with a lower incidence of the combined end-point of death or heart failure (adjusted Hazard Ratio [95% C.I] = 0.46 [0.23–0.89], P = 0.02).

Conclusions: These data demonstrate that the "benign mitral leaflet syndrome", i.e. mitral regurgitation due to flail leaflets with no or minimal symptoms, 1) develop a high incidence of death or heart failure, and 2) suggest that in these patients an early surgical treatment is associated with an improved outcome despite the "benign" presentation.

P2937 Frequency components of heart rate variability signal in patients with syncope and mitral valve prolapse

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The aim of our study was to assess the relationship between symphatho-vagal balance as a ratio of low to high frequency components of heart rate variability spectrum and occurrence of syncope regardless of its causative factor among patients (pts) with mitral valve prolapse MVP.

Methods: we studied a group of 62 pts (47 females and 15 males), mean age 38.3 years with primary MVP confirmed by echocardiography.Diagnosis of MVP was established according to Perloff's major criteria.The pts were divided in two subgroups: those with syncope in last year (defined as a spontaneously transient sudden temporary loss of consciousness associated with a deficit of postural tone) and those without syncope. The control group consisted of 36 healthy people without any changes in echocardiographic examination, well chosen in relation to age, sex and body surface. Spectral analysis of heart rate variability with the aid of a computerised system using FFT method from 15-minute ECG recordings was performed. All patients, in a drug-free state and a control group, were examined in the same conditions between 08:00 and 10:00 a.m. after half-hour rest. We compared the ratio of amplitude of low frequency component (LF 0.05–0.15 Hz) to high frequency component (HF 0.15–0.4 Hz) (LF/HF).

Results: There were no significant differences in left atrial and left ventricular dimension between subjects with MVP and syncope and those without syncope. Also presence of significant mitral regurgitation in both groups was similar. Comparisons between mean values of LF/HF ratios in MVP subgroups with and without syncope and between control group is shown below (table).

Table

Group	n	LF/HF (mean ± SD)	p value
MVP with syncope	32	0.72 ± 0.37	
MVP without syncope	30	0.48 ± 0.31	0.007*
control group	36	0.47 ± 0.29	0.003**, 0.9***

*MVP with syncope vs MVP without syncope, **MVP with syncope vs control group, ***MVP without syncope vs control group

Conclusions: Patients with MVP and syncope have relatively higher component of low frequency HRV spectrum in relation to the control group and pts with MVP without syncope. It suggests that these pts have increased stimulation of sympathetic nervous system.

P2938 Incidence and prognostic meaning of mild periprosthetic leaks detected early after valve surgery by transesophageal echocardiography

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Leaks with severe regurgitation usually require surgical correction. On the contrary, little is known about the most appropriate management and prognosis of leaks with mild and subclinical regurgitation. Aim of this study was to assess the incidence of mild periprosthetic leaks detected early after valve surgery by echocardiography and their prognostic meaning in a mid-term follow-up.

Methods: 98 consecutive patients (pts) (61 males, 37 females, mean age 58 ± 8 years) underwent transthoracic (TTE) and transesophageal (TEE) echocardiography within 20 days (mean 14) after valve surgery. After echocardiography, all pts entered a follow-up program to assess subsequent mortality and morbidity.

Results: Among the 98 pts, there were 15 mitral and 12 tricuspidal valve repairs (VR) and 57 aortic, 44 mitral, 1 tricuspidal prosthetic valves (PV); of the 102 PV, 87 were mechanical and 15 biological. Leaks with mild regurgitation were detected in 12 (12.2%) pts at TTE and TEE (8 at TEE only): 7 were in mitral (5 PV, 2 VR) and 5 in aortic site (5 PV). After a follow-up period of 20 months (range 12–31), the following prespecified end-points were observed: cardiac death in 6 (6.1%) pts and non-fatal adverse clinical events (re-intervention, cerebral or peripheral embolism, severe gastrointestinal hemorrhage, severe hemolytic anemia) in 12 (12.2%) pts. 4 of the echocardiographic and clinical variables tested at univariate analysis had a statistical correlation with the end-points considered and were then tested in a multivariate model. Results are shown in the table.

Univariate and multivariate analysis

	Cardiac Death		Non-fatal Events	
	p univ.	p multiv.	p univ.	p multiv.
Leak	0.15	ns	0.0058	0.001
LVEF≤40%	0.06	0.05	ns	ns
LVEDD > 55 mm	0.13	ns	ns	ns
Tricuspidalization	0.13	ns	ns	ns

Conclusions: TEE early performed after valve surgery detected mild and subclinical periprosthetic leaks in 12.2% of the pts, with a better sensitivity than TTE. Only LVEF was predictive of cardiac mortality; however, leak presence was associated with a significantly higher incidence of non-fatal adverse clinical events, independently of other risk markers.

P2939 Preoperative effective regurgitant orifice area is a strong predictor of long-term outcome in patients undergoing surgery for chronic mitral regurgitation

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Background: Post-operative LV dysfunction after chronic mitral regurgitation (MR) can be predicted by left ventricular size and function, but these variables are only partially reliable for prediction of LV dysfunction or survival. The purpose of the study was to explore the additional value of doppler echocardiographic parameters to identify patients at risk of development of long term postoperative death or LV dysfunction.

Methods: We prospectively evaluated 112 patients (p), (mean age: 62 ± 7 years; 64% male) with organic MR, using transthoracic echocardiography. Baseline ejection fraction (EF) was 58 ± 8%; 82% of p had myxomatous degenerative disease. Fifty-seven p underwent mitral valve (MV) repair (50.9%) and 55 p MV replacement (49.1%). The following parameters were analyzed: LV volumes and diameters, left atrial diameter, regurgitant fraction, regurgitant volume, effective regurgitant orifice area (ERO) and pulmonary systolic pressure.

In order to identify those variables predicting EF < 50% and/or late mortality (combined end-point), we performed univariate analysis and a Cox regression model multivariate analysis, after controlling for the effects of age, gender, atrial fibrillation, New York Heart Association functional class, history of congestive heart failure, type of surgery, etiology, concomitant coronary artery disease and vasodilator treatment.

Mean follow-up was 25 ± 12 months.

Results: Forty-four p (38%) had EF < 50% and 14 p (12.5%) died during follow-up. The reported cut-off point value for the different variables was based on the receiver operating curve (ROC) plotted against the primary end-point. The area of the ROC curve of the ERO for prediction of events was 0.85 (SE 0.056) with a likelihood ratio for a cut-off point of 0.55 cm^2 = 6.2 (CI 95% 2.3–12.5). Kaplan Meier analysis showed a significant difference between survival curves of both groups (p value < 0.001 log rank test). Multivariate analysis identified ERO > 0.55 cm^2 (hazard ratio: 4.7, CI 95%: 2.3–7.8; p < 0.0001); end-systolic diameter > 4.5 cm (hazard ratio: 2.2, CI 95%: 1.2–3.8; p < 0.02) and EF < 60% (hazard ratio: 2.0, CI 95%: 1.1–3.7; p < 0.04) as independent predictors of outcome.

Conclusion: In patients undergoing MV surgery for organic MR, ERO is a strong independent predictor of late ventricular dysfunction or mortality and adds to known prognostic variables such as left ventricular size and function.

P2940 An echocardiographic analysis of the relation between degenerative changes of cardiac valves with aging and their dysfunction in non-rheumatic adult subjects

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Purpose: Although rheumatic fever had been a primary etiology of valvular heart failure, importance of degeneration, sclerosis and calcification with aging is increasing as a cause of valvular diseases in the elderly in the developed countries. We echocardiographically analysed the relation between valvular deformity, especially, its calcification and valvular diseases in the elderly.

Methods: The mitral and aortic valves were assessed by two-dimensional and Doppler echocardiography in 726 serial adult subjects (average of age; 66.8 ± 13.5 y/o) without congenital heart disease, myocardial infarction, rheumatic valvular disease, or cardiomyopathy. We analysed sites of valvular calcification, pressure gradient across the valve, and degrees of valvular regurgitation in three age groups (middle age group; less than 65 y/o (221 subjects, 50.8 ± 11.6 y/o), old group; 65 to 75 y/o (302 subjects, 69.4 ± 2.8 y/o), super old group; 75 y/o or more (203 subjects, 80.4 ± 4.5 y/o)).

Results: The incidence of aortic valvular calcification was increasing with age (middle age group; 21.3% (47/221), old group; 52.0% (157/302), super old group; 65.5% (133/203), middle age group vs old group; $p < 0.001$, old group vs super old group; $p < 0.01$). In old and super old groups, single calcification of noncoronary cusp of the aortic valve was most frequent (29.0%), followed by calcification of all the three cusps (23.8%). Aortic valvular calcification had statistically significant relation with the presence of aortic regurgitation ($p < 0.01$) or aortic stenosis ($p < 0.01$), and the degree of aortic regurgitation ($p < 0.01$). Seventeen cases of middle age group (7.7%), 52 cases of old group (17.2%) and 49 cases of super old group (24.1%) showed the mitral valvular calcification. The incidence became higher with age (middle age group vs old group; $p < 0.005$, old group vs super old group; $p < 0.05$). Single calcification of posterior leaflet of the mitral valve was 47.5% (56/118), while that of anterior leaflet was less frequent (30.5%, 36/118). The incidence of mitral valvular calcification was higher in women than in men in only old group. Mitral valvular calcification was also related to the presence of mitral regurgitation ($p < 0.01$), mitral stenosis ($p < 0.01$), or atrial fibrillation ($p < 0.02$).

Conclusions: These results suggest that valvular calcification with aging can increase the incidence of valvular diseases and atrial fibrillation, which may result in heart failure in the elderly.

P2941 A prospective investigation of the prevalence of anorexigen induced valvular disease in 353 patients

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Background: Dexfenfluramine and Phentermine-fenfluramine use for weight loss has been previously associated with increased prevalence of valvular heart disease. This association was based on a small number of patients, no control population, and limited data on dose and duration of therapy. Our study involved 353 obese subjects enrolled in a prospective, strict weight loss, research protocol from September 1994 to September 1997.

Methods: All subjects underwent transthoracic echocardiography for significant valvular lesions within a mean of 121 days from the manufacturer's announcement of the withdrawal of fenfluramine and dexfenfluramine. All echocardiograms were interpreted by two independent readers.

Results: The study population included 292 females and 61 males with a mean age of 46.5 ± 9.1 years and mean starting body mass index of 40.1 ± 7.8 kg/m^2. Using the FDA criteria for significant valvular disease, aortic regurgitation was detected in 21 subjects (5.9%) and mitral regurgitation in 3 subjects (0.9%). Only one patient had significant regurgitation of both aortic and mitral valves. No patients had 3+ or 4+ regurgitation. Significant valvular disease did not correlate with the dose or duration of Dexfenfluramine or Phentermine-fenfluramine therapy. There was no statistically significant difference in the prevalence of valvular disease when compared to the patients in the Framingham study who were similar in regards to age, gender, and geographic location.

Valvular Regurgitation

	No regurg	trace regurg	1+ regurg	2+ regurg
Aortic	263 (74.5%)	69 (19.5%)	18 (5.1%)	3 (0.8%)
Mitral	117 (33.1%)	198 (56.1%)	35 (9.9%)	3 (0.8%)
Tricuspid	135 (38.2%)	205 (58.1%)	13 (3.7%)	0 (0.0%)
Pulmonic	274 (77.6%)	76 (21.5%)	3 (0.8%)	0 (0.0%)

regurg = regurgitation

Conclusions: Anorexigen therapy is associated with a low prevalence of significant valvular regurgitation. Valvular regurgitation in our subjects may reflect age-related degenerative changes. Late valvular abnormalities from the use of Dexfenfluramine and Phentermine-fenfluramine await long-term, prospective studies.

ARRHYTHMIA MECHANISMS

P2942 Decremental conduction property in human infarcted ventricular myocardium: correlation with histology

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Decremental properties have been used for risk stratification in patients with hypertrophic cardiomyopathy. The mechanism of decremental conduction in diseased myocardium is unknown. In this study we attempted to elucidate the mechanism of decremental conduction in human infarcted ventricular myocardium.

Methods: We performed high-resolution epicardial mapping (247 terminals, interelectrode distance 0.3 mm) at three left ventricular sites of an explanted human infarcted heart during Langendorff perfusion. Basic (600 ms) and premature stimuli (from 500 ms down to the refractory period) were applied several mm away from the edges of the electrode. Histology of subepicardial layers was correlated with electrophysiology.

Results: Histology showed substantial fibrosis at one recording site but not at the other two. Activation patterns during propagation transverse to the fiber direction were more irregular than during longitudinal propagation. Marked delay was observed in the area with substantial fibrosis during transverse propagation. The activation delay as a function of coupling interval was integrated (s^{-2}) for each series of premature stimuli, and was greatest during transverse propagation in fibrotic tissue (table).

Integrated delay ($\times 10^{-3} s^{-2}$)			P	N	
(1) Transverse	1.44 ± 0.45	<0.05	<0.001	0.74	4
(2) Longitudinal	0.75 ± 0.22	–	<0.001	<0.01	4
(3) Transverse + Fibrosis	5.15 ± 0.59		–	<0.05	2
(4) Longitudinal + Fibrosis	1.56 ± 0.08			–	2
	Compared with	(2)	(3)	(4)	

Conclusion: Decremental conduction in human infarcted ventricular myocardium was mainly caused by propagation transverse to the fiber orientation in the area with substantial fibrosis.

P2943 A new index of cardiac vagal tone assessed in the West of Scotland Coronary Prevention Study population

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Background: The West of Scotland Coronary Prevention Study involved 6,595 men, aged 45–64 years on entry, with moderately raised cholesterol who were randomised to placebo or Pravastatin 40 mg daily and followed for 5 years. The primary end-point was coronary heart disease death or non-fatal myocardial infarction. This study group was used to assess a new ECG based index of cardiac vagal tone (CVT).

Methods: All study ECGs were analysed by automated methods. From the baseline ECG, minor changes were defined as moderate amounts of ST depression and/or T wave inversion. CVT was measured by phase demodulation of pulse synchronised delays in RR intervals available from 8 seconds of ECG. 6,281 subjects with ≥4 RR intervals excluding SVES or VES were included. Hazard ratios were derived from both univariate and multivariate Cox proportional hazard models.

Results: The CVT index was skewed (mean 5.55 ± 3.93; 96% range 1.0–17.2) and so log (CVT) was assessed. Univariately for the primary endpoint, (i) for an increment of 0.5, log (CVT) had a hazard ratio of 0.89 (CI 0.82–0.95: $P = 0.0011$); (ii) quartiles 2, 3 and 4 of log (CVT) had increasing levels of risk (0.78, 0.71, 0.61) with respect to quartile 1; (iii) those with CVT ≤ 3 had a hazard ratio of 1.44 (CI 1.17–1.77: $P = 0.0005$) compared to those with CVT > 3. Multivariately, in 2 models involving (i) log (CVT) plus only ECG variables (rate, QT, minor ECG changes), or (ii) log (CVT) plus only clinical variables (treatment, diastolic BP, smoking, etc.), log (CVT) was not independently predictive in each case. Similar results were obtained for all cause mortality.

Conclusion: These data indicate that, even with a standard resting 12-lead ECG recording, information of clinical value relating to cardiac vagal tone can be obtained by analysing heart rate variability.

P2944 Significance of ventricular fibrillation complicating acute myocardial infarction in the thrombolytic era

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Several studies performed in the prethrombolytic era (PTE) showed that ventricular fibrillation (VF) complicating AMI carries high early mortality. We compared the incidence and short- and long-term outcome of primary VF (1°VF) and secondary VF (2°VF) in the hrombolytic era (TE) and the PTE.

Methods: A prospective, nationwide survey of 3321 consecutive pts admitted with AMI in all CCUs in Israel during Jan.–Feb. of '92 and '96 (TE), compared with a previous Israeli study of 5839 AMI pts (SPRINT Registry) in 1981–83 (PTE).

Results: *1° VF:* In the TE the baseline characteristics of pts with 1°VF (n = 85) were comparable to their reference group without 1°VF (n = 2326). The crude and multivariate adjusted 30-day (4.8 vs. 5.0%; OR = 1.01, 95% CI 0.30–2.54) and the 1-yr mortality rates (11.0 vs. 8.0%; HR = 1.46, 95% CI 0.74–2.86) of both groups were similar. The incidence of 1°VF in the TE and PTE (2.6% vs. 2.0%) was similar. The 30-day (4.8 vs. 21.0%; OR = 0.19, 95% CI 0.05–0.60) and the 1-yr mortality rates (11.0 vs. 24.4%; HR = 0.42, 95% CI 0.19–0.93) of 1°VF pts were significantly lower in the TE vs. the PTE.

2° VF: The baseline characteristics of pts with 2°VF in the TE (n = 43) were comparable to their reference group without 2°VF (n = 725). The 30-day (51.2 vs. 14.6%; OR = 6.62, 95% CI 3.44–12.80) and the 1-yr mortality rates (58.1 vs. 26.6%; HR = 3.32, 95% CI 2.17–5.09) of 2°VF pts were significantly higher. The incidence of 2°VF in TE was significantly lower than in the PTE (1.3% vs. 2.5%, $p < 0.01$). The 30-day (51.2 vs. 58.3%; OR = 0.63, 95% CI 0.27–1.46) and the 1-yr mortality rates (58.1 vs. 67.4%, HR = 0.77, 95% CI 0.48–1.25) of 2°VF pts in the TE and the PTE were similar.

Conclusions: 1) In the TE, the outcome of pts with and without 1°VF complicating AMI was similar. Although the incidence of 1°VF in the TE and the PTE did not change, the outcome of 1°VF pts in the TE improved. 2) In pts with 2°VF, their outcome in the TE was significantly worse than in counterparts without 2°VF. Although the incidence of 2°VF in the TE declined, the outcome of 2°VF pts in the TE did not change despite recent advances in AMI pts management.

P2945 1B ventricular fibrillation depends on critical cellular coupling in the isolated regionally ischaemic pig heart

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Introduction. Ventricular fibrillation during the 1B phase of acute ischemia (1B VF) is associated with the occurrence of cellular uncoupling. We hypothesized that a critical amount of cellular coupling is required for the induction of 1B VF, and that progression of uncoupling terminates the substrate for 1B VF.

Methods. Pig hearts (n = 12) were Langendorff perfused with blood and the left anterior descending artery was ligated to produce ischemia. We recorded epicardial and intramural electrograms at 105 sites in 3 pigs. In 9 pigs attempts to induce VF were undertaken repetitively with up to 3 premature stimuli (PS) (twice diastolic threshold current pulses of 2 ms duration). Tissue impedance was measured with the four electrode technique, difference between baseline and final values is expressed as relative Rt rise (dRt).

Results. Before coronary occlusion VF could be induced in 0/9 pigs with 3 PS, after ischemia VF could be induced in 8/9 pigs repetitively from 17.0 ± 9.1 min (mean ± SD) up to 55.1 ± 11.4 min. dRt was 0.12 ± 0.09 at the start and 0.54 ± 0.21 at the end of the 1B phase. At dRt up to 0.4, VF inducibility was maximal, VF in 8/9 pigs ($p < 0.001$ vs control). VF was inducible in 4/9 pigs at dRt 0.5 ($p = 0.07$ vs dRt < 0.4, p = NS vs control). At dRt exceeding 0.5, VF induction ranged between 5/8 and 3/9 pigs. At the start of the 1B phase, intramural electrodes showed signs of activation in 48 ± 18% whereas epicardial sites were excitable in 97 ± 5% ($p = 0.01$). At 50 minutes ischemia, 4 ± 3% of intramural sites were excitable vs 22 ± 16% of the epicardial sites (p = NS).

Conclusions. 1B VF is inducible during a distinct period in time, determined by dRt < 0.4 and coincides with a difference in number of excitable sites between epicardial and transmural sites. This study suggests that 1B VF depends on a critical degree of coupling, and that coupling between subepicardium and midmyocardium might play a key role in the genesis of these arrhythmias.

P2946 Ventricular late potentials in myotonic dystrophy: correlation with CTG trinucleotide repeat length

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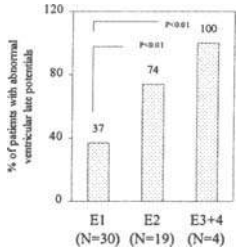
Myotonic dystrophy (MD) is the most common dystrophy in adults characterised by multiple systemic effects. Cardiac involvement is frequent and is manifested as an impairment of the conducting system. Nevertheless, in these patients there is a high incidence of sudden death not always attributable to a conduction block. Spontaneous ventricular tachycardia was also reported raising the possibility that ventricular arrhythmias play a major role in the mortality of patients with MD. Abnormal ventricular late potentials (LP), caused by slowed and fragmented conduction through damaged areas of myocardium, represent a substrate for malignant reentrant ventricular arrhythmias. The aim of the study was to further evaluate the relation between the myocardial involvement, assessed by LP positivity, and DNA analysis. Forty-two MD patients (21 females and 31 males) entered the study. The severity of skeletal muscle involvement was scored as mild (n = 32), moderate (n = 13) and severe (n = 7). An inverse correlation between age at disease onset and CTG expansion ($r = -0.37$, $p < 0.05$) was observed. The subjects were classified into 3 subgroups on the basis of the number of CTG trinucleotide (MD mutation) repeat expansions: $E_1 = 30$ pts. with 0 to 500 CTG repeats; $E_2 = 19$ pts. with up to 1,000 repeats; $E_{3+4} = 3$ pts. with equal or more than 1,500 repeats. Twenty-eight out 52 patients (54%) showed abnormal LP. Sex, age of disease onset, skeletal muscle involvement did not significantly discriminate these patients from remain sample. A significant positive trend between the presence of abnormal LT and number of CTG repeats (figure, $p < 0.01$) was observed. In particular, a significant difference between prevalence of abnormal LP between E1 and E2 groups ($p < 0.01$) was detected indicating that CTG expansion more than 500 repeats is related to a substantial myocardial involvement.



Our findings suggest that in patients with myotonic dystrophy the LP-molecular correlation could provide additional information regarding the morbidity and prognosis in these patients. Prospective study is planned to better understand the predictor value of abnormal late potentials in survival of this kind of patient.

P2947 Mental stress and sudden cardiac death? From anecdote to electrophysiological basis

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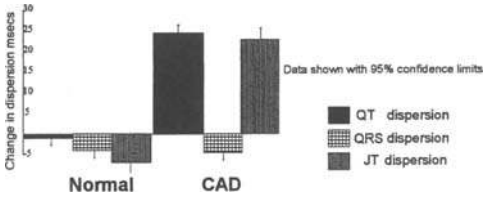
Sudden cardiac death (SCD) remains a significant cause of mortality among patients with coronary artery disease (CAD): most deaths are arrhythmic. The association between acute psychological stress and SCD is largely anecdotal. Psychometric testing has been shown to induce psychological stress and regional ischaemia in patients with CAD. Using this technique we have examined the propensity for mental stress to influence QT dispersion (dispersion of repolarisation), JT dispersion (dispersion of action potential duration) and QRS dispersion (dispersion of conduction) in patients with and without CAD. 12 lead ECGs were recorded during psychometric testing from which QT, JT and QRS dispersion were measured. QT dispersion increased in patients with CAD (n = 14) (change = 25 msecs) ($p < 0.001$) but not in those with normal coronaries (n = 7). The increase in QT dispersion occurred by virtue of an increase in JT dispersion ($p < 0.0001$) rather than QRS dispersion.



Psychological stress increases QT dispersion (reflecting JT dispersion) in patients with CAD but not in normal subjects. These findings could be explained by an inhomogeneity of repolarisation secondary to regional ischaemia and provide a link between stress and arrhythmia.

P2948 Analysis of human right atrial conduction properties and velocities during atrial flutter determined by non-contact mapping

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Characterisation of the complex relationship between right atrial anatomy and function may give further insight into the mechanisms and aetiology of human atrial flutter (AFL).

Methods and Results: A non-contact mapping system was used to map the right atrium (RA) of 12 patients (pts) with a history of AFL. The system was used to generate an anatomically based "virtual" endocardial model (VE) onto which reconstructed electrograms were superimposed producing isopotential maps. The Cartesian co-ordinates of points on the VE were used to calculate the tricuspid annulus-inferior vena cava isthmus (IS) length and the CV of the AFL wavefront within the IS, and either side of the crista terminalis (CT) delineating smooth from trabeculated RA. IS was anatomically defined by locator signal labelling of anatomical landmarks using fluoroscopic guidance and the entrance and exit of the IS defined as a distinct narrowing and re-expansion of the mapped wavefront during AFL. The CT was defined as a line of conduction block located in the lateral RA with craniocaudal activation on one side and caudocranial activation on the other. In 1 pt the IS could not be clearly defined and in another a line of block could not be seen in the lateral RA. Ten pts had counter clockwise and 2 had clockwise AFL. The IS length was 50 ± 24.27 mm (mean ± SD) and CV was 0.78 ± 0.35 m/s (range 0.34 to 1.7 m/s). CV was similar for the smooth and trabeculated RA being 1.16 ± 0.48 m/s and 1.22 ± 0.65 m/s respectively ($p = 0.67$). Smooth RA CV was faster than isthmus CV ($p = 0.045$) but trabeculated RA CV was not ($p = 0.06$).

Conclusion: Non-contact mapping has demonstrated that conduction velocity within the IS can be significantly slower than other portions of the RA but that IS conduction velocity varies considerably between pts.

P2949 Initiation of sustained monomorphic ventricular tachycardia originating from the right ventricular outflow tract: sympathetic versus parasympathetic tone activity

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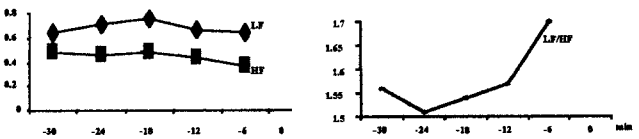
The relation between autonomic nervous system (ANS) activities and genesis of ventricular tachyarrhythmias is well known. Changes in frequency domain measures of heart rate variability (HRV) preceding the onset of ventricular tachycardia (VT) associated with ischemic heart disease are reported. VT arising from the right ventricular outflow tract (RVOT) is facilitated to occur when sympathetic nervous system is increased, but the role of sympathovagal balance assessed by HRV in the genesis of VT of this particular type has not been thoroughly analysed yet. This study aimed to assess the ANS activity during the last few minutes preceded the onset of episodes of sustained VT originating from RVOT.

Methods: Six pts (2 M, 4 F, 41 ± 8 years) with sustained idiopathic VT, originating from RVOT were enrolled in the study, and underwent a 3 channel 24 hour Holter monitoring (Marquette 8000, 5.8) in a drug free state. We evaluated the ANS activity using spectral analysis of HRV. We measured the normalised units (nu) of power spectrum in the low frequency (LF) (0.008–0.15 Hz) and high frequency (HF) (0.15–0.40 Hz) and the ratio LF/HF of 6 min intervals over a 30 min period before the onset of VT. Twenty episodes of sustained VT from the six recordings formed this study.

Results: The power spectrum in the HF were: 0.47 ± 0.06 nu for the period of 30-24 min and 0.37 ± 0.04 nu for the period of 6-0 min before the onset of VT ($p < 0.05$). There were no differences in the LF in between these periods. The ratio LF/HF was 1.56 ± 0.1 for the period of 30-24 min and 1.7 ± 0.17 for the period of 6-0 min before VT ($p < 0.05$). Therefore, the increase in the LF/HF is caused largely from a decrease in the HF without any significant change in the LF.



Conclusions: There is a significant change of the sympathovagal balance during the period preceding the onset of sustained VT, originating from RVOT. These changes of the autonomic influence on the heart are mainly resulted from decreased vagal activity rather than enhanced sympathetic drive to the myocardium.

P2950 The assessment of cardiac sympathetic innervation in patients with arrhythmogenic right ventricular dysplasia

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Arrhythmogenic right ventricular dysplasia (ARVD) affecting primarily the right ventricle is clinically characterized by ventricular arrhythmias and/or even sudden cardiac death in patients with no apparent heart disease. Metaiodobenzylguanidine (MIBG) scintigraphy is able to demonstrate the disruption of myocardial sympathetic innervation of the left ventricle. The aim of this study was to evaluate the significance of myocardial sympathetic dysfunction in 10 patients (9 men, mean age 40 ± 14) with ARVD. The diagnosis of ARVD was made by clinical history (9 patients had documented sustained VT, 1 survived sudden cardiac death due ventricle fibrillation), echocardiography, angiography of right ventricle and MRI, electrophysiological study was performed in all patients. Ischemic heart disease was excluded by coronary angiography. All ten patients had normal ejection fraction of left ventricle. The uptake of iodine-123 MIBG was measured as the heart/mediastinum activity ratio 4 hours after isotope administration (H4/M4 index). 123I-MIBG SPECT (single photon emission computed tomography) and thallium-201 SPECT was performed to demonstrate abnormal distribution of MIBG. A group of 10 patients with supraventricular arrhythmias without structural heart disease served as a control group.

Results: H4/M4 index was 1.87 ± 0.31 in ARVD group, and 2.38 ± 0.35 in control group ($p < 0.003$). Thus eight of ten patients with ARVD showed reduced uptake of 123I-MIBG. The abnormal areas were located predominantly in posterior and posteroseptal segments of the heart. The greatest defect was detected in survivor of sudden cardiac death despite of normal ejection fraction of left ventricle. 201 TI-SPECT was normal in all ten patients.

In conclusion: This data suggest that I123-MIBG scintigraphy allows detection of depressed sympathetic innervation of left ventricle in ARVD patients and may be helpful in assessing of the extent of the disease.

P2951 Sport activity in young athletes with documented arrhythmogenic right ventricular disease: which recommandations?

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This study reports the outcome of sport practice in 26 top-level athletes who were referrred for Arrhythmogenic Right Ventricular Disease (ARVD). Diagnosis was based on the criteria of the ESC task-force.

Patient population consisted of males, mean age 29.6 ± 7.8 years, participating in sport competition (cycling: n = 13; running, n = 8; football, n = 3; basketball: n = 1; and rugby, n = 1) with a training time ≥ 10 hrs per week. All pts complained of exercise related symptoms including syncope or near-syncope in 18. Spontaneous sustained VT could be documented in 8.

After ARVD diagnosis pts were recommended to stop all competitive activities and were treated by beta-blockers. After a mean follow-up (FU) time of 5.3 ± 4 years the actual sport status was assessed by questionnaire in the 25 survivor pts. Sport competition was actually stopped in 24 pts. Only 1 pt (racing cyclist) continued and suffered aborted sudden death during competition 3 years after diagnosis. 7 pts (30.4%) definitively resumed sport. Surprisingly the other 16 pts still have regular sport practice of 3.5 ± 2.4 hrs a week. The type of sport stayed the same for all pts, but intensity and duration had decreased. None of these pts experienced further arrhythmic events during FU with optimized medical or non pharmacological (ablation: n = 4; ICD: n = 1) treatment.

These date are consistent with the conclusions of the 26-th Bethesda Conference recommending that "athletes with ARVD don't participate in any sport in competition". Nevertheless, this study suggests that pts with controlled arrhythmias may continue sport practice of low intensity, under condition of regular cardiovascular control.

P2952 Influence of ventricular stimulation and stimulation site on coronary flow and flow reserve

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To assess the influence of ventricular stimulation and stimulation site on coronary flow and flow reserve 14 consecutive patients were studied. All patients were selected for pacemaker implantation because of symptomatic sick-sinus-syndrome. All had sinus rhythm with normal intraventricular conduction (QRS complex ≤ 120 msec). Intra coronary flow and flow reserve was measured using an intracoronary Doppler flow wire at baseline and during maximal hyperemia using adenosine i.c. All patients had normal coronary arteries. Intracoronary Doppler flow velocity (CF) and coronary flow reserve (CFR) was measured in the LAD and CX coronary artery during inherent rhythm (IR) and during stimulation in the right ventricular apex (RVAP) and outflow tract (RVOT). Pacing was performed in the VDD mode; and AV delay was adjusted 2–5 msec shorter than the AV delay of IR.

		IR	RVAP	RVOT
LAD	CF	21 ± 5	22 ± 6	23 ± 6
	CFR	3.2 ± 0.8	2.5 ± 0.7*	2.0 ± 0.7*#
CX	CF	15 ± 5	17 ± 6	17 ± 7
	CFR	2.8 ± 0.7	2.4 ± 0.6	2.5 ± 0.6

* $p < 0.05$ compared to IR; # $p < 0.01$ compared to RVAP and IR.

Conclusion: ventricular stimulation is associated with impaired coronary flow reserve in the LAD. Right ventricular apex stimulation resulted in a higher flow reserve as compared to outflow tract pacing.

P2953 Comparison of effects of anodic versus cathodic pacing on ejection fraction through in ovo pacing of the chick embryo heart

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Background: Anodic stimulation is not classically used to pace the heart because 1) stimulation threshold is higher and 2) refractory period is shorter and could facilitate arrhythmias. Anodic stimulation has regained interest in the emerging era of multisite pacing as in biventricular pacing for heart failure or biatrial pacing for prevention of atrial arrhythmias. Very few experiments were performed in the past to compare anodic to cathodic stimulation and almost none were designed to measure potential haemodynamic modifications.

Methods: We used an experimental setup developed in our laboratory, allowing to study cardiac volume modifications of a chick embryo heart under various pacing modes. Through a microsurgical opening of the thoracic wall, two fine isolated platinum electrodes were placed in ovo over the heart of stage 21 chick embryos. The pacemaker was set to 125% of the intrinsic heart rate at 2 time the diastolic threshold amplitude of the anodic mode. After 2 minutes of control recording, one minute period of either cathodic or anodic stimulation followed. End diastolic (EDV) and end systolic volumes (ESV) were derived from computerized image analysis; stroke volume (STV) and ejection fraction (EF) were calculated accordingly.

Results: In all five cases, EDV, ESV and STV were significantly lower under pacing as compared to sinus rhythm. The heart volume was even more decrease by anodic pacing as compared to cathodic pacing, but EF was unchanged.

Conclusion: The observed differences between pacing and control corresponds to well known observations, the added modification induce by anodic as compared to cathodic stimulation warrants further investigation of this problem. It is concluded that anodic and cathodic stimulation have different effects on LV function and that more investigations has to be done to characterize the properties and understand the intracellular mechanisms of the anodic stimulation that should be considered for further optimizing cardiac stimulation.

P2954 The activation of platelet function, coagulation and fibrinolysis during radiofrequency catheter ablation in heparinized patients

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Catheter ablation may be complicated by clinical thromboembolism in about 1% of patients.

Methods: We studied the activation of coagulation (prothrombin fragment 1+2 (PF1+2)), platelets (beta-thromboglobulin (b-TG)) and fibrinolysis (plasmin-antiplasmin complexes (PAP) and D-dimer) during RF ablation in 13 patients. They received heparin 100 U/kg i.v. after the initial electrophysiological study, prior to the delivery of RF current; thereafter 1,000 U/hour throughout the procedure.

Results: PF1+2 increased fourfold ($p < 0.001$) during the diagnostic study, but gradually declined to upper reference value during heparin administration. There was a strong correlation between procedure duration prior to heparin bolus (range 39–173 min.) and a) maximal rise of PF1+2 ($r = 0.83$, $p < 0.001$) and b) increase of PF1+2 from baseline to end of procedure ($r = 0.74$, $p = 0.004$). There was no correlation between post-heparin changes of PF1+2 and a) post-heparin procedure duration (range 40–317 min), b) number of RF pulses (range 1–16) or c) RF current duration (range 46–687 s). Plasma b-TG concentration showed similar trends. Fibrinolytic activity increased moderately from baseline until heparin administration; then remained around the upper reference values. PAP at the end of procedure and D-dimer at the time of heparin administration both correlated with pre-heparin procedure duration ($r = 0.70$, $p = 0.007$ and $r = 0.69$, $p = 0.01$, respectively). All parameters were normal the next morning.

Conclusion: Procedure duration prior to heparin administration, and not the delivery of RF current per se, determines activation of hemostasis and fibrinolysis during RF ablation. This study supports the use of heparin in right-sided as well as left-sided procedures.

P2955 Reduced radiation exposure during cardiac electrophysiologic procedures

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During cardiac electrophysiologic (EP) studies including catheter ablation procedures, radiation exposure is a serious issue for both patients and operators.

Methods and Results: Since 1996, we took various measures to reduce X-ray exposure. Originally, our biplane fluoroscopy system was 12.5 Hz pulsed in the RAO and continuous in the LAO direction. With an annual load of 170 catheter ablation procedures and 100 diagnostic investigations, the total depth dose of all operator badges was 7.4 mSv per month as measured over a 1.5-year period. In July 1996, two measures were taken. 1) First, both X-ray beams were extra filtered with 0.3 mm copper plus 2 mm aluminum to reduce the amount of soft radiation. This resulted in a slight but for EP procedures acceptable reduction of image quality. Measurements with tissue-equivalent phantom models, however, showed a threefold reduction of skin dose. 2) The second measure was the introduction of the LocaLisa system to allow for real-time non-fluoroscopic display of mapping/ablation catheter positions. In the ensuing 9 months, total badge readings of all operators combined decreased to 1.4 mSv per month, while the annual number of catheter ablation procedures increased to 220. Thereafter, 2 additional measures were taken. 1) The lateral fluoroscopy was upgraded from the continuous to the 12.5 Hz pulsed mode. 2) A lead glass screen was installed to protect the operator against scattered radiation. During the ensuing 11 months, these last 2 measures resulted in a further reduction of the total of all badge readings to 0.3 mSv per month, while the annual number of catheter ablations increased to 250.

Conclusions: Adequate measures resulted in a 25 fold reduction of operator radiation exposure. The use of extra copper-aluminum filters for the reduction of soft radiation alone is an easy measure to achieve an estimated threefold reduction of radiation exposure during cardiac electophysiologic procedures.

P2956 Radiofrequency catheter ablation using a multipolar irrigated-coiled electrode catheter: in vivo studies assessing the induction of linear lesions

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The induction of continuous linear lesions is prerequisite for successful radiofrequency (RFC) ablation of atrial flutter and fibrillation. Ablation catheters with multiple coiled electrodes seems to be a good tool for it. However the risk for coagulum formation with these electrodes is increased. Irrigation of the coils might reduce this risk. A novel 7 F ablation catheter with 4 irrigated-coiled ablation electrodes (electrode length: 6 mm; interelectrode distance: 2 mm; Medtronic, USA) was investigated in 7 anesthetized sheeps. Irrigation of the electrodes was achieved via 4 holes at both edges of each electrode (10–15 ml/min). The skin over the thigh muscle was incised and raised to form a cradle which was superperfused with heparinized blood (37°C). The catheter was placed along the muscle with standardized 10g contact pressure. RFC energy was delivered sequentially between each ablation electrode and a skin patch for 90 seconds with a power of 10, 20, 30 or 40 Watt (W) respectively. The width and depth of the 87 induced lesions was compared between the different power levels: (*$p < 0.05$ vs. 20 W) Lesions were continuous in all cases except those achieved with 10 W RFC pulses. Coagulum formations were not observed following any RFC delivery.

	10 W (n = 12)	20 W (n = 16)	30 W (n = 31)	40 W (n = 28)
Width (cm)	0.24 ± 0.06	0.82 ± 0.22	0.77 ± 0.14	0.98 ± 0.02
Depth (cm)	0.14 ± 0.07	0.47 ± 0.13*	0.74 ± 0.13*	0.75 ± 0.16*
Continuity	3/12 (25%)	16/16 (100%)	31/31 (100%)	28/28 (100%)

(*$p < 0.05$ vs. 20 W)

Conclusions: Continuous linear lesions could be induced using irrigatied-coiled RFC ablation electrodes with a power of 20–40 W. Lesion depth of more than 0.7 cm developed already with a power of 30 W. Coagulum formation were not observed using power up to 40 W.

P2957 Differences in dual av nodal properties between men and women

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A discontinuous antegrade AV nodal conduction curve (Dual AVN) is a common finding during electrophysiologic studies (EPS). Females are more common in patients referred for catheter ablation of AV nodal re-entry tackycardias (AVNRT). The objective of this study was to determine if Dual AVN was a more frequent finding among women than among men in patients referred for EPS, excluding patients with AVNRT.

Methods: 80 consecutive patients undergoing EPS due to other causes than AVNRT were evaluted. AV nodal conduction curves were determined at two different pacing rates with both single and double extrastimuli with 10-msec decrements.

Results:

	No	Jump	%	FPERP	SPERP	Window
Female	34	20	59	321	248	73
Male	46	28	61	327	292	35
					p = 0.0040	p = 0.0096

FPERP: fast pathway effective refracory period; SPERP = slow pathway effective refractory period

Conclusion: No gender difference in the occurrence of Dual AVN was found. Women, though, have a significantly shorter SPERP, resulting in a wider window (FPERP-SPERP). This increases the possibility that a premature atrial depolarisation results in retrograde activation of the right atrium through the fast pathway and to initiate AVNRT. This finding might be one part of the explanation why AVNRT seems to be more common among women than among men.

P2958 Does gender differ in ventricular repolarization and in response to dofetilide (an I_{Kr}-blocker) in isolated rabbit Purkinje fibres?

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Woman are known to have a longer QT-interval than man and an increased propensity toward drug-induced "torsades de pointes" (TdP). However, little is known about these gender differences in isolated cardiac tissues. In the present study, we evaluated potential gender differences in the ventricular repolarization in isolated rabbit Purkinje fibers using microelectrode.

Methods: Isolated rabbit Purkinje fibers were perfused in Tyrode solution containing K^+ 4.7 mM and at 37.5 °C in a condition of a normal rhythm (1 Hz) as well as in a extreme bradycardiac rhythm (0.2 Hz) with and without dofetilide (1×10^{-M}).

Results: Female Purkinje fibers (n = 10) tended to have a longer duration of the action potential at 90% repolarization (APD_{90}) than male ones (n = 10): 345 ± 13 ms (mean ± SEM) versus 289 ± 18 ms at 1 Hz (p = 0.047); 611 ± 57 ms versus 449 ± 51 ms at 0.2 Hz (p = 0.06), respectively. Dofetilide (1×10^{-8} M) tended to increased more APD_{90} in female Purkinje fibers (n = 10) than in male (n = 10): 638 ± 39 ms versus 431 ± 64 ms at 1 Hz at 20-min after the infusion (p = 0.02), and 800 ms versus 746 ± 37 ms at 0.2 Hz at the end of 25-min infusion (p = 0.07), respectively. Furthermore, dofetilide (1×10^{-8} M) resulted in a higher incidence of early after depolarizations in female Purkinje fibers than in male ones during 0.2 Hz (100% versus 50%; p = 0.03).

In Conclusion: we conclude that female Purkinje fibers have longer ventricular repolarizations and a higher risk for drug-induced early afterdepolarizations in a slow stimulation rate than male ones. This may contribute to gender difference in QT-interval and to female being a more prone than man to develop drug-induced TdP.

P2959 "Asynchronized" autonomic decline occurs in middle-aged men, not in women

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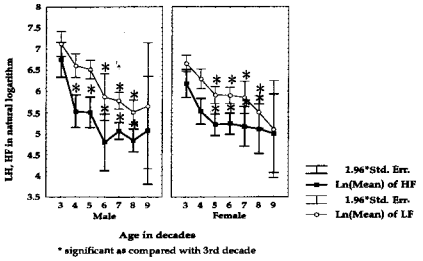
Many investigators had shown us that decline in autonomic activities was a naturally aging process. However, the different patterns of the autonomic decline between males and females were not well delineated.

Methods: We carried out power spectral analysis of heart rate variability in 685 healthy, random, eligible subjects (M:F = 408:277, aged 57.75 ± 15.89 years old). We assumed high frequency power (HF, 0.15 ~ 0.4 Hz) to stand for parasympathetic activity and low frequency power (LF, 0.04 ~ 0.15 Hz) for sympathetic activity. The LF/HF ratio stood for balance in sympathetic and parasympathetic activity. The baseline data were not different in males and females. We divided subjects into 7 age groups. We applied an ANOVA test to see the aging effect on decline of LF, HF, and LF/HF.



Results: Both age and gender did not influence LF/HF. Age influenced LF and HF significantly. A post hoe analysis disclosed both LF and HF decreased significantly at fourth decade in women. However, in men, LF decreased significantly at fifth decade and HF at third decade (graph).

Conclusion: There exists an asynchronized autonomic decline in men but not in women. The significance remained to be determined.

P2960 Electrophysiological effects of combined block of the rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier potassium current: potential for excessive prolongation of cardiac repolarization

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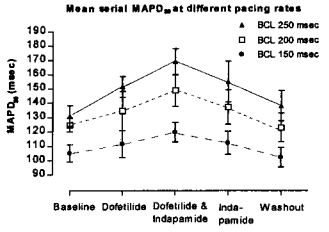
The rapid component of the delayed rectifier potassium current (I_K), I_{Kr}, is the target of most drugs that prolong repolarization. Electrophysiological effects resulting from combined block of I_{Kr} and the slow component of I_K, I_{Ks}, still need to be characterized. Studies in isolated, buffer-perfused guinea pig hearts (n = 15) were undertaken to compare lengthening of cardiac repolarization ($MAPD_{90}$) under conditions of I_{Kr} block alone (dofetilide (dof.)), I_{Ks} block alone (indapamide (ind.)), or combined block of I_{Kr} and I_{Ks}. Measurements were taken at basic pacing cycle lengths (BCL) of 250, 200 and 150 msec. Sequential perfusions with dof., dof./ind. and ind. showed significant increases in $MAPD_{90}$ versus baseline after isolated dof. or ind. perfusion at BCL 250 and 200 msec. A further significant rise versus isolated drug perfusions of combined dof./ind. was seen at BCL 250 and 200 msec. At BCL 150 msec only combined dof./ind. caused a significant increase in $MAPD_{90}$ (figure).



Rate-dependent decreases in $MAPD_{90}$ from BCL 250 to 150 msec were not significantly different during the different perfusions (20% decrease at baseline, 26% after dof., 29% after dof./ind. and 27% after ind.).

Conclusions: 1. Combined I_{Kr} and I_{Ks} block may lead to excessive lenghtening of cardiac repolarization and can predispose to proarrhythmia. 2. Reverse-use dependence is maintained in the presence of combined I_{Kr} and I_{Ks} block.

P2961 ST-T variation assessment with a multilayer perceptron network

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Alternans measurements are expressed by a single value. In order to assess the utility of multidimensional variation measurement for categorization, we performed a feasiability study on CAD patients and healthy subjects. High-resolution beat-to-beat ECG's (16 bit, 1000 Hz) were recorded from 51 healthy volunteers (age 24 ± 4.2 ys) without any structural heart disease and no cardiac risk factors and 44 patients (age 61 ± 8.8 ys) with coronary heart disease, a history of myocardial infarction and inducible sustained ventricular tachycardia (>30 s). Microvariability measurement of the ST-T-signal was based on 250 consecutive sinus beats per individual.

ST-T microvariation was measured from the vector of standard deviations of the amplitude of corresponding points of the ST-T-signal. A window of 400 ms starting from the QRS-off point was analyzed. Prior to the quantification of variability, the beats were preprocessed to suppress the main electrical waveform by subtracting each beat from its cubic spline smoothed version. A multilayer perceptron neural net was trained using conjugate gradient descent with line search. Different training runs with variing number of hidden neurons (range: 3–8) were performed. The optimal net consisted of 400 inputs, 3 hidden neurons and 2 output neurons. The network performance using leaving-one-out was (%):

Accuracy	Sensitivity	Specificity	PPV	NPV
81.1	75.0	86.3	82.5	80.0

We conclude that multidimensional ST-T variation assessment gives classification results equivalent to other noninvasive tests. The main advantage of the multilayer perceptron is its capability of forming arbitrary decision boundaries without prior knowledge. The independence of an exact determination of T-wave endpoints together with the inclusion of the complete ST-T wave in the decision process, make this a promising new approach.

P2962 Autonomic tone prior to and following episodes of spontaneous, non-sustained ventricular tachycardia

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Spontaneous episodes of non-sustained ventricular tachycardia (NSVT) are preceded by increases in heart rate variability (HRV) in the frequency domain. On the contrary, a decrease in HRV has been observed before episodes of sustained ventricular tachycardia (VT), though results are conflicting. In an attempt to further elucidate the role of autonomic nervous system in ventricular arrhythmogenesis, we assessed HRV changes not only before the onset of NSVT but also following its termination.

Methods: A total of 19 patients with structural heart disease were studied. Arrhythmia substrate was coronary artery disease in 7 and dilated cardiomyopathy in 12. All had 24-hour Holter ECG recordings comprising one episode of spontaneous NSVT. Normalized values of low frequency power (LF), high frequency power (HF) as well as LF/HF ratio were used as indexes of autonomic input to the heart. We assessed 24-hour average measures of these HRV indexes and compared them to 1-hour calculations a) prior to NSVT onset and b) following its termination.

Results: LF and HF power were increased relatively to 24-hour values, not only prior to NSVT initiation (44.3 ± 14.9 and 34.7 ± 18.4 vs 32.4 ± 24.0 and 18.3 ± 13.6 respectively, $p < 0.04$ and <0.004) but, also, following its termination (43.8 ± 13.5 and 39.2 ± 22.4 vs 32.4 ± 18.4 and 18.3 ± 13.6, $p < 0.03$ and <0.004). LF/HF ratio prior to and following NSVT remained unchanged relatively to its 24-hour value. No difference was observed in HRV parameters tested 1 hour prior to NSVT and 1 hour after its termination.

Conclusion: An increase in both sympathetic and vagal modulation of the heart exists not only before the onset of NSVT, but also following its termination. This finding might represent protective autonomic activation against the development of sustained VT.

P2963 Circle maps of respiratory sinus arrhythmia patterns: a new method to differentiate cardiac denervation from vagal modulations after atrioventricular node modification

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Respiratory sinus arrhythmia, an indicator of vagal cardiac innervation decreases with age and after AV-node modification (AVNM), both suggesting vagal denervation. We hypothesized that AVNM only modulates parasympathetic ganglia, adjacent to the slow pathway ablation site, whereas aging causes chronic denervation. Circle maps (CMs), a new method of analyzing RSA phase dynamics independent of amplitude dynamics can potentially differentiate between both forms of changes in vagal tone. The Kulback information (KI) quantifies differences in CMs, increased KI indicating decreased vagal innervation.

Methods: 12 young (22 ± 4 y, 8 m, 4 f) and 11 old (58 ± 11 y, 5 m, 6 f) healthy probands underwent 24-hour ECG recording (24-R) and a paced breathing protocol (PBP). 10 consecutive patients (46 ± 19 y, 7 f, 3 m) underwent 24-R and the same PBP before and 1 day AVNM. High frequency bands (HF) and HF/LF ratio were analyzed from 24-R. RSA-Amplitudes (A) were analyzed for spontaneous breathing (SB) and PB. CMs were obtained and differences in cardiac dynamics analyzed with the KI.

Results:

ms	HF ms^2	LF/HF	SB-A	SB-KI	PB-A	PB-A KI
Young	908 ± 98*	2.6 ± 04*	92 ± 37*	0.41 ± 0.03*	230 ± 90*	0.4 ± 0.7*
Old	188 ± 100	3.8 ± 1.5	43 ± 16	0.55 ± 0.07	74 ± 24	0.56 ± 0.09
Pre	696 ± 285	1.8 ± 0.6	53 ± 28+	0.34 ± 0.08	138 ± 74	0.45 ± 0.08
p	287 ± 125*	2.8 ± 1.3*	39 ± 21	0.3 ± 0.08	127 ± 860	0.47 ± 0.09

*$p < 0.05$ compared to pre = before young, AVNM, p = post

Conclusions: In contrast to HF bands, CMs can differentiate between vagal modulation by AVNM and vagal denervation by aging.

P2964 Circle maps of respiratory sinus arrhythmia: a new method to fast and reliably determine autonomic cardiac innervation

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Determination of the autonomic tone is essential for risk stratification in cardiac disease. Respiratory sinus arrhythmia is reliably characterized by mean values of time and frequency domain in the 24-hour ECG. Recordings over a few minutes however, show high intraindividual variability (Var) with decreased reliability. Circle maps (CM), a new method to analyze RSA phase dynamics seperated from amplitude dynamics, allow reliable measurements of autonomic tone within 10 minutes.

Methods: 7 young (24 ± 5 years; 3 f, 4 m) and 9 old (58 ± 9 years; 4 f, 5 m) healthy probands (P) underwent a 10 minute paced breathing protocol three times on different days. RSA during spontaneous (SB) and paced breathing (PB) [7.5 s cycle] was characterized by amplitudes in time domain (RSA-A) and phase dynamics of CMs. The intraindividual differences in information of the consecutive CMs were quantified by the Kulback-Information (KI-CM). The 3 obtained measurements of RSA-A and KI-CM were averaged, the standard deviations (SDs) were expressed as % of the average values and defined as normed SDs. The normed SDs were used as parameter for the Var of RSA-A and KI-CM.

Results:

	RSA-A young P	KI-CM young P	RSA-A old P	KI-CM old P	RSA-A all P	KI-CM all P
SB	23 ± 8	8 ± 6*	23 ± 7	10 ± 4*	23 ± 8	9 ± 3*
PB	18 ± 7	7 ± 3*	18 ± 7	9 ± 3*	18 ± 6	8 ± 3*

Normed SDs *p < 0.05 compared with RSA-A

Var of autonomic tone determined by CM of RSA-patterns issignificantly lower than with RSA-A. PB decreases Var of RSA-A, whereas KI-CM is very reliable both during SB and PB.

Conclusions: CMs of RSA pattern provide a new method for determination of the autonomic tone within 10 minutes. Even short measurements are very robust at PB and SB, as opposed to RSA-A.

P2965 Electrophysiologic effects of partial and complete autonomic nervous system blockade in awake dogs

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Background: The autonomic nervous system plays a major role in arrhythmogenesis. As autonomic influences on repolarization are far from being completely understood we aimed to characterise the electrophysiological effects of sympathetic blockade by means of thoracic epidural anesthesia (TEA) and additional complete pharmacological autonomic nervous system blockade (ANSB).

Methods: In 6 anaesthetized mongrel dogs an epidural catheter and two 6F sheaths in the right jugular vein were percutaneously implanted one day before the electrophysiologic study. Thereafter, in awake dogs two quadripolar monophasic action potential (MAP) catheters were placed in the right ventricle via the sheaths. TEA was performed with lidocaine 0.4 mg/kg through the epidural catheter at the level of Th 2. In the presence of TEA, ANSB was performed by application of propanolol (2 mg/kg), atropine (3 mg/kg), and hexamethonium (20 mg/kg).

Results: No ECG changes were documented in the presence of TEA alone, or both TEA and ANSB. TEA decreased heart rate from 118 ± 24/min at baseline to 108 ± 28/min. Induction of ANSB increased heart rate to 146 ± 31/min. Ventricular pacing thresholds remained constant. TEA resulted in a rate-dependent increase in right ventricular refractory period (RP) (cycle length (CL) 400 ms: +9.7 ± 4%; CL 300 ms +12 ± 2%; CL 200 ms +16 ± 5%). This effect was even more marked after ANSB which led to a 27% and 34% prolongation of RP for CLs of 300 and 200 ms, resp. These changes were paralleled by prolongation of right ventricular MAP duration at 90% repolarization. Thus, no change in postrepolarization refractoriness was observed.

Conclusion: Sympathetic and complete blockade of the ANS prolong repolarization in awake dogs. This may indicate a protective role of blocking the autonomic system with regard to arrhythmogenesis.

P2966 Neurohormonal activation and heart rate variability in cardiovascular diseases

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Neurohormonal activation is reported to accompany various cardiovascular diseases and is believed to contribute to their pathogenesis and complications, including disease progression, arrhythmia and sudden death. In this report, we correlated the hormone profile of 127 "cardiac" patients with their tendency to ventricular arrhythmias.

Methods: We studied 61 patients (pts) with hypertension and left ventricular hypertrophy (LVH), mean age 51 ± 10 yrs (52 ♂, 9 ♀), 42 pts with congestive heart failure (CHF) mean age 62 ± 9 yrs (36 ♂, 6 ♀), and 24 pts with a first acute myocardial infarction (AMI) mean age 57 ± 9 yrs (19 ♂, 5 ♀). We measured plasma renin activity (PRA, ng/ml/hr) arginine vasopressin (AVP, pg/ml), norepinephrine (NE, ng/ml), epinephrine (E, ng/ml), and hemodynamic and functional parameters. We also performed Holter monitoring for arrhythmias, including runs of ventricular tachycardia (VTR) and parameters of heart rate variability (HRV), i.e. SD, SDAN, SDNN and pNN50.

Results: Results are shown in table.

	PRA	AVP	NE	E	SD	SDAN	PNN 50
LVH	1.9 ± 1.8	0.9 ± 7	0.3 ± 1	0.04 ± 0.02	46 ± 15	112 ± 39	6 ± 5
CHF	4.9 ± 6	1.2 ± 9	0.45 ± 2	0.05 ± 0.07	36 ± 10	85 ± 39	3.8 ± 3
AMI	3.3 ± 5	7.7 ± 6	1.15 ± 7	0.2 ± 0.1	50 ± 18	67 ± 28	14 ± 10

PRA levels were higher in CHF vs LVH ($p < 0.005$). AVP levels were higher in AMI vs LVH ($p < 0.0000$) and vs CHF ($p < 0.0000$). NE levels were higher in AMI vs LVH ($p < 0.0000$) and vs CHF ($p < 0.0000$) and in CHF vs LVH ($p < 0.003$). E levels were higher in AMI vs LVH ($p < 0.0000$) and vs CHF ($p < 0.0003$). From HRV parameters SD was lower in CHF vs LVH ($p < 0.05$) and AMI ($p < 0.04$), SDAN was lower in AMI vs LVH ($p < 0.0007$) and in CHF vs LVH ($p < 0.05$) and pNN 50 in CHF vs AMI ($p < 0.0007$) and in LVH vs AMI ($p < 0.0003$). In CHF, PRA levels were correlated with VTR ($r = 0.58$, $p < 0.04$) and NE levels with SD ($r = -0.67$), $p < 0.04$) and E levels with VTR ($r = 0.89$, $p < 0.0002$).

Conclusion: Low HRV parameters (indicating autonomic disequilibrium and propensity to ventricular ectopy) were significantly correlated with high NE and were more pronounced in AMI and CHF. Consistent with this, AMI and CHF had also significantly higher levels of E and PRA, which were significantly correlated with VTR's, in accordance to the known high rates of ventricular arrhythmia and sudden death in these conditions.

P2967 Effect of β-blockade on baroreflex sensitivity and heart rate variability in Ca-channel blocker administered cardiac patients

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While Ca channel blocker (CA) has been used widely in ischemic heart disease patients, who do not necessarily improve the prognosis. Sympathetic activation by CA has been supposed as a possible cause of deterioration of prognosis and beta-blockade has been reported to improve the prognosis in ischemic heart disease patients. However, the precise mechanism of improvement of prognosis by beta-blockade still remains to be elucidated. Baroreflex sensitivity (BRS) and heart rate variability (HRV) serve powerful predictors of cardiac sudden death in myocardial patients. In this paper we studied the effects of beta-blockade (atenorol 12.5–50 mg daily) on BRS and HRV in cardiac patients taking CA. Thirteen cardiac patients were enrolled in this study. Resting supine position ECG was recorded for ten minutes, two hours after the morning administration of drugs. Finger arterial blood pressure (BP) was monitored using Finapres. RR intervals, systolic and diastolic BP were filed in the computer for later analysis. For analysis of 5-min. records, RR intervals were analyzed using FFT to calculate HF power (0.15–0.5 Hz). BRS was estimated by the sequential method. The computer selected all sequences of three or more successive heart beats in which there were concordant increases or decreases in systolic BP (SBP) and RR interval. If the coefficient between SBP value and RR intervals had a value less than 0.92, the data was discarded from the analysis. A linear regression was applied to each of the sequences, and an average regression slope was calculated. This slope represents BRS (msec/mmHg).

Beta-blockade	RR interval (msec)	log (HF)	BRS
OFF	833 ± 89	1.46 ± 0.34	5.31 ± 2.07
ON	1037 ± 111*	1.82 ± 0.46*	8.17 ± 4.73*

meam ± SD, *p < 0.01 Beta-blockade OFF vs. ON

Beta-blockade decreased heart rate and increased HF power and BRS. These beneficial effects on HRV and BRS of beta-blockade might be one of the possible mechanisms of improving the prognosis of ischemic heart disease patients.

P2968 Evidence of three independent inter-atrial conduction systems: observation of the retrograde conduction

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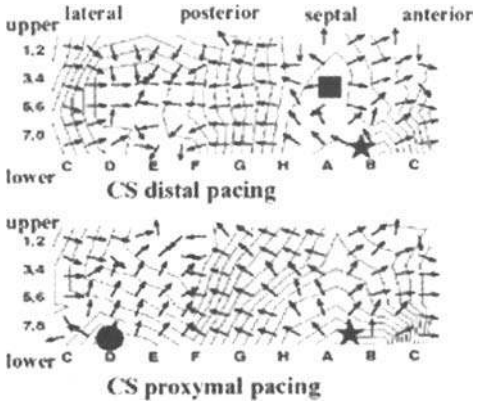
Electrial preferential connections between the right atrium (RA) and left artium (LA) have been suggested to be located at high inter-atrial septum (Bachmann's bundle), low inter-atrial septum and ostium of the coronary sinus. The purpose of this study is to determine these inter-atrial connections based on their retrograde conduction. Twelve patients without structual heart disease were studied. Activation sequence of the RA during coronary sinus (CS) pacing was examined by a standard basket catheter.

Results: The earliest activation of RA during CS pacing was the low inter-atrial septum (IAS) (stars indicated the locations in the figure) in all patients. In 8 of 12 patients, the activation sequence was clearly changed when the pacing site in the CS was moved. The earliest activation was shifted to the high IAS (box in the figure) during CS distal pacing in 6 of 12 patients and to the low lateral RA (circle in the figure) during CS proximal pacing in 4 of 12 patients.



Conclusions: These findings indicate that there are three different retrograde inter-atrial preferential conduction systems in the low IAS, the high IAS and the low CS ostium.

P2969 Site of pacing affects ventricular activation delay after premature stimulation in the explanted human heart

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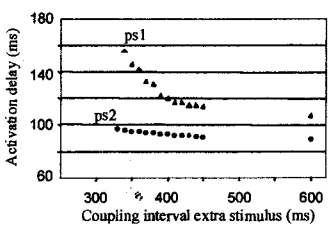
Background: Progressive ventricular activation delay after premature stimulation at a remote site has been used for risk stratification in patients with hypertrophic cardiomyopathy. We hypothesize that decremental conduction properties are present in dilated cardiomyopathy as well and that the site of stimulation importantly affects the amount of decremental conduction.

Methods: In 2 Langendorff perfused human hearts from patients with dilated cardiomyopathy (no antiarrhythmic drugs), ventricular electrical activity was recorded at 194 sites (98 epi- and 96 endocardial sites, homogeneously distributed). Unipolar recordings were made during pacing at different sites with basic (600 ms) and premature stimulation (from 450 ms in steps of 10 ms down to the refractory period). Conduction curves were determined of the main component of the fractionated electrograms.

Results: Conduction curves showed decremental characteristics at virtually all epicardial and endocardial recording sites. Steepest increase of delay occurred for recording sites remote from the site of stimulation. The amount of increase in activation delay was highly dependent on the site of stimulation (see figure).



Conduction curves at one recording site (rs) after stimulation from two pacing sites (ps).

Conclusions: Decremental conduction properties are present in human hearts with dilated cardiomyopathy. The amount of increase of activation delay highly depends on the site of stimulation. The latter has impact when clinically performed conduction curves are used for risk stratification for sudden death.

P2970 What is the impact of a non-diagnostic baroreflex sensitivity measurement on mortality in patients with structural heart disease

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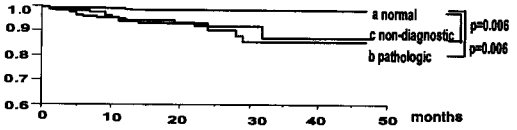
Impaired baroreflex sensitivity (BRS) has been demonstrated to be a valuable method for risk stratification in patients (pts) with structural heart disease (SHD). Though correctly performed measurement of BRS is often non-diagnostic (no correlation between blood pressure and heart rate after norphenephrine administration).

Aim of this study was to evaluate the clinical importance of a non-diagnostic BRS regarding long-term outcome of patients (pts) with SHD. In 634 pts (75% male) measurement of BRS was performed. Mean age was 62 ± 11 years, ejection fraction 38 ± 15%. Organic heart disease was in 82% of pts coronary artery disease, in 14% dilative cardiomyopathy, in 4% others. Follow up was 20 ± 11 months. 17% of pts had diabetes, 37% hypertension. In 481 pts BRS was diagnostic: in 338 pts normal (BRS > 3 ms/mmHg) (a) and in 143 pts pathologic (BRS ≤ 3 ms/mmHg) (b). In 153 pts BRS was non-diagnostic (c).

Results: There were no differences in clinical parameters between pts with normal, pathologic or non-diagnostic BRS. Total mortality was 4.5%. In contrast to pts with normal BRS (mortality 1.5%) mortality in pts with pathologic BRS was 7.7% and in pts with non-diagnostic BRS 7.8%.



Conclusions: 1. In frac14 of pts BRS was non-diagnostic. 2. Mortality in pts with non-diagnostic BRS was as high as in pts with pathologic BRS (7.8% vs 7.7%). 3. A non-diagnostic BRS has the same prognostic impact as a pathologic BRS in pts with SHD.

P2971 Differentiated sympathetic nerve response to acute ACE inhibition in healthy subjects

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Background: In patients with hypertension, enalaprilat reduces blood pressure without provoking a baroreceptor-mediated increase in heart rate, muscle and overall sympathetic nerve activity. The aim of the present study was to explore the cardio-renal sympathetic nerve response to acute inhibition of angiotensin converting enzyme (ACE) in healthy subjects.

Methods: We measured mean arterial pressure (MAP), heart rate (HR), pulmonary capillary wedge pressure (PCW, n = 5), arterial angiotensin II plasma concentration (AII, pg/ml), cardiac (n = 12), renal (n = 19) and total body norepinephrine spillover (TB NE sp, pmol/min) in 22 healthy subjects. The isotope dilution technique was used to estimate overall and cardio-renal sympathetic nerve activity. Arterial, coronary sinus and renal vein blood samples were drawn simultaneously at baseline and 30 min after enalaprilat, given intravenously.

Results and Interpretation: Arterial AII plasma concentration decreased by 28 ± 5% (mean ± SEM, $p < 0.01$) after enalaprilat. Renal NE sp increased by 60 ± 20% ($p < 0.01$), whereas HR, cardiac and TB NE sp remained unchanged after enalaprilat. PCW decreased by 40 ± 28% (ns) after enalaprilat and there was a slight reduction in MAP by 3 ± 2% ($p = 0.05$).

Conclusions: Acute administration of an ACE inhibitor to healthy subjects provokes a differentiated sympathetic nervous response, with a selective increase in outflow to kidneys, whereas cardiac and overall sympathetic nerve activity remain unchanged. This differentiated sympathetic response pattern possibly reflects a central nervous effect by ACE inhibition. Given the effect on salt and water excretion by renal nerve stimulation, the elevated renal sympathetic nerve activity after acute ACE inhibition may have clinical implications.

P2972 Risk stratification after individually optimized therapy of acute myocardial infarction: the role of impaired baroreflex sensitivity

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Methods: In a prospective single center study 365 consecutive patients (pts, mean age 61 ± 12 yrs, 281 male, 84 female) with acute myocardial infarction (AMI, anterior MI 45%) were enrolled after individually optimized acute therapy (acute revascularisation: 87%, aspirin 92%, β-blocker 87%) plus optimised long term treatment (aspirin 88%, β-blocker 81%, ACE-inhibitors 80% and statins 42%). Aim of this study was: which risk indicator (RI) identifies high risk pts best following optimal treatment in the 1990ies? All pts underwent risk stratification at day 7–14. Positive RI were predefined: 1) EF ≤ 40%; 2) Holter ECG positive, if one of the following parameters was positive: a) ≥10 VPB/h, b) ≥4 couplets/24 h, c) ≥1 salves/24 h; 3) late potentials (LP); 4) heart rate variability (HRV) ≤ 75 ms, 5) baroreflex sensitivity (BRS) ≤ 3 ms/mmHg.

Results: The 1-year-mortality in this pt population was 9%. Frequency of RI and pos./neg. predictive values (PPV/NPV) for 1-year-mortality were:

	Incidence	Sensitivity	Specificity	PPV	NPV
EF ≤ 40	30%	50%	72%	15%	94%
Holter positive	21%	50%	82%	19%	95%
LP positive	27%	36%	74%	9%	94%
HRV ≤ 75 ms	13%	19%	87%	16%	93%
BRS ≤ 3 ms/mmHg	24%	50%	78%	16%	95%
EF ≤ 40 + Holter pos	8%	28%	93%	26%	94%
EF ≤ 40 + HRV ≤ 75 ms	5%	6%	95%	10%	92%
EF ≤ 40 + BRS ≤ 3 ms/ mmHg	5%	29%	96%	36%	94%

Conclusions: In the era of acute revascularisation of AMI and adjuvant therapy (including aspirin, betablocker, ACE-inhibitor and statins) high risk pts are best identified by the combination of EF ≤ 40% plus impaired BRS with a PPV of 36%.

P2973 Autonomic cardiovascular regulation in obesity

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Objective: Obese persons suffer from an increased mortality risk supposedly due to cardiovascular disorders related to either continuously lowered parasympathetic or altered sympathetic activation.

Method: Our cross-sectional correlation-study establishes the relationship between obesity and autonomic regulation as well as salivary cortisol levels. Three patient cohorts were sampled, covering ranges of body mass index (BMI) of 27.5 to 32 (n = 17), 33 to 39 (n = 12), and above 40 kg/m^2 (n = 12), and stratified for age, sex, and menopausal status. Patients were assessed by cardiovascular activity (ECG), continuous finger blood pressure, and respiratory activity recorded at baseline and during a stress reaction-time task. Salivary cortisol was concurrently collected. Autonomic cardiovascular regulation was assessed by use of heart rate variability and continuous blood pressure recordings; spectral-analytical calculation yields indices of sympathetic and parasympathetic activation and baro-reflex-sensitivity.

Results: 42 patients (18 males, 24 females (15 premenopausal)) with a mean age of 42.7 ± 9.3 years were included. Contrary to expectation, BMI and waist/hip-ratio (WHR) were inversely related to sympathetic activity. This was true for resting conditions ($r = -0.48$, $p < 0.05$; $r = -0.33$, $p < 0.04$ for BMI and WHR respectively) and for mental challenge ($r = -0.36$, $p < 0.03$ for BMI). Resting baro-reflex-sensitivity was strongly related to the degree of obesity at rest (BMI: $r = -0.42$, $p < 0.03$, waist: $r = -0.43$, $p = 0.01$) and for mental challenge (BMI: $r = -0.54$; $p < 0.001$, waist: $r = -0.47$, $p < 0.01$). Salivary cortisol correlated significantly with BMI ($r = -0.33$, $p < 0.05$).

Conclusions: With increasing weight, no overstimulation was found but a depression in sympathetic and parasympathetic activity together with a significant reduction in baro-reflex functioning and in salivary cortisol levels.

P2974 Modulation of baroreflex sensitivity during physical stress

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Decreased baroreflex sensitivity (BRS) has been shown to be a sign of poor prognosis and to reflect an increased incidence of sudden death in patients with cardiovascular disease. BRS is usually evaluated by administering a vasoactive drug that raises arterial pressure, however, this technique is not always applicable in all clinical situations. We studied the modulation of BRS during physical stress, exercise, and the head-up tilt test (HUT), without infusing drugs.

Subjects and Method: Fourteen normal volunteers (7 males and 7 females, 34.4 ± 10.0 yr) performed the exercise test. Submaximal ramp and 50-watt one-step (7 min) exercises were performed. HUT (80 degree for 15 minutes) was assessed in 20 young subjects (10 males and 10 females), whose age was 29.6 ± 4.8 yr. Blood pressure and ECG were monitored continuously during tests. Finger arterial blood pressure was measured by using Finapres. Oxygen uptake was measured during exercise. To analyze 5-minute records at rest and during physical stress, the computer selected all sequences of three or more successive heartbeats in which there were concordant increases or decreases in systolic blood pressure (SBP) and RR interval. If the correlation coefficient between SBP and RR intervals was less than 0.92, the data were excluded from the analysis. Linear regression was applied to each of the sequences, and an average regression slope was calculated. This slope represents baroreflex sensitivity (BRS msec/mmHg).

Results: BRS was decreased during HUT (19.6 ± 6.6→6.8 ± 3.3, $p < 0.01$). The ratio of oxygen uptake during 50-watt exercise to uptake during peak exercise averaged 56%. BRS was lower during exercise (2.6 ± 1.2) than at rest (8.2 ± 2.7). The rate of reduction of BRS during exercise was highly correlated with the ratio of oxygen uptake during 50-watt exercise to uptake during peak exercise.

Conclusion: BRS is usually assessed in the supine position and modulation of BRS during physical stress has seldom been investigated. BRS is not constant and can be reduced by ordinary physical stress, such as changes in position and an exercise. During exercise, BRS decreased according as exercise intensity increased.

P2975 Right thoracoscopic sympathicotomy increases QT hysteresis during exercise in man

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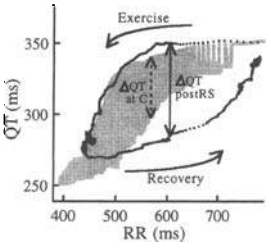
An altered adaptation of ventricular repolarisation to changes in heart rate may play an important role in arrhythmogenesis. Experiments in animals have indicated that right stellectomy might promote arrhythmias by uncoupling the QT from the RR interval response to exercise. Whether a similar phenomenon occurs in humans is not known.

Methods and Results Nine subjects (age 22–42 years), referred for thoracoscopic sympathicotomy for idiopathic hyperhydrosis, were studied before (C) and 6 weeks after *right* T1-2 sympathicotomy with T2 diathermy (postRS). High resolution ECG signal (Frank leads) was acquired during supine exercise at 70% VO_{2max} (Ex, 7 min) and recovery (Rec, 15 min), and a newly developed algorithm was employed to measure the RR and QT intervals on a beat-to-beat basis. RR and QT (ms) were increased postRS, both at rest (915 ± 32 *v* 1088 ± 46 and 375 ± 6 *v* 399 ± 7, mean ± SEM, $p < 0.05$) and during steady-state Ex (443 ± 16 *v* 493 ± 19 and 272 ± 5 *v* 291 ± 5, $p < 0.05$). PostRS QT remained shortened during Rec despite the lenghtening of RR, forming a wide hysteresis loop in the QT/RR relationship (typical raw data in Fig, C = shaded). The "width" of the hysteresis loop was taken as $\Delta QT = QT_{Ex} - QT_{Rec}$ (ms), and was measured at $RR = (RR_{Rec} + RR_{Ex})/2$ (see Fig). PostRS Δ QT was markedly higher than ΔQT at C (70 ± 5 *v* 43 ± 4, $p < 0.05$). This was accompanied by an increase in the time lag (s) of QT adaptation to a steady-state RR during exercise (54 ± 6 at C *v* 93 ± 9 postRS) or during recovery (13 ± 3 at C *v* 35 ± 3 postRS, $p < 0.05$).



In summary, we have found that right T1-2 sympathicotomy significantly alters the kinetics of the QT adaptation to changes in cycle length during exercise. These data provide novel insights into the role of the sympathetic nervous system in the regulation of the QT/RR relationship in man.

P2976 Risk assessment in patients with systemic amyloidosis is improved by heart rate variability analysis

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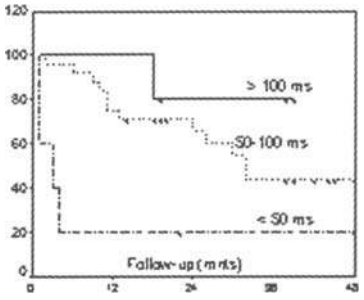
Introduction: In patients with systemic amyloidosis, mortality is high. Cardiac involvement and autonomic neuropathy are considered important risk factors. However, identification of patients at high risk remains troublesome. In this study, we assessed the prognostic value of heart rate variability (HRV) analysis in amyloidotic patients.

Methods: We evaluated 39 patients (mean age 61 ± 10 yr, 17 male, 22 female) with AA- or AL- amyloidosis (n = 18 and 21, respectively). At baseline, patients were hemodynamically stable, those with heart failure NYHA classes III or IV were excluded from participation.

Results: During a median follow up of 19 months (range 1–48), 21 patients died. In 10 patients with a low HRV, defined as a standard deviation of all normal RR intervals (SDNN) less than 50 ms, 8 died after a median follow-up of 4 months. Mortality was 50% in patients with an SDNN between 50 and 100 ms, and 20% in patients with an SDNN > 100 ms (see figure, p = 0.0007). Using the median value of SDNN of 67 ms as cut-off value resulted in a sensitivity of 67% and a specificity of 56% for all-cause mortality. Of 15 patients with probable or definite signs of cardiac amyloidosis on echocardiography, 12 died during follow up. Echocardiography had a sensitivity of 57% and a specificity of 78% for mortality. Combining SDNN with echocardiography increased sensitivity to 71% with a specificity of 78%. Inability to perform some or all Ewing tests resulted in a limited prognostic value of traditional autonomic function testing.



Survival in relation to SDNN.

Conclusion: HRV analysis provides important prognostic information in patients with systemic amyloidosis, especially in combination with echocardiography. This may be useful in identifying patients who may benefit from aggressive additional treatment.

P2977 Selective inhibition of sarcolemmal K_{ATP} channels does not abolish ischaemic preconditioning against myocardial infarction in rabbits

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Pharmacological findings have implicated mitochondrial ATP-dependent K^+ ($mitoK_{ATP}$) channels rather than sarcolemmal ($surfaceK_{ATP}$) channels as end-effectors of ischemic preconditioning (IPC). To test the role of $surfaceK_{ATP}$ channels in the cardioprotection afforded by IPC, we examined 1) the effects of HMR1883, a novel cardioselective K_{ATP} channel blocker, on $surfaceK_{ATP}$ and $mitoK_{ATP}$ channels in rabbit ventricular myocytes, and 2) the effect of HMR1883 on IPC against myocardial infarction in rabbits.

Methods and Results: HMR1883 (Na^+ salt, 30 μM) inhibited the $surfaceK_{ATP}$ current activated by 2,4-dinitrophenol (100 μM) (from 2.22 ± 0.89 nA to 0.52 ± 0.14 nA, $P < 0.05$), whereas the drug did not blunt diazoxide (100 μ M)-induced flavoprotein oxidation, an index of $mitoK_{ATP}$ channel activity (from 41 ± 8% to 42 ± 9%). Anesthetized rabbits were subjected to 30 min of left anterior descending coronary artery occlusion followed by 120 min reperfusion. IPC with two cycles of 5 min occlusion and 10 min reperfusion significantly reduced infarct mass (TTC staining) as compared to non-IPC group (21 ± 4% of risk mass vs. 41 ± 3%,). Glibenclamide (0.3 mg/kg) given prior to IPC totally reversed the infarct mass reducing effect (42 ± 2%). In contrast, HMR1883 (3 mg/kg) given prior to IPC did not interfere with the protective effect of IPC (21 ± 3%). These results indicate that the selective inhibition of $surfaceK_{ATP}$ channels by HMR1883 did not abolish the infarct mass reducing effects of IPC.

We conclude that selective inhibition of $surfaceK_{ATP}$ channels in rabbits do not interfere with IPC against infarction. The results provide additional evidence that $mitoK_{ATP}$ channels are likely effectors of IPC.

P2978 Is it possible to replace the "heart" connexin43 by the "liver" connexin32? Electrophysiological studies in transgenous mice

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Background. Connexins (Cx) are crucial for gap junctional cell-to-cell communication. In the mammalian heart, connexin (Cx) 37, 40, 43, 45, 46, and 50 were observed. Cx43 is predominantly expressed in the atrial myocardium, the distal regions of the bundle branches, the Purkinje fibres, and the ventricular myocardium. Cx32 has not been found in cardiac tissue, but is expressed predominantly in the liver. Homozygous Cx43 deficient mice are not viable. Heterozygous Cx43 deficient mice have a reduced cardiac conduction velocity. This study was thought to determine the electrophysiological effects of Cx43 replacement by Cx32 in transgenous mice.

Methods and Results: Transgenous mice were generated by gen targeting. Nine homozygous ($Cx43^{32/32}$) and 10 heterozygous ($Cx43^{43/32}$) transgenous mice as well as 10 Cx43 wildtype mice ($Cx43^{43/43}$) were investigated by surface electrocardiogram recordings and by transesophageal atrial stimulation under general anaesthesia with avertin. Following this procedure, the transgenous mice were dissected and underwent macroscopic anatomical evaluation. Heterozygous ($Cx43^{43/32}$) and homozygous ($Cx43^{32/32}$) transgenous mice are viable and did not show differences in the relative heart weight as compared to Cx43 wildtype mice ($Cx43^{43/43}$). In addition, no differences were found between $Cx43^{32/32}$, $Cx43^{43/32}$, and $Cx43^{43/43}$ mice with regard to P wave duration (20 ± 2 vs 20 ± 3 vs 22 ± 2 msec), PQ interval (57 ± 15 vs 65 ± 29 vs 50 ± 5 msec), QRS duration (16 ± 2 vs 16 ± 2 vs 15 ± 5 msec), sinus node recovery time (203 ± 71 vs 181 ± 41 vs 155 ± 30 msec), and 1:1 AV conduction time (100 ± 18 vs 98 ± 26 vs 88 ± 7 msec). In none of the mice, atrial burst stimulation resulted in atrial or ventricular arrhythmias.

Conclusions: Whereas Cx43 deficiency is associated with developmental disturbances and a decreased ventricular conduction velocity, Cx32 can fully replace Cx43 with regard to cardiac development and electrophysiological fuction.

P2979 Upregulation of the sarcolemmal Na^+/Ca^{2+}-exchanger in patients with chronic atrial fibrillation

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Background: Contractile remodeling after the cessation of atrial fibrillation (AF) has been hypothesised to result from altered intracellular Ca^{2+} handling. The aim of this study was to determine the protein expression of the Na^+/Ca^{2+}-exchanger (NCX) and of calcium transport proteins of the sarcoplasmic reticulum (SR) in atrial myocardium of patients with chronic (≥6 month) AF compared to patients who were still in sinus rhythm.

Methods: In homogenates of right atrial appendages from patients undergoing coronary artery bypass graft surgery (CAB, n = 26) or mitral valve repair (MVR, n = 22) the protein expression of the NCX, the SR Ca^{2+}-ATPase (SERCA), phospholamban (PLB), and calsequestrin (CALS) were measured using Western blot analysis.

Results:

	Mean protein expression ± SEM (10^3 cpm/mg protein)			
	NCX	SERCA	PLB	CALS
MVR sinus rhythm n = 13	3.6 ± 0.4	22.2 ± 1.5	16.6 ± 1.5	26.1 ± 2.2
MVR AF n = 9	5.4 ± 0.6*	24.8 ± 1.7	17.6 ± 3.1	26.4 ± 2.2
CAB sinus rhythm n = 15	2.6 ± 0.2#	25.3 ± 1.7	21.4 ± 2.2	39.0 ± 3.7#
CAB AF n = 11	4.3 ± 0.6*	22.3 ± 1.9	17.2 ± 2.7	34.4 ± 5.7

*: $p < 0.01$ AF versus sinus rhythm. #: $p < 0.05$ CAB versus MVR.

Conclusion: AF-induced atrial contractile dysfunction cannot be explained by changes of SERCA, PLB or CALS protein expression. However, an increased expression of the Na^+/Ca^{2+}-exchanger is a specific change in atrial myocardium of AF patients and might contribute to contractile remodeling.

P2980 Endothelin-1 induced arrhythmias in rat heart: the underlying mechanisms

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Endothelin-1 (ET-1), a positive inotroph, has also been identified as a potent arrhythmogenic agent in heart. The levels of endogenous ET-1 are increased in many pathophysiological conditions including acute myocardial infarction, unstable angina and cardiac failure, by which many patients die each year due severe rhythm disturbances and sudden cardiac death. It has been proposed that ET-1 may play an important role in these disturbances, however, the mechanisms underlying the arrhythmogenic effects of ET-1 have yet to be elucidated. Consequently, we have examined the cellular Ca^{2+} and pH regulation in rat atrial myocytes, which may contribute to endothelin induced arrhythmias. Ca^{2+} transients were monitored by the measurement of Indo-1 fluorescence, and pH changes with SNAFL-2, in isolated rat atrial myocytes which were either quiescent or electrically paced (0.3 Hz, 2 ms duration, amplitude 25–40 V).

ET-1 (0.1 μM) caused spontaneous Ca^{2+} transients in quiescent myocytes 5–10 minutes after application. Multiple effects of ET-1 (0.1 μM) application were observed in electrically paced cells. Firstly, the Ca^{2+} fluorescence transient amplitude was increased by 9.08 ± 1.13% (n = 7) after 10 minutes. Secondly, spontaneous Ca^{2+} transients were observed in theelectrically-driven myocytes, with a similar time course to the automaticity observed in non-paced cells. The time course of the spontaneous Ca^{2+} transients resembled that of Ca^{2+} signals causing delayed-after depolarisations (DADs). The non-selective endothelin antagonist SB 209670 (5 μM) blocked both the inotropic and the arrhythmogenic Ca^{2+} transients induced by ET-1. However the two ET_A-selective blockers, BQ123 (1 μM) and A-147627 (1 μM) failed to antagonise the effects of 0.1 μM ET-1, ruling out the involvement an ET_A-receptor in mediating these effects in rat atria.

Intracellular pH in response to ET-1 activation in rat atrial myocytes was also monitored. An alkalinisation of the cytoplasm by ~0.25 pH units was observed, this effect occurred prior to the onset of the increase in the Ca^{2+} transient amplitude. This change in pH suggests an increase in Na^+/H^+ exchange activity upon ET-1 activation; Na^+/H^+ exchangers are down-stream targets of protein kinase C (PKC).

In summary, the positive inotropic and arrhythmogenic effects of ET-1 in rat heart are mediated through activation of a non-ET_A receptor subtype, possibly ET_B. ET-1 receptors appear to mediate their effects though activation of several intracellular pathways, in particular, this study suggests a role for the PKC signaling pathway. The most plausible explanation for this is an increase in Na^+/H^+ exchange that would lead to an elevated Na^+ concentration, thereby inducing the Na^+/Ca^{2+} exchanger to operate in reverse mode (causing Ca^{2+} influx). An increased Ca^{2+} load of the sarcoplasmic reticulum would result, thus inducing positive inotropy and generation of arrhythmias.

P2981 A new recording technique of midmyocardial repolarization from isolated rabbit hearts

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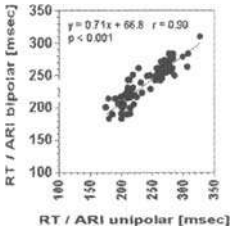
Intramural repolarization characteristics are paramount in the genesis of long QT associated arrhythmias, and possibly play a role in the genesis of electrical alternans. A recording technique of midmyocardial repolarization in isolated whole heart models is lacking. In an established isolated rabbit heart model for the evaluation of myocardial repolarization by means of multiple monophasic action potentials (MAPs), teflon-coated Tungsten wire electrodes (76 μm, deisolated at the tip) were spring-mounted onto the contact MAP holders and inserted pairwise (distance 2–3 mm) to the myocardium at prespecified depth. Bipolar recordings from the midmyocardium (4 mm) of the LV and the endocardium (8 mm) of both ventricles were compared to unipolar recordings from each electrode measured against Wilson central terminal (WCT, from volume-conducted ECG). After insertion of the wire electrodes a local injury current ensued, permitting the recording of MAPs against WCT. If the local reference electrode exhibited a neutral potential, ie was free of injury, MAPs were also observed in the bipolar recordings. Because injury at either one electrode was usually not sustained, most signals changed continuously to an electrogram within 15–30 min after insertion. MAPs were measured at 90% repolarization (APD90), electrograms for activation recovery intervals (ARIs) according to standard definitions.



Scatter plot.

The figure shows the correlation scatter plot of all data points generated from a total of 8 isolated rabbit hearts. Correlation coefficients were high both for MAP contact electrodes ($r = 0.93$, $p < 0.001$) and for wire electrodes ($r = 0.83$, $p < 0.001$). In conclusion Tungsten wire electrodes permit the evaluation of midmyocardial repolarization characteristics in an isolated rabbit heart model.

P2982 Inhibition of the ATP-dependent potassium current IK(ATP) by HMR 1883 in human cardiomyocytes

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Purpose: The activation of the myocardial, ATP-dependent potassium current (IK(ATP)) during ischemia causes potassium efflux and shortening of the action potential duration (APD). This increases the dispersion of the repolarisation between ischemic and non-ischemic myocardium and predisposes to arrhytmias including ventricular fibrillation. The novel cardioselective IK(ATP) inhibitor HMR 1883 allows selective block of the sarcolemmal myocardial K(ATP)-channel without effecting the pancreatic K(ATP)-channel (which would cause hyperinsulinaemia and hypoglycaemia) or the mitochondrial K(ATP)-channel (interfering with potentially beneficial preconditioning). Therefore, we studied the concentration and pH-dependence of HMR 1883 in human ventricular myocytes.

Methods: Single cardiomyocytes were isolated enzymatically from the free ventricular wall of human hearts. IK(ATP) was measured with the patch-clamp technique in the whole cell configuration at 35°C. Action potentials were recorded using amphotericin B in perforated patch conditions to maintain the intracellular environment. In voltage clamp experiments, the K(ATP)-channel, which is closed under physiological conditions, was activated by application of 1 μM rilmakalim, a K(ATP)-channel opener. In action potential recordings, 0.1 μM rilmakalim was used.

Results: At physiological pH (pH = 7.3) half-maximal block of the rilmakalim-induced current occurred at 0.6 μM HMR 1883 (at 0 mV membrane potential); under more acid conditions (pH = 6.5), half-maximal block was achieved at markedly lower concentrations (IC50 = 0.3 μM). In current clamp experiments, block of IK(ATP) by HMR 1883 was capable of reversing the action potential shortening induced by rilmakalim, and restored the action potential plateau.

Conclusions: HMR 1883 appears to be useful to prevent IK(ATP)-induced shortening of the action potential in human ventricular myocardium. More acid conditions, as observed in ischemia, increase the sensitivity to HMR 1883, leading to block of IK(ATP) at lower concentrations, indicating a more potent effect in ischemic myocardium. Thus, HMR 1883 may be a useful agent to prevent action potential shortening and dispersion of repolarisation during ischemia, which may protect against ischemic venticular arrhythmias.

P2983 Evidence for membrane potential modulated control of calcium release and reuptake from the sarcoplasmic reticulum in mammalian heart muscle

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Background: Until recently, it has been accepted that calcium (Ca) release from sarcoplasmic reticulum (SR) in cardiac myocytes is controlled through calcium induced calcium release (CICR). In the absence of transmembrane Ca entry we have shown that membrane depolarisation is still able to elicit an intracellular calcium (Cai) transient. We have termed this mechanism 'voltage activated calcium release' (VACR). The mechanisms responsible for termination of Ca release from the SR and therefore relaxation of contraction are not yet known. We investigated whether membrane repolarisation might play a role terminating SR release.

Methods: Experiments were carried out in guinea-pig ventricular myocytes at 370°C, using whole-cell patch clamp. Cells were internally dialysed with a 100 mM cAMP (3′5′ cyclic adenosine monophosphate) Na-free (to abolish reverse mode Na/Ca exchange) pipette solution and held at a post-conditioning potential of −40 mV in the presence of 8 mM Ni (to block Ca entry via L-type Ca channels and Na/Ca exchange). The superfusate was changed to a Na-free (NMDG) solution (to abolish forward mode Na/Ca exchange) containing 8 mM Ni, 4 seconds before a test depolarisation to +20 mV. Cells were repolarised to −80 mV at the end of the test pulse. Cai transients were measured using the fluorescent dye, FURA2.

Results: In the absence of transmembrane Ca entry, membrane depolarisation was still able to elicit Cai release of 70.2 ± 8.0%; (mean ± SEM; n = 8) of total SR Ca content. Repolarisation in the presence of an external Na-free, 8 mM Ni solution elicited a rapid decline of the Ca transient to baseline (t = 211 ± 26 ms; n = 24 cells). This Ca decline could not be due to Ca extrusion via Na/Ca exchange, as this is inhibited by Na-free external solution and also by 8 mM Ni.

Conclusion: We provide evidence that cardiac myocytes dialysed with cAMP possess voltage sensitive mechanisms which are not only able to elicit SR Ca release, but may also terminate SR release directly. We suggest the existence of a voltage sensor which couples the sarcolemma to the SR release channels, enabling depolarisation and repolarisation to gate the opening and closing of SR release channels. The implications of such phenomena are far reaching and may provide us with important information about myocyte behaviour under adrenergic stimulation and in disease states.

P2984 Potential cellular mechanism for the antifibrillatory properties of fish oils: potent blockade of the Kv4.3 encoded transient outward current

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The vast majority of human transient outward current (Ito) is encoded by the Kv4.3 gene. The interaction of this current with other plateau phase currents during myocardial ischaemia is implicated in the development of heterogeneity of repolarisation, which predisposes to the development of potentially fatal reentrant tachyarrhythmias. Omega-3 polyunsaturated fatty acids, present in fish oils, have potent antifibrillatory properties and we propose that this effect may in part result from their ability to block the Kv4.3 current.

Methods: We have stably transfected the Kv4.3 gene into the Chinese hamster ovary cell line and using single electrode patch clamp techniques have described the biophysics of the resultant current in this cell line, both at 23°C and 37°C. (All results quoted are at 23°C unless otherwise stated). Modulation of current biophysics was assessed after superfusion with the omega-3 polyunsaturated fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), as well as arachidonic acid.

Results: Kv 4.3 current activation and steady state inactivation are voltage dependent, with V1/2 of −6.7 ± 2.3 mV and −48.4 ± 1.0 mV respectively. The current rapidly inactivates with a biexponential course (tau1 = 20.1 ± 1.2 ms and tau2 = 96.6 ± 6.7 ms at +45 mV), and displays rapid recovery from inactivation which is voltage dependent and well fit by a monoexponential function (time constant of 276 ms at −85 mV). Current activation, steady state inactivation and recovery from inactivation are accelerated at 37°C compared to 23°C. The omega-3 fatty acids DHA and EPA block the Kv4.3 current with IC50s of 3.6 ± 1.5 and 2.3 ± 1.5 μmol/L respectively, an order of magnitude more potent than that observed with arachidonic acid.

In conclusion: Omega-3 fatty acids potently block the Kv4.3 current. This property would tend to limit the degree of heterogeneity of repolarisation that develops during myocardial ischaemia, and may in part explain why consumption of at least one fatty fish meal per week has been shown to decrease the risk of primary cardiac arrest by 50%.

P2985 The role of the slow component of the delayed rectifier potassium current in dog ventricular muscle and Purkinje fibre repolarization

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Two distinct components of the delayed rectifier potassium current (I_K), i.e. slowly (I_{Ks}) and rapidly (I_{Kr}) activating components have been identified in mammalian heart muscle. Specific blockers of I_{Kr} have been widely shown to lengthen cardiac action potential duration (APD) and this is consistent with their strong antiarrhythmic potency. The lack of specific blockers of I_{Ks}, however, has made it impossible to evaluate directly the physiological role of I_{Ks} in cardiac repolarization.

Methods: Therefore, the aim was to examine the possible role of I_{Ks} in cardiac repolarization using the two recently developed specific I_{Ks} blockers, chromanol 293B (Ch) and L-735, 821 (L). A comparison with the role of I_{Kr} was also made using the specific I_{Kr} blockers d-Sotalol (S) and E-4031 (E). Conventional microelectrode and the whole-cell configuration of the patch-clamp techniques were applied to dog ventricular muscle and Purkinje fibres at 37°C.

Results: S (30 μM) and E (1 μM) markedly decreased the amplitude of I_{Kr} tail current in isolated dog ventricular myocytes. In the same preparations Ch (10 μM) almost completely inhibited I_{Ks} tail current, while L (100 nM) completely abolished this current. Suprisingly, however, Ch and L lengthened APD by less than 7% in dog ventricular papillary muscle and also in dog Purkinje fibres. In contrast, S and E markedly prolonged APD in dog Purkinje fibres (48.2 ± 4.6%, n = 8 and 68.9 ± 8.6%, n = 8, respectively [mean ± SEM]), as well as in ventricular papillary muscle (18.5 ± 2.4%, n = 7 and 20.5 ± 4.2%, n = 6, respectively). In dog ventricular myocytes I_{Ks} activated slowly (τ = 1705.3 ± 110.6 ms, n = 14 at +50 mV) and deactivated rapidly (τ = 78.9 ± 4.6 ms, n = 14 at −40 mV), while I_{Kr} activated rapidly (τ = 53.8 ± 5.8 ms, n = 15 at +30 mV) and deactivated slowly ($\tau 1$ = 360.3 ± 26.3 ms, $\tau 2$ = 3310 ± 280 ms, n = 15 at −40 mV). Calculation of the current density expected to develop during the plateau phase (150 ms at +20 mV) of an action potential, indicated that the activation of I_{Kr} was more than 10 times larger than that of I_{Ks}.

Conclusions: Therefore, our results suggest that I_{Ks} unlike I_{Kr} plays little part in the repolarization of normal cardiac ventricular muscle and Purkinje fibres, and the role of I_{Ks} in cardiac repolarization should be re-evaluated.

P2986 Cardiac electrophysiological and vascular effects of fluoxetine

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Fluoxetine is a widely used antidepressant compound having selective serotonin reuptake inhibitor properties. In this study we investigated the effects of fluoxetine (F) on transmembrane action potentials (AP) and ionic currents of rat, rabbit, guinea-pig and canine ventricular preparations and on the vasomotors responses of first order arterioles of rat gracilis muscle

Methods: conventional microelectrode and whole cell voltage clamp techniques were used. The internal diameter of isolated, pressurized arterioles (98 μm at 80 mmHg perfusion pressure) was evaluated by microvideoangiometry.

Results: low concentrations of F (1–10 μM) caused significant shortening of action potential duration (APD) and depression of the plateau phase in guinea pig and rabbit papillary muscles and single canine ventricular myocytes. In rat papillary muscle, APD was not affected by F (up to 100 μM), however, the drug decreased the force of contraction with EC_{50} of 10 μM. F (10 μM) decreased also the maximum velocity of depolarization and the overshoot of AP in each species studied, without changing the resting membrane potential level. In voltage clamped canine ventricular myocytes 10 μM F decreased the amplitude of the peak Ca^{2+} current (ICa) by 55 ± 4.5% at 0 mV (n = 5). F did not alter the gating kinetics (voltage-dependence of activation, steady-state inactivation and time constant for inactivation) of I_{Ca}. The increasing concentrations of F dilated arterioles up to 155 μm with an EC_{50} of 2.5 ± 0.5 μM. Removal of endothelium, application of 4-aminopyridine (4-AP, 0.01–1 mM) or use of glibenclamide (1 μM) did not affect the vasodilatory response to F. Norepinephrine (1 nM–10 μM) and 5-hydroxytryptamine (1 nM–10 μM)-induced constrictions were significantly attenuated by F (1–10 μM). Increasing concentration of Ca^{2+} (0.1–30 mM)-induced constrictions were markedly reduced and abolished by F (2 μM, 10 μM, respectively)

In conclusion these data suggest that fluoxetine may inhibit cardiac Ca^{2+} and Na^+ as well as vascular CA^{2+} channels and this effect may explain most cardiovascular side-effects observed occasionally with fluoxetine.

P2987 P_2 purinoceptors contribute to adenosine-5′-triphosphate-induced inhibition of L-type Ca^{2+} current in rabbit atrial myocytes

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Activation of P_1 (A_1) purinoceptors by adenine compounds inhibits the L-type Ca^{2+} current (I_{Ca}) in the heart, and produces negative inotropic, chronotropic and dromotropic effects. However, these compounds simultaneously activate P_2 purinoceptors. We therefore elucidated whether or not (and how) P_2 purinoceptor activation modifies the effects of adenosine-5′-triphosphate (ATP) in rabbit cardiac myocytes.

Methods: The perforated patch clamp method was employed on single cells isolated from the rabbit atrium. I_{Ca} was elicited by depolarization from a holding potential of −40 mV to 0 mV.

Results: ATP did not change basal I_{Ca}. In contrast, ATP (0.1 μM–3 mM) consistently inhibited I_{Ca} under prestimulation with isoproterenol (ISO, 30 nM). This inhibition of I_{Ca} was abolished when the cells were dialyzed with 8bromo cAMP, were stimulated by forskolin plus 3-isobutyl-1-methylxanthine, or were pretreated with pertussis toxin (PTX). The concentration response curve indicated that at least two different pathways mediate the I_{Ca} inhibition by ATP. Both 1,3-dipropyl-8-cyclopentylxanthine (DPCPX, A_1 blocker) and suramin (P_2 blocker) partially blocked the ATP-induced inhibition of I_{Ca}, while their co-application completely abolished the effect of ATP. ATP-γS, a non-hydrolyzable ATP analogue, showed a suramin-sensitive inhibition of I_{Ca}. DPCPX did not change the effect of ATP-γS. When the enzymatic degradation of AMP to adenosine was blocked by α,β-methylene-ADP, suramin completely abolished the effect of ATP.

Conclusions: P_2, not only P_1, purinoceptors contribute to the ATP inhibition of ISO-stimulated I_{Ca} via the PTX-sensitive and cAMP-dependent pathway. The P_1 stimulation by ATP results from hydrolysis of ATP to adenosine.

SUPRAVENTRICULAR ARRHYTHMIAS

P2988 Dynamic patterns of high and low-frequency atrial activation potentials recorded at the posterior input to the atrioventricular node using a split-tip electrode catheter and a long stabilizing sheath

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Antegrade and retrograde patterns of bipolar local activation at the posterior input to the AV node were investigated in 12 pts with AV nodal reentrant tachycardia (AVNRT) through a custom-made 7 F quadripolar-tip (split-tip) miniaturized electrode ablation catheter (Cordis-Webster). To optimize stability, the catheter was advanced to the target region through a long sheath. Local activation was assessed in all pts during atrial and ventricular programmed electrical stimulation and during AVNRT.

Results. During sinus rhythm, a double potential consisting of a high-frequency (HF) component followed by a low-frequency (LF) component was found in all pts in the midseptal area of Koch's triangle. During programmed atrial stimulation, conduction through the AV node was associated with non-decremental patterns of HF and decremental patterns of LF potentials in all pts; multiple distinct LF potentials (up to 5) were recorded in response to atrial extrabeats resulting in antegrade jump and AV node echoes or AVNRT. The antegrade AV nodal refractory period occurred either before and after LF potential activation. During retrograde slow pathway conduction, LF potentials were recorded before HF potentials. One radiofrequency pulse (range, 1–12) at sites where both HF and LF potentials were recorded successfully abolished AVNRT in all pts.

Conclusions. LF potentials reflect local activation of transitional areas involved in slow pathway conduction. Use of split-tip miniaturized electrodes and long sheaths increases the local resolution and allows an accurate detection of LF-potential dynamic patterns in response to pacing maneuvers and during AVNRT.

P2989 A novel approach to electrocardiographic diagnosis of pre-excited atrial fibrillation

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Background: Atrial fibrillation (AF) in patients with Wolff-Parkinson-White syndrome (AFWPW) may easily be confused by non-specialist electrophysiologists with AF with bundle branch block (AFBBB) or ventricular tachycardia (VT). Yet essential diagnosis of this arrhythmia is essential to avoid inappropriate and potentially dangerous therapy with atrioventricular nodal blocking agents or class 1B antiarrhythmic drugs. We have applied a simple ECG based criteria to improve diagnosis of this arrhythmia.

Methods: 104 12 lead ECGs (31AFBBB, 41AFWPW, 32VT – latter 2 diagnoses confirmed electrophysiologically) were blindly analysed randomly by a trainee in electrophysiolgy (RKP) and a medical registrar (ST). Three ratios were calculated: 1) 10 successive RR intervals (RR) were measured to the nearest 0.5 mm. The maximum (max) minus minimum (min) value was divided by the widest QRS complex in mm ($RR_{max\text{-}min}$/QRS ratio); 2) 5 successive isoelectric to R wave peak measurements in the lead with the tallest R wave were made. The max minus min value was divided by the min value ($R_{iso\text{-}peak}$ ratio); 3) 5 successive peak to trough measurements in the lead with the largest QRST complex were made. The max minus min value was divided by the min value ($QRST_{peak\text{-}trough}$ ratio). RKP and ST were also asked for a clinical diagnosis of each ECG.

Results:

	Sensitivity	Specificity (AFWPW)
$RR_{max\text{-}min}$/QRS ratio of 0.6–2.0	98%	86%
$R_{iso\text{-}peak}$ ratio of ≥ 0.22	85%	92%
$QRST_{peak\text{-}trough}$ ratio > 0.15	92%	97%
$RR_{max\text{-}min}$/QRS & $QRST_{peak\text{-}trough}$ ratios	95%	91%

Clinical diagnosis – RKP	AFWPW 100%	AFBBB 100%	VT 100%
Clinical diagnosis – ST	AFWPW 78%	AFBBB 100%	VT 56%

Application of both the $RR_{max\text{-}min}$/QRS and $QRST_{peak\text{-}trough}$ ratios (using ST's ECG measurements) to ST's 23 misdiagnosed ECGs resulted in 19 (83%) to be correctly diagnosed.

Conclusions: Application of an easily executable algorithm of RR interval and QRST height variability enables correct diagnosis of AFWPW with high sensitivity and specificity. Application of these criteria would improve the acute and long term management of this potentially life threatening condition.

P2990 Differences in onset of delta wave between different electrocardiographic leads: implications for prediction of accessory pathway location and for catheter ablation

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Endocardial sites with local ventricular activation time preceding the onset of the delta wave are considered suitable for radiofrequency application in the WPW syndrome. Onset of ventricular preexcitation is occasionally earlier and better appreciated in some ECG leads than in others, and, therefore, it is advisable to chose the optimal ECG lead to reference the endocardial activation time before radiofrequency application. However, it has not been established whether these differences in the recognition of onset of ventricular preexcitation between different ECG leads are significant and related to the AP location.

Methods: 64 consecutive patients were studied prior to the catheter ablation of a single manifest AP. The onset of the delta wave (ODW) – referred to the onset of the P wave – was simultaneously measured in all 12 ECG leads at 200 mm/sec and by electronic callipers. The following variables were studied: ODW in all ECG leads, difference in ODW between the earliest lead and the mean ODW in all 12 leads, and difference in ODW between the latest lead and the mean ODW in all 12 leads. These variables were also analysed according to a left (n = 33), right (n = 15) or posteroseptal (n = 16) location of the AP.

Results: There was a difference in ODW between the earliest and latest leads and the mean ODW of 17.9 ± 8.8 ms (CI 95%: 15.7–20.2) and 43.9 ± 18.9 ms (CI 95%: 39.1–48.6) respectively. The earliest and latest ODW were most frequently recorded in leads V3 and aVL respectively. There greatest difference in ODW between the earliest and mean ODW was found in the right sided AP group (−26.5 ± 10.0 ms) compared with the left-sided (−15.8 ± 10.6 ms) or posteroseptal (−14.2 ± 4.5 ms) AP groups (ANOVA, $p < 0.0001$). The earliest ODW in right-sided AP was recorded in leads V1 and V2 and a difference in ODW between the earliest and mean ODW in V1/V2 greater than 20 ms had showed 81% sensitivity and 98% specificity for right-sided AP.

Conclusions: 1) Differences in recognition of ODW between different ECG leads are often substantial and, therefore, it should be strongly recommended – specially in right-sided AP – to select the appropriated ECG lead for ablation. 2) An ODW recognised more than 20 ms earlier in V1/V2 than in other ECG leads suggests a right-sided location of the AP.

P2991 Differential diagnosis of paroxysmal supraventricular tachycardias by administration of adenosine during sinus rhythm

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Background: Atrioventricular node reentrant tachycardia (AVNRT) represents the most commonly encountered type of paroxysmal supraventricular tachycardias (PSVT). Administration of adenosine-5′-triphosphate (ATP) during sinus rhythm was shown to be a valuable test in demonstration of dual AV node pathway physiology indicated by an at least 50 msec jump in AH interval between two consecutive sinus beats. Adenosine, the end-product of the ATP metabolisation cascade with a very short half-life has been widely used to terminate supraventricular tachycardias with less adverse effects than ATP. The aim of our investigation was to test the potential of adenosine in revealing dual AV node pathway physiology in a consecutive series of patients undergoing invasive electrophysiology study and radiofrequency ablation for PSVT.

Methods: 38 patients (23 female, age: 16–63 years) were enrolled. All patients had documented narrow QRS complex tachycardias and either AVNRT or atrioventricular reentrant tachycardia (AVRT) was confirmed at electrophysiology study. A rapid iv bolus of adenosine was administered at 6 mg and 12 mg doses to all patients prior to atrial stimulation. Dual AV node pathway physiology was defined as a ^{3} 50 msec increment in AH interval between two consecutive sinus beats after adenosine or after a 10 msec decrement in coupling interval during atrial extrastimuli.

Results: AVNRT was diagnosed based on atrial extrastimulus testing in 20 patients. In 14 of these 20 patients dual AV node pathway physiology was revealed with adenosine test. None of the 18 patients with atrioventricular reentrant tachycardia showed signs of dual AV node pathways with adenosine. Adenosine test had a 70% sensitivity and 100% specificity in the diagnosis of dual AV node pathways. No adverse effect of adenosine was found in any of the patients.

Conclusion: I.v. adenosine administration is a safe test with excellent sensitivity and specificity for differentiation of arrhythmia mechanism in patients with PSVT.

P2992 Extrastimuli from two different directions provide the distance between the dual atrioventricular nodal inputs

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We have reported that extrastimuli from two different directions can help to reveal the functional difference between the dual pathways ('98AHA). It is impossible to know the positions of the dual inputs exactly. To evaluate the distance between dual inputs is important to avoid the AV block induced by slow pathway (SP) radiofrequency (RF) ablation.

Methods. Fourteen consecutive patients (pts) with typical AV nodal reentrant tachycardia underwent successful selective SP RF ablation guided by SP potentials or a fractionated atrial electrogram. Steerable electrode catheters were simultaneously positioned anterior (A) to the His bundle catheter and posterior (P) near the coronary sinus ostium before the RF procedure. We applied extrastimuli from either the A or P site in 14 pts [Group1 (G1): transient VA block during SP ablation, 4 pts, Group2 (G2): no VA block during SP ablation, 10 pts]. In all pts, we measured the atrio-His interval from A2 at the stimulating site to H2. A1A2 vs A2H2 conduction curves (CC) were obtained by stimulation applied from either of two different sites. ΔAH (longest A2H2 – shortest A2H2), and MaxAH (maximum increase in A2H2 for a 10 ms decrement in A1AZ), were measured in each CC.

Results: All 14 pts showed a ΔAH (A/P) ≥ 1. ΔAH (A/P) in G2 was significantly larger than in G1.

	ΔAH (A)	ΔAH (P)	ΔAH (A/P)	MaxAH (A)	MaxAH (P)
G1	233 ± 49 ms	220 ± 50 ms	1.07 ± 0.06*	65 ± 36 ms	65 ± 43 ms
G2	248 ± 93 ms†	195 ± 79 ms	1.3 ± 0.19	134 ± 78 ms#	87 ± 70 ms

*$p < 0.05$ vs G2, †$p < 0.01$ vs ΔAH (P) in G2, #$p < 0.05$ vs MaxAH (P) in G2

Conclusions. In patients with a small difference in the ΔAH obtained by extrastimuli from two different directions, the distance between the dual AV nodal inputs was estimated to be short. ΔAH (A/P) provides an electrophysiological marker for the risk of AV block induced by slow pathway ablation.

P2993 Role of an early follow-up electrophysiologic study after acutely successful radiofrequency ablation of accessory pathways and atrioventricular nodal re-entrant tachycardia

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Background: Recurrence rates of accessory pathway (AP) conduction (cond) and AV nodal reentrant tachycadia (AVNRT) after initially successful radiofrequency ablation (RF) are reported to be up to 8% and 5%, repectively. We report our results of a routinely performed electrophysiologic study (EP study) 4–6 weeks after acutely successful RF for WPW syndrome and AVNRT.

Methods: 263/332 pts (79%) with AVNRT (group I) and 265/340 pts (74%) with WPW syndrome (group II) underwent an EP study a mean of 36 days after the RF session. Studies were performed off all antiarrhythmic drugs for at least 5 half lives with two catheters positioned to record a His bundle electrogram and the HRA and RVA, respectively.

We performed incremental and programmed atrial pacing with up to two extrastimuli and incremental and programmed ventricular pacing with 1 extrastimulus in all patients at baseline and on isoproterenol in pts in group I.

Results: In group I 17 pts (6.5%) had an EP recurrence. Only 5 of them had palpitations suggestive of recurrent AVNRT. 11 of these pts underwent a successful repeat ablation.

In group II 12 pts (4.5%) demonstrated recurrent AP cond either uni- or bidirectionally. Only 2 pts had symptoms suggestive of AVRT since the ablation. 5 of the 12 pts underwent a second ablation procedure, that was successful in all.

Thus, a therapeutic consequence of the early invasive follow-up study resulted in 4.2% of pts with AVNRT and 1.9% of pts with WPW syndrome.

Conclusion: The low recurrence rate of AVNRT and AP conduction after an initially successful RF ablation suggests that in asymptomatic pts an early invasive follow-up study is not warranted.

P2994 A simplified ATP test for the non-invasive diagnosis of dual atrioventricular nodal pathways and the assessment of the results of slow pathway ablation in patients with atrioventricular nodal reentry tachycardia

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We have recently shown that administration of ATP during sinus rhythm identifies dual AV nodal pathways (DAVNP) in 76% of 41 patients with inducible sustained AV nodal reentry tachycardia (AVNRT (Circulation 1998; 98: 47). In that study, ATP test was considered to be positive for DAVNP only when the results were reproducible once at a given dose of ATP. The present study evaluated the sensitivity of a simplified adenosine triphosphate (ATP) test in the noninvasive diagnosis of dual AV node pathways (DAVNP) and assessment of the results of radiofrequency ablation (RFA) of the slow pathway in a large group of patients with inducible sustained slow/fast AVNRT.

Methods: The value of a single given dose of ATP was studied in 105 patients with inducible sustained slow/fast AVNRT. ATP (10 to 60 mg, at 10 mg increments) was injected during sinus rhythm until ECG signs of DAVNP (>50 ms increase or decrease in PR interval in 2 consecutive beats, or >1 AV nodal echo beat) or 2nd degree AV block were observed.

Results: The test could be completed in 96 patients. DAVNP by ATP test were seen in 72 (75%) of 96 patients. DAVNP by electrophysiologic criteria were demonstrated in 82 (85%) of the 96 patients. DAVNP were present by ATP test in 59 (72%) of the 82 patients with and in 13 (93%) of the 14 patients without DAVNP by electrophysiologic criteria (p = NS). DAVNP by ATP test disappeared in 27 (96%) of 28 patients who underwent slow pathway abolition and in 18(60%) of 30 patients who underwent slow pathway modification. In the 12 patients with persistent DAVNP by ATP test after slow pathway modification, the number of beats conducted over the slow pathway was significantly reduced (2.5 ± 2.2 vs 6.3 ± 3.3, $p < 0.002$).

In conclusion: A single administration of ATP during sinus rhythm at a given dose enables the noninvasive diagnosis of DAVNP in a high percentage of patients with inducible slow/fast AVNRT and reliably predicts the results of RFA of the slow pathway.

P2995 Electrophysiologic and antiarrhythmic effects of a new atrial selective 5-HT4 receptor antagonist in experimental atrial flutter and fibrillation

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Stimulation of the 5-HT4 receptor increases atrial chronotropic and inotropic response, but whether it has other electrophysiologic effects is unknown. In humans and swine the 5-HT4 receptor is present only in the atrium. Therefore, the effects and the antiarrhythmic potential of a new 5-HT4 receptor antagonist, RS-100302, were studied. In order to delineate the role of this receptor in modulating atrial electrophysiologic properties, the partial receptor agonist cisapride was also evaluated.

Methods: In 17 anesthetized, open-chest,pigs, atrial flutter or fibrillation were induced by rapid right atrial pacing with or without a crush-injury of the right atrial free wall, respectively. Atrial effective refractory period (ERP), conduction velocity (CV), wavelength, and dispersion of refractoriness were determined during programmed stimulation via a 56-electrode mapping plaque sutured to the right atrial free wall. Ventricular electrophysiologic parameters were also measured. All electrophysiologic parameters were measured at baseline and following infusion of RS-100302 and cisapride.

Results: In the atrium RS-100302 prolonged mean ERP (115 ± 8 vs 146 ± 7, $p < 0.01$)and wavelength (8.3 ± 0.9 vs 9.9 ± 0.8, $p < 0.01$), reduced dispersion of ERP (15 ± 5 vs 8 ± 1, $p < 0.01$), and minimally slowed CV (72 ± 4 vs 67 ± 5, $p < 0.01$). These effects were all partially reversed by cisapride. RS-100302 produced no ventricular electrophysiologic effects. RS-100302 terminated atrial flutter in 6 of 8 animals and atrial fibrillation in 8 of 9 animals. Re-induction of sustained tachycardia was prevented in all animals.

Conclusions: The electrophysiologic effects of the new atrial 5-HT4 receptor agotagonist RS-100302 suggest that it may have important atrial antiarrhythmic potential, without producing ventricular proarrhythmic effects.

P2996 Predisposing factors, histology and treatment of superior vena cava stricture complicating radiofrequency modification of the sinus node

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Radiofrequency modification (RFM) of the sinus node (SN) is an accepted therapy of drug resistant inappropriate sinus tachycardia (IST). During this procedure mapping and sequential ablation of the earliest atrial activation site is continued until the SN response to Isoproterenol infusion (I) is decreased to less than 120 bpm. The only recognized specific complication of this procedure is sinus arrest with junctional escape rhythm neccessitating pacemaker (PPM) implant. We describe superior vena cava (SVC) obstruction as a late complication of RFM, its contributory factors and its management. From Oct. 1997 to May 1998, 14 patients (pts), (12 female) with drug resistant IST underwent RFM of SN. Caudal shift of the earliest atrial activation with a SN response to I of <120 bpm was observed acutely in every pt. PPM implantation occurred in three patients: two prior to the procedure due to complete heart block and one due to complication of the procedure. All three patients developed SVC syndrome at 64 ± 15 day's post RFM. The number of RF applications was similar to the uncomplicated pts. Trans-esophageal echocardiography (TEE) was diagnostic in all cases correctly identifying the stricture at the SVC-right atrial junction. Angiography confirmed a mean gradient of 25 ± 3 mmHg with histology in one pt demonstrating full thickness tissue fibrosis. One pt underwent surgical repair of the stricture while in two, percutaneous transluminal balloon dilation (PTBD) successfully reduced the gradient to less than 5 mmHg. There was no recurrence at 3 ± 1 months.

Conclusion: 1) SVC obstruction is not an uncommon complication of RFM of SN. 2) The presence of PPM may be a strong predisposing factor to this complication. 3) TEE is the diagnostic test of choice while PTBD of the stricture appears to be a successful therapeutic modality.

HEART FAILURE AND HEART TRANSPLANTATION

P2997 Importance of left anterior hemiblock development in inferior wall acute myocardial infarction

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New left anterior hemiblock (LAHB) in anterior wall myocardial infarction (MI) is the most frequent intraventricular conduction defect. On the other hand, the coronary angiographic significance of LAHB development in patients with acute inferior wall MI (AIMI) is known to be less significant. This study was planned to investigate this phenomenon by comparing the patient groups with and without LAHB after AIMI.

Methods: One-hundred and seventy-two patients (141 men and 31 women) between 28 and 84 years of age (mean 55 ± 10) with the diagnosis of AIMI were included in the study. Patients with previous LAHB finding were excluded. Patients were divided into two groups according to ECG criteria: group I – 25 patients in whom an ECG pattern characteristic of LAHB developed; group II-147 patients without this pattern. Patients were placed in group I if there was an axis deviation of <30° of the mean frontal plane to the left with the following pattern: increased S-wave voltage and decreased R-wave voltage in leads II, apparence of deep S-wave in lead II, and terminal positive R wave in lead aVR. Coronary angiography was performed within 1 weeks. A coronary stenosis was considered significant if the vessel diameter was narrowed by >50%. The dominant coronary artery was classified as right and left or balanced. LV ejection fraction (EF) was calculated from the single-plane right anterior oblique 30° projection of left ventriculography.

Results: There was non-significant difference between two groups according to risk factors of coronary disease. The frequency of the left dominant or balanced coronary artery, left anterior descending (LAD) and multivessel coronary artery diseases was found to be significantly higher in group I comparing to group II (44% Vs 17%, $p = 0.018$; 80% Vs 38%, $p < 0001$; 84% Vs 52%, $p = 0.001$ respectively). The average age of patients in group I was significantly higher (58 Vs 54, $p = 0.007$) while the mean LV EF was found to be lower than group II (51% Vs 56%, $p = 0.04$). The peak CKMB values were higher in group I, however the difference was not statistically significant (216 Vs 162, $p = 0.09$).

As a result our study suggest that the LAHB development during AIMI can be an indicator of LAD lesions, multivessel coronary artery diseases and impaired left ventricular systolic function. Therefore the coronary angiography should be considered for these kinds of patients.

P2998 Pacing transplanted patient: 10-year experience

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We reviewed the 61 permanent pacemakers implanted in a series of 930 cardiac transplants 6.7%) between 1988 and 1998, 54 sinus node dysfunction (SND), 4 atrio ventricular blocs (AVB) and 3 both. 90% were male, mean age 46 ± 11 years.

All patients had undergone the orthotopic transplantation using the classical Shumway technique. Half of the population (31) were implanted during the first 6 post-operative weeks. The incidence of early implantation ranged from 4 to 8 by year up to 1995, and then decreased to one or none since 1996. The other half (30) were implanted later, between 1 to 10 years, 5 every 2 years.

Pacing mode was VVI (7) for 5 paroxysmal AVB, one unexcitable atrium, and one paroxysmal SND with right bundle branch block. AAI (5) or AAIR (25) for isolated SND without AVB or chronotropic incompetence (3). DDD (15) + DDDR (18) for SND with various degree of AVB, for SND without ventricular escape, or elective.

Mean atrial thresholds were 0.9 ± 0.4 V, with endocardial potential of 3.36 ± 1.38 mV. The only post-implant complications were the early dysfunction of two leads, one atrial and one ventricular, that had to be repositioned.

Two months after implant, 52% were found in normal sinus rhythm, and 48% permanently paced in early as in late implantation.

Mean follow-up was 110 ± 79 months. Survival was 95% at one year, and 75% at five years. The only late complication was the dislodgment of a ventricular lead during a biopsy. No patient with isolated SND developed late AV block.

Pacing in transplanted heart is uneventful, and simple atrial pacing should be considered in most SND.

P2999 Endocardial biventricular pacing through jugular transseptal catheterization in end-stage heart failure

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Biventricular pacing may improve functional and hemodynamic status of patients with end-stage heart failure (HF) but transvenous left ventricular (LV) pacing through branches of the coronary sinus can not always be achieved. Endocardial LV pacing may be an alternative to epicardial LV pacing, which requires thoracotomy or thoracoscopy.

Methods: We developed a modified technique for LV pacing, performed with transseptal catheterization through the internal jugular vein. Five patients with end-stage cardiomyopathy and widened QRS linked to left bundle branch block (n = 4) or right ventricular pacing (n = 1) were included in this preliminary study. Transseptal catheterization was achieved via the internal jugular vein using a brockenbrough needle with a more curved tip than the standard model. An unipolar tined (n = 3) or screw-in (n = 2) lead was easily placed in the LV through a flexible long sheath. The proximal tip of the LV lead was tunneled and connected, with a special bipolar connector, to the ventricular channel of a dual (n = 3) or simple (n = 2) chamber pacemaker located in the subclavian area.

Results: Efficient acute sensing (V wave amplitude = 12 ± 3 mV) and pacing (acute pacing threshold = 0.6 ± 0.3 V) were obtained in the 5 patients. Early loss of capture occurred in the 2 first patients requiring lead replacement. At 6 month follow-up, biventricular pacing was maintained in all patients (mean LV threshold 1.1 V) with QRS duration reduction always observed when compared with right ventricular pacing (QRS duration: 140 ± 20 ms *vs* 220 ± 25 ms, respectively; $p < 0.001$). Clinical status improved dramatically and was maintained at follow-up in all patients who were free of clinical embolic event with oral anticoagulant therapy.

In conclusion, endocardial LV pacing can be achieved via jugular transseptal catheterization and could be an alternative to venous or epicardial pacing in end-stage heart failure.

P3000 The role of ischaemia in early sinus node dysfunction after orthotopic transplantation

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We reviewed the 57 permanent pacemakers (PM) implanted in a series of 930 cardiac transplants between 1988 and 1998 for persistent sinus node dysfunction (SND). The mean age was 46 ± 11 years, 90% were male.

All patients had undergone the orthotopic transplantation using the classical Shumway technique. Half of the population were implanted during the first 6 post-operative weeks. The incidence of early implantation ranged from 4 to 8 by year up to 1995, and then decreased to one or none since 1996. The other half were implanted later, between I to 10 years, 5 every 2 years.

To evaluate risk factors for implant, multivariate analysis was performed in the 49 subjects with complete data including biopsies information. They were separated in two group: 20 patients with early SND ≤ 6 weeks without rejection group I, and 29 patients, with early (3) or late SND at a time of rejection (16), and 7 late SND without rejection. Early SND only differed from the other group by aortic cross clamping time (ACCT) (116.6 ± 37.1 vs 91.5 ± 18.8 min; $p = 0.047$) and graft ischemia (GI) (165.93 ± 62.1 vs 126.9 ± 48.2 min; $p = 0.039$).

There was no PM implant in the 45 other patients transplanted between 1996 and 1998 with operative procedure preserving the superior vena cava. In this group, ACCT was 108 ± 21 min, and GI 159 ± 56.

In the absence of rejection, early SND is related to the ischemia of a sinus node damaged by the classical technique. This is suggested by the fact that despite similar ischemic times, there is no more early pacemaker implantation with operative procedures preserving the superior vena cavae as used since 1996. However late sinus node dysfunction can still be found in patients from the older series, especially at time of rejection.

P3001 Multisite pacing with short atrioventricular delays acutely improves diastolic and systolic function in patients with congestive heart failure

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The PATH-CHF study included patients (pts) with CHF, NYHA class III–IV, QRS-width > 120 ms and PR-interval > 150 ms. All pts received 2 DDD pacemakers (PM) allowing VDD pacing either from the right ventricular apex (RV), left ventricle (LV) or both ventricles (BV) at a short (AV-S, 50–130 ms) and long (AV-L, 120–260 ms) AV delay adjusted to the individual PR interval. Pulsed-wave Doppler analysis of transmitral inflow and continuous-wave doppler measurement of aortic outflow velocity time integral (A_{VTI}) was performed in sinus rhythm (SR) and all pacing modes.

Results: 25 pts were analyzed. Mitral inflow velocity time integral (M_{VTI}) acutely increased by 11–19% and A_{VTI} by 3–6% with LV and BV pacing at AV-S compared to SR. RV and AV-L resulted in only minor changes. Similar effects were observed for diastolic filling time (FT) and early filling wave deceleration time (Edt).

		Short AV-delay			Long AV-delay		
	SR	RV	LV	BV	RV	LV	BV
M_{VTI} (cm)	16.2±4.6	17.9±5.1*	18±5.7*	19.3±6.3#	17.1±4.6	17.2±5.2	17.3±4.6
FT (ms)	385±129	406±120*	421±147#	435±141#	390±123	384±128	386±102
Edt (ms)	181±65	222±97*	203±89	236±112#	210±110	197±96	205±110
A_{VTI} (cm)	23.2±5.6	23.7±6.2	24±5.9	24.5±5.7*	23.2±5.5	22.9±4.8	23.6±5.8

* = $p < 0.05$ vs. SR; # = $p < 0.01$ vs. SR

Conclusions: LV and BV pacing with short AV delays acutely improve doppler indices of diastolic function and stroke volume in patients with congestive heart failure compared to SR and RV pacing. Diastolic filling time and Edt are prolonged with an increase in mitral inflow during the early filling phase. There is no significant improvement at long AV delays.

P3002 Long-term performance of a transvenous system for atrio-biventricular pacing in patients with dilated cardiomyopathy and congestive heart failure

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The InSync clinical trial is a prospective, non-randomized study evaluating cardiac resynchronization therapy in patients with dilated cardiomyopathy (LVEDD ≥ 60 mm), advanced heart failure (NYHA class III/IV, EF ≤ 35%), and ventricular conduction deficits (QRS ≥ 150 msec).

Methods: All pts were implanted with the InSync system, including the Medtronic Attain Model 2187 unipolar (71 pts) or Model 2188 bipolar (25 pts) transvenous LV leads. 16 centers in Europe and Canada are participating in the study, and pts are followed for 12 months. Data summarizing the performance for the Models 2187 and 2188 leads through 6-months of follow-up are presented here.

Results: 103 pts were successfully implanted with an InSync system out of 118 attempts (success rate = 87.3%). The average LV lead implant time was 52 ± 45 min.; the average total procedure time was 128 ± 76 min. Data shown below represent paired results (to time of implant) for electrical parameters for the Models 2187 and 2188 leads.

Model 2187 LV lead	BiV Thresholds (V) (@0.5 msec)	Impedance (Ω)	R-Wave (mV)
1 month	1.9 (N = 27)	478* (N = 39)	12.2 (N = 29)
3 months	1.9 (N = 16)	499* (N = 29)	11.5 (N = 21)
6 months	2.3 (N = 13)	469 (N = 19)	13.1 (N = 14)

*p value ≤ 0.05

Model 2188 LV lead	BiV Thresholds (V) (@0.5 msec)	Impedance (Ω)	R-Wave (mV)
1 month	2.5 *(N = 10)*	463* (N = 14)	9.6 (N = 13)
3 months	3.0 *(N = 8)*	506* (N = 13)	12.5 (N = 9)
6 months	2.7 *(N = 9)*	527* (N = 13)	11.5 (N = 11)

*p value ≤ 0.05

Conclusions: Stable biventricular (BiV) capture thresholds, sensing, and lead impedances were observed for the Models 2187 and 2188 transvenous LV leads through 6 months following implant of the InSync system. Further studies will contribute to overall experience and success with transvenous lead placement for cardiac resynchronization.

P3003 Right ventricular mural endocarditis after central catheter

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Valvular endocarditis is well known and did motivate numerous publications. We report a case of a right mural infective endocarditis in a child.

A 15 years old boy was admitted for acute left schoulder osteitis complicated with septicaemia due to *Staphylococcus aureus* and purulent pericarditis. The evolution was favorable after drainage, lavage of pericardium and schoulder and antibiotics infusion with a central subclavian catheter during 15 days (oxacillin, netromycin, rifampicin). We obtained sterilization of sepsis and total regression of pericardial effusion without constriction at regular echocardiography control.

We removed the central catheter after 15 days. Culture of the tip found coagulase negative *Staphylococcus* with high level of resistance.

Four days after removing the catheter, the transthoracic echocardiography, done to control the pericardium, revealed a large vegetation (17 mm long) on the basal wall of the right ventricule, near from the IV-septum, with a large implantation. The patient felt well without fever. Blood culture were sterile and sedimentation rate was high.

The child received new antibiotics during 6 weeks (vancomycin, pyostacin) with a good evolution on the vegetation's size after one month of treatment, and disappearing of infection signs.

In conclusion: This case report seems to be unusual. It focus on unusual localization of endocarditis and may be explained by satellite lesions due to the jet stream from the catheter striking the right ventricule endocardium.

P3004 Natural course of severe asymptomatic rheumatic mitral regurgitation

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Surgical correction of severe asymptomatic rheumatic mitral regurgitation (MR) remains controversial. The purpose of the study was to determine the natural course of severe asymptomatic rheumatic MR.

Methods. Thirty patients with grade3 and 20 patients with grade4 MR according to Sellers angiographic classification had clinical and echo-Doppler evaluation at baseline and at a mean follow-up (F/U) of 6 ± 4 (range 2–14) years. Mean age was 16.7 ± 7 (4–17) years. The rheumatic origin was assessed according to Jones criteria. The interval between the acute attack and entry in the study was 8 ± 5 (4–16) months. Forty six patients (92%) were in NYHA fuctional class I and 4 patients were in class II. Baseline pulmonary capillary wedge pressure was ≤16 mmHg in all patients.

Results: Functional status remained unchanged in 48 patients (96%), 2 patients evolved to functional class III and underwent surgical correction. Mitral regurgitation decreased to grade2 in 5 patients and to grade1 in 3 patients. It remained unchanged in 42 patients (84%). Left ventricle dimensions (DD = diastolic diameter, SD = systo-lic diameter, FS = fractional shortening) and left atrium (LA) dimension remained unchanged (p = NS):

	DD (mm)	SD (mm)	FS (%)	LA (mm)
Baseline	57 (43–77)	34 (23–51)	40 (28–51)	36 (20–54)
F/U	55 (44–4)	36 (25–51)	36 (30–47)	33 (21–38)

In conclusion: Severe asymptomatic rheumatic MR remains unchanged in the majority of patients. It decreases in few patients. Functional status deterioration is very rare.

Day 5

Wednesday, September 1, 1999

ATRIOVENTRICULAR NODAL RE-ENTRY TACHYCARDIAS

3121 Morphology of the anterior-superior approach region in the light of atrioventricular nodal re-entry tachycardia fast pathway ablation

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Atrioventricular nodal reentry tachycardia (AVNRT) base on reentry circulation in nodal-perinodal area. The radical treatment of choice is radiofrequency fast or slow pathway ablation. Procedure approached from the anterior-superior (fast) region sufficients a few seconds of energy delivery for succes, however this can result often in a-v block. The possibility that arrhythmias substrate may lie very superficial (succes of ablation) and damage of the normal structures (complication) in the perinodal region must be considered.

In order to confirm this hypothesis we took observation on the autopsy material of 30 normal hearts, both sexes from 18 to 81 years of age (control) and 30 hearts with a-v total block 45–95 years of age (block group). Koch's triangle was divided in the sagittal plane into 3 parts: inferior, central and superior. We paid attention on the morphology of the nodal artery (NA), atrial inputs (AI).

It was observed that NA at the level of central fibrous body was positioned in 94% in the central and in 6% in the inferior part of the Koch's triangle. It was removed from the endocardium 3–6 mm in control and 2–5 mm in block group respectively (no significant). Besides, we observed in 30% of controls small parietal thrombi and in 90% of block group ($p < 0.05$). In the perinodal area we distinguish AI that directly joined the a-v compact node. They composed 2 layers: superficial (right part of the interatrial septum) or deep (left part). The first of mentioned occurred in 100% of controls and in 80% of block groups (NS), and the last in 80% of control group and in 33.3% in block respectively ($p < 0.05$).

Conclusions: 1) the real substrate of arrhythmia in anterior-superior region lies very superficial and far from the conduction tissue 2) NA in examined hearts was laying deep beneath the endocardium 3) ablation of the deep part laing close to the node could result in a-v block

3122 High-resolution mapping of the canine atrioventricular node after endocardial resection reveals functional dissociation: the substrate for re-entry?

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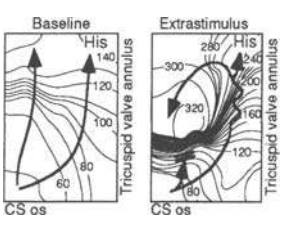
During atrioventricular (AV) nodal reentry, reentrant excitation is supposed to involve 2 functionally distinct pathways. Since direct mapping of nodal extracellular electrograms could not yet be performed, controversy continues regarding the mechanism and the site of reentry.

Methods: In 8 isolated, blood perfused dog hearts, the endocardium overlying the AV node was carefully resected until AV nodal extracellular signals could be identified with a roving electrode. A 247-terminal electrode (19 × 13) with an interelectrode distance of 0.3 mm, was used to map AV nodal activation during programmed atrial extrastimulation.

Results: Antegrade functioning of the AV node did not change significantly after endocardial resection. In 4 hearts, electrical activation of the AV node revealed functional dissociation. As illustrated, after a shortly coupled atrial extra-stimulus (right panel, S_1S_2 190 ms), block occurred in the anterior area and activity reached the His bundle via the posterior area. The anterior area was then activated retrogradely. However, antegrade conduction delay was never sufficient to allow complete recovery of the anterior area and the occurrence of an atrial echo.



Conclusions: Functional dissociation of the canine AV node in response to premature atrial stimulation gives rise to conduction block in the anterior area and retrograde activation of this area. This can be the substrate for AV nodal reentry.

3123 ATP test: a bedside diagnostic-tool for identifying patients with palpitations who are likely to benefit from electrophysiologic evaluation

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Patients with atrioventricular nodal reentry tachycardia (AVNRT) or AV reentry tachycardia (AVRT) are generally referred for electrophysiologic studies (EPS) because these arrhythmias are curable with radiofrequency ablation. However, AVNRT and AVRT are often short-lasting arrhythmias that elude clinical diagnosis. We showed that administration of adenosine triphosphate (ATP) during sinus rhythm may expose dual AV node physiology (DAVNP) [Circulation 1998; 98: 47]. Also, some data suggest that ATP may unmask a concealed accessory pathway (AP). Thus, we used our "ATP test" to identify AVNRT or AVRT among patients with "palpitations of unclear etiology."

Patients with palpitations were included if: 1) Their history suggested a paroxysmal supraventricular tachycardia, but spontaneous arrhythmias could not be documented. 2) Arrhythmias had been documented (mainly on single-lead recordings) but their mechanism remained unclear. Patients with antegradely conducting AP were excluded.

ATP was given intravenously during sinus rhythm using 10 mg increments. The ATP test was "positive" when signs of DAVNP (a PR "jump" of $^{3}50$ msec in consecutive sinus beats) or concealed AP (induction of AVR echo beats) were disclosed. The ATP test was "negative" when ^{3}IIo AV block without "PR jump" or AVR echoes ensued. These results were correlated with the results of a subsequent EP evaluation.

Sixty six patients were studied (20 with "palpitations but no documented arrhythmias" and 44 with "arrhythmias of unclear mechanism"). A positive ATP test predicted the presence of AVNRT or AVRT with a positive predictive value of 93% (sensitivity = 72%) but a negative predictive value of 29% (specificity = 67%).

A "positive ATP test" is highly predictable of AVNRT or AVRT. This bedside test may be used to select patients with palpitations who will benefit from early referral to EPS.

3124 The slow pathway potential (A_{SP}) indicates the activation of an anatomical input to the atrioventricular node

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Background: Although the so-called "slow pathway potential" or A_{SP} is often used as target for ablation of AVNRT, it is still a matter of debate in how far this potential represents indeed the activation of a discrete anatomical pathway, or is the functional result of the nonuniform anisotropic conduction properties of the posterior AV nodal inputs. We postulated that if functional properties would determine the A_{SP} morphology, it would depend on the direction of the activation wavefront.

Methods: We recorded A_{SP} during sinus rhythm (SR) and pacing at 3 atrial sites in 33 pts with Slow/Fast AVNRT (28 women; 39 ± 12 y). Pacing was performed from the atrial appendage (RAA), proximal coronary sinus (CS) and dorso-septal right atrium (800 ms). The stability of the A_{SP} was confirmed by comparing its morphology during intermittent SR. Power-controlled RF delivery was directed at the A_{SP} site (20–25 W).

Results: Measurements were not possible in 7 pts due to instability of the Asp recording catheter or absence of a clear A_{SP} potential. In 18 of the 26 remaining pts (69%), the Asp morphology was identical or highly similar during pacing from the different positions, with clear variations in the relative timing of the first (presumably) atrial deflection and the A_{SP} potential. In 8 pts, A_{SP} was different during pacing from at least 1 position. The median number of RF applications for ablation of the slow pathway was 1 respectively 2 in both groups (2.1 ± 2.0 vs. 1.9 ± 0.6: NS).

Conclusion: A similar A_{SP} morphology in the majority of pts indicates that it is not (or not always) generated by functional conduction properties (e.g. nonuniform anisotropy) but that the posterior input to the AV node is entered via the same anatomical corridor. Moreover, since the A_{SP} site results in ablation of AVNRT, the A_{SP} electogram must be due to activation of the reentrant circuit (i.e. AV node extensions or the atrial posterior input), and the small preceding deflection due to far-field atrial potentials or to activation of overlying isolated atrial tissue. Both are generated separately.

3125 Atypical patterns of re-entry in patients with atrioventricular nodal tachycardia

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Similar or identical His-to-atrium (H-A) intervals during tachycardia (T) and ventricular (V) pacing (P) at the T cycle length (H-AP) ([H-AT]-[H-AP] ~ 0) are suggestive of a lower reentrant circuit turn-around located in close proximity to the proximal His bundle and account for most patterns observed in the typical slow/fast [s/f] form of AVNRT.

Methods: Out of 219 pts with AVNRT, we investigated the [H-AT]-[H-AP] in 29 (13%) pts presenting with an atypical AVNRT. The H-AT was defined as negative if the first retrograde A activation at time of T induction preceded the H deflection of the first T QRS complex.

Results: Seven pts presented with a f/s, 8 with a s/s, 8 with a f/s and a s/f, 3 with a s/s and s/f, and 1 with a s/s, f/s and s/f form; in 2 more pts, retrograde s pathway (p) emerged at the anterior input to the AV node. At time of T induction, the H-AT was negative (−83 ± −28 ms) in 9 and positive (173 ± 76 ms) in 20 pts. H-AP matching retrograde A conduction through the s p as during T were available in all 9 pts of the former and in 13 pts of the latter group. The [H-AT]-[H-AP] was 249 ± 93 ms in pts with negative H-AT and 100 ± 55 ms in pts with positive H-AT at time of T induction. Ablation was achieved in all pts with 2 (range, 1–17) RF pulses delivered at the posteroseptal-to-midseptal A-tricuspid region.

Conclusions: Atypical AVNRT: 1) accounts for ~10% of all AVNRTs referred for RF ablation; 2) is related to a retrograde s p emerging at the posterior and anterior AV nodal input in ~90% and ~10% of cases, respectively; 3) is associated with antegrade f p conduction in ~50% and s p conduction in ~50% of cases. During retrograde s p conduction, H-AT invariably shorter than H-AP are suggestive of a lower turn-around of the reentrant circuit away from the entrance of the compact node into the His bundle.

3126 Site of recording of the His potential in relation to the angiographic triangle of Koch in patients with atrioventricular nodal re-entry tachycardia

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In a series of 37 consecutive patients (Pts) with AV nodal reentry tachycardia in whom a right atrial angiogram (RA-angio) was performed to disclose the angiographic boundaries of the triangle of Koch (TK), we have measured the amplitude of the atrial (A), ventricular (V) and His bundle (H) electrograms recorded near the anterosuperior vertex of the TK in relation to the distance between the tip of the His bundle catheter (Hbcath) an the angiogaphic margin of the tricuspid valve. Care was taken to place the HBcath at the site of recording of the largest possible H potential. Six Pts were excluded because the H-V interval was <36 ms. Intracardiac recordings obtained at the time of performing RA-angio were filtered between 30–500 Hz. The distance between the tip of the HBcath and the anterosuperior vertex of the TK (as defined with RA-angio) was 2.5 ± 6.9 mm (from +19 mm to −10 mm; negative values were those obtained when the tip of the HBcath was beyond the angiographic limit of the tricuspid valve). Patients were divided into 3 groups (Gr) according to the relation between the tip of the HBcath: Gr A (8 Pts [26%]) with a distance H-vertex of the TK more negative than −2 mm; Gr B (9 Pts [29%]) with an H-vertex of 0 ± 2 mm; Gr C(14 Pts [45%]) with an H-vertex > +2 mm. There was no relation between the site of recording of the His potential and the site of successful ablation of the slow pathway within the triangle of Koch. In no instance ablation resulted in unwanted transient or permanent AV block.

Electrograms in relation to the the TK

Gr	H-vertex mm	A mV	H mV	V mV	H-V ms
A	−4.8 ± 3	0.33 ± 0.25	0.38 ± 0.23	2.4 ± 0.9	47 ± 7
B	0.2 ± 0.9	0.30 ± 0.30	0.15 ± 0.05	2.1 ± 1.0	44 ± 5
C	8.3 ± 5.5	1.10 ± 1.0	0.29 ± 0.16	1.4 ± 0.9	49 ± 6

Gr C had significantly larger A and smaller V than the other 2 Grs.

Conclusions: the relations between the angiographic TK (as defined with RA-angio) and the A-V conduction system (as defined by the HBcath) show a wide variation in Pts with AVNRT. The HBcath is a better marker to avoid unwanted AV nodal-His ablation than the angiographic definition of the triangle of Koch.

ATRIAL AND ATRIOVENTRICULAR NODAL REMODELLING

3127 Right atrial appendage monophasic action potentials for assessment of atrial electrical remodelling in patients with successfully cardioverted chronic atrial fibrillation

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Aim: Conventional electrophysiological studies (EPS) have shown that rapid atrial depolarization rates result in changes of the electrical properties of the atrium. In this study we used repeated monophasic action potential (MAP) recordings in order to assess the changes in atrial electrical behavior in successfully cardioverted chronic atrial fibrillation patients.

Methods: Consecutive chronic atrial fibrillation patients were studied after successful intracardiac low energy conversion to sinus rhythm. Antiarrhythmic drugs were stopped for at least five half lives before procedure. All patients underwent two consecutive electrophysiological studies, the first within fifteen minutes after conversion, and the second 24 hours later. A special catheter, capable of simultaneous pacing and MAP recording, was advanced to within the right atrial appendage and stabilized in a position where it was possible to record satisfactory MAPs and to stimulate the atrium at a low diastolic threshold. Atrial effective refractory period at a basic cycle length of 500 ms and the duration of MAP recordings until 90% of repolarization (MAPd90) were evaluated after one minute of continuous pacing at five separate cycle lengths (600, 500, 450, 400, 350 ms).

Results: Satisfactory MAP recordings were possible in nine out of eleven patients (mean age 68 ± 9, six male) who were initially recruited. The values of the parameters measured in the two studies are given in the table below. All values are expressed as mean ± SD. MAPd90 differed significantly only between the two measurements marked by an asterisk (*).

	A-ERP	MAPd90	MAPd90	MAPd90	MAPd90	MAPd90	p
	500	600	500	450	400	350	
0 h	202 ± 15	232 ± 30*	228 ± 22	224 ± 21	215 ± 20	206 ± 21*	0.03*
24 h	250 ± 26	272 ± 34	274 ± 41	268 ± 29	250 ± 17	243 ± 16	0.26
p	<0.001	0.054	0.132	0.049	0.008	0.004	

Conclusions: These results suggest that MAP duration, similarly to atrial ERP, increases with time after the electrical conversion of chronic atrial fibrillation to sinus rhythm. In contrast, normal adaptation of MAP duration to cycle length was not confirmed.

3128 Is acute "reversed" atrial remodelling a transient phenomenon in man?

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Aim: The Atrial Effective Refractory Period (ERP) shortens following episodes of AF (remodelling). The temporal changes in the ERP following DC Cardioversion in patients with persistent AF is unknown.

Methods: The atrial ERP was measured at two sites, the mid lateral right atrium (MLRA) and the right atrial appendage (RAA), at cycle lengths of 600 and 400 ms immediately, 24 hours and 2 weeks post DC Cardioversion. 34 patients (pts) (mean age 67 (SD 9), 57% male) were enrolled. All pts had persistent AF for >1 month prior to cardioversion. All cardioactive drugs were stopped 5 half lives prior to the study.

Results: 32 pts were in SR at 24 hrs and 14 pts in SR at 2 weeks. *24 hrs:* Post cardioversion the ERP was significantly shorter at the RAA site for both cycle lengths when compared to the MLRA ($p < 0.03$). A significant increase in ERP occurred at both atrial sites and cycle lengths from 0 hrs to 24 hrs ($p < 0.0001$). Despite this increase, the RAA ERP remained significantly shorter than the MLRA at 24 hrs ($p < 0.03$).

Site	0 hr	24 hrs	Site	0 hr	24 hrs
RAA600	211 (25)	254 (31)	MLRA600	225 (28)	275 (40)
RAA400	208 (25)	242 (30)	MLRA400	219 (34)	256 (43)

2 weeks: There was a significant rise in ERP at both sites and cycle lengths between 0 and 24 hrs. A significant fall in ERP occurred between 24 hrs and 2 weeks at RAA (600 & 400 ms) and MLRA 600 ms ($P < 0.01$)

	0 hr	24 hrs	2 week
RAA600	214 (21)	256 (40)	221 (43)
RAA400	211 (23)	249 (46)	217 (36)
MLRA600	226 (38)	280 (44)	235 (31)
MLRA400	230 (50)	265 (46)	242 (36)

There was no significant difference in ERP at 0 hrs or 24 hrs between pts who then reverted to AF and those in SR at 2 weeks.

Conclusions: 1) A significant increase in ERP occurs from 0 to 24 hrs post Cardioversion. **2)** The significant difference in refractoriness between the RAA and MLRA persists to 24 hrs. **3)** The change in ERP does not predict post shock duration of SR. **4)** Pts still in SR at 2 weeks show a significant fall in ERP from 24 hr values back to immediate post cardioversion levels. This data suggests that acute 'reversed' remodelling is transient in man.

3129 Atrial electrical remodelling due to dilatation or rapid pacing is diminished by verapamil, but not by glibenclamid or cariporide, in Langendorff-perfused rabbit hearts

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Atrial dilatation (AD) and rapid pacing (RP) cause electrical remodeling (ER) by reducing atrial effective refractory periods (AERPs). We investigated the effects of Verapamil (Ve), a blocker of the L-type Ca^{2+}-channel (LTCC), Glibenclamid (Gli), a blocker of the ATP-dependent K^+-channel (K^+_{ATP}), and Cariporide (Car), a Na^+/H^+-channel blocker on ER due to AD and RP in a rabbit Langendorff-model of sustained atrial fibrillation (SAF). In 20 hearts basal (b) AERPs were measured under stepwise increase in IAP [cm H_2O] up to 20 cm H_2O. Episodes of (SAF) defined as lasting >10 minutes, were protocolled. After deflation AERPs were measured every 2 minutes for 10 minutes of RP [20 Hz/min]. Then Ve [0.5 mg/l] (n = 7), Gli [0.05 mg/l] (n = 7), or Cariporide [0.3 mg/l] (n = 6) were added to the perfusate and the protocol was repeated.

Results:

cm H_2O	0	6	10	Pre RP	P 4 min	P 10 min
AERP b	83 ± 9	72 ± 15	61 ± 12*	84 ± 9	65 ± 9	54 ± 8*
AERP Ve	69 ± 12#	73 ± 13	79 ± 18+	84 ± 7	79 ± 9	72 ± 15
AERP Gli	89 ± 10	77 ± 4	66 ± 13*	82 ± 10	64 ± 11	60 ± 13*
AERP Car	88 ± 10	79 ± 8	66 ± 7*	81 ± 6	65 ± 3	59 ± 7*

*$p < 0.01$ compared to 0 cm H_2O and pre RP, respectively; #$p < 0.01$, +$p < 0.05$ compared to b, all parameters in ms

ER occurs both after AD and RP. Ve significantly shortens AERP at 0 cm H_2O. However, Ve abolishes ER after AD and significantly reduces it after RP. After Gli and Car, ER both due to RP or AD is not significantly altered. Ve prevented the induction of SAF in all hearts, Gli and Car did not prevent SAF in any heart.

Conclusions: The Langendorff-perfused rabbit heart shows ER both due to RP and AD to a similar extent. LTCC seems to play a crucial role in the process of ER both due to AD and RP, suggesting similar pathophysiological mechanisms. K^+_{ATP} and Na^+/H^+-channel did not influence ER, suggesting that ischemia and acidosis do not play a substantial role in either form of ER in this model.

3130 Electrophysiological remodelling of the atria after internal cardioversion of atrial fibrillation

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Early recurrence of atrial fibrillation after internal cardioversion (IC) remains an unsolved problem of the implantable atrioverter. Electrophysiological remodelling of the atria (LA/RA) after IC of chronic (cAF) and intermittent AF (iAF) (AF-duration < 24 h) has not been studied. After IC of cAF in 15 patients (Pt) (AF duration: 64 ± 50 months, LA: 45 ± 5 mm) and iAF (LA: 37 ± 6 mm) in 15 Pt continuous registration and computer analysis of the duration of monophasic action potentials at 90% repolarisation (APD90) in the right atrial appendage was performed and interatrial conduction times (CT) between high RA and coronary sinus (CS) in sinus rhythm (SR) and during stimulation with a cycle length (CL) of 500 ms were measured during a time period of 20 min.

Results: APD90 was prolonged by a mean of 52 ± 30 ms. There was significantly more APD90 prolongation in minute 0–3 with 46 ± 21 ms as compared to minute 3–20 with 10 ± 9 ms ($p < 0.05$). Interatrial CT did not significantly change. APD90 and CT were not significantly different in the 11 Pt (37%) with 3 ± 2 AF recurrences after 3 ± 2 min and comparing Pt with cAF and iAF ($p > 0.05$).

APD90 and CT (ms)

	0 min	1 min	3 min	10 min	20 min
APD90/SR	161 ± 20	199 ± 35	210 ± 32	215 ± 31	213 ± 34
CT/RA– > CS/SR	98 ± 30	81 ± 22	91 ± 26	86 ± 25	98 ± 30
CT/RA– > CS/500		142 ± 35	131 ± 16	130 ± 50	135 ± 21
CT/CS– > RA/500		136 ± 15	135 ± 10	133 ± 19	138 ± 10

Conclusions: (1) There is a significant prolongation of atrial monophasic action potential duration in minute 0–3 after internal cardioversion regardless of AF duration and atrial size. (2) The prolongation of atrial action potentials does not significantly differ between Pt with and without recurrence of atrial fibrillation in the first minutes after internal cardioversion.

3131 Electrical remodelling of atrioventricular conduction in patients with chronic atrial fibrillation

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Aim: Long periods of very rapid atrial depolarizations probably affect the electrical properties of atrioventricular conductive tissue. In this study we looked for such effects of chronic atrial fibrillation on the atrioventricular node (AVN) and the His bundle.

Methods: Fourteen consecutive patients with chronic atrial fibrillation (>3 months duration) electrically converted to sinus rhythm were studied. Their mean age was 67 ± 7 years and nine were male. All were free of antiarrhythmic drugs for at least five half lives. They underwent two electrophysiological studies, the first immediately after conversion, and the second 24 hours later. Basic intervals (AH, HV), right atrial effective refractory period (A-ERP), AVN functional refractory period at a basic cycle length of 500 ms (AVN-FRP) and the Wenckebach point (WP) were evaluated.

Results: The values of the parameters measured in the two studies are given in the table below.All values are expressed in ms and are represented as mean ± SD.

	AH	HV	A-ERP	AVN-FRP	WP
0 h	112 ± 44	49 ± 5.7	202 ± 15	386 ± 78	431 ± 76
24 h	108+46	50+6	250 ± 26	345 ± 92	401 ± 75
p	NS	NS	<0.001	<0.05	<0.05

Conclusion: Electrical remodeling resulting from chronic atrial fibrillation also affects the atrioventricular node, apart from atrial tissue. These changes subside significantly within the first 24 h after conversion to sinus rhythm.

NEW POTASSIUM CHANNEL BLOCKERS

3132 Dose response for azimilide treatment of paroxysmal supraventricular tachycardia

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Azimilide (AZ) is an investigational class III antiarrhythmic agent the effect of which on paroxysmal supraventricular tachycardia (PSVT) has not previously been reported. In three randomized, placebo-controlled, double-blind trials, patients with symptomatic PSVT received 35, 75 or 100 mg AZ. The studies were identical in design, except for the duration of follow-up (180–270 days) and the dosage. AZ was dosed generally as an outpatient, twice a day for 3 days (loading phase), and then once per day. In each study the primary outcome variable was the first symptomatic recurrence of supraventricular arrhythmia after completion of the loading phase, as documented using transtelephonic ECG monitoring. Efficacy data from all 3 trials were tested for a trend across doses using a log-rank trend test with placebo = 0 mg and all 3 AZ doses. Data were stratified by trial to control for variation in placebo group event rates. Recurrent arrhythmias were defined by recording trans-telephonic ECG.

Results: A total of 133 patients were enrolled (65% female), aged 58 ± 14.9, with 50 receiving placebo (P) and 83 receiving AZ. Heart failure was present in 8% and coronary artery disease in 23%. The log-rank trend test was statistically significant with chi-square = 6.53 and p = 0.01. There were no cases of torsades de pointes. Thus, AZ showed a positive dose-response relationship over the dose range tested. The 100 mg dose demonstrated a clinically important treatment effect with hazard ratio (placebo:azimilide) of 2.35 (CI 1.18, 4.68) and p = 0.015.

Conclusions: AZ demonstrates a dose-response relationship over the dose range of 35–100 mg daily in patients with symptomatic PSVT. The 100 mg daily dose has both statistically significant and clinically important antiarrhythmic effects.

3133 Dofetilide reduces hospitalisations in patients with atrial fibrillation or flutter and left ventricular dysfunction: a DIAMOND sub-analysis

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Patients (pts) with left ventricular (LV) dysfunction and co-existing atrial fibrillation or flutter (AF/AFl) may suffer substantial morbidity due to impaired haemodynamic function. Dofetilide (D), a class III antiarrhythmic agent, has been shown to be effective in the restoration and maintenance of sinus rhythm (SR). In this DIAMOND (Danish Investigations of Arrhythmia and Mortality ON Dofetilide) sub-analysis of the pre-defined endpoint of hospitalisation with worsening congestive heart failure (CHF), the effect of D therapy on subsequent hospitalisation was assessed in the 506 pts with AF/AFl at baseline. All pts had LV dysfunction (equivalent to left ventricular ejection fraction ≤ 35%).

Methods: Pts were randomly assigned to 250 μg bid D (n = 249) or placebo (Pl) (n = 257) with D subsequently adjusted based on creatinine clearance and QTc interval. Over the course of the study, SR was pharmacologically restored in 112 D (45%) and 35 Pl (14%) pts and electrically restored in 36 D (15%) and 51 Pl (20%) pts. Time to hospitalisation was assessed during the follow up period of 12–42 months.

Results: Both first hospitalisation due to CHF (risk reduction 0.69; p = 0.014) and first hospitalization for all-causes (risk reduction 0.70; p = 0.004) were significantly reduced on D compared with Pl therapy. There was no difference in the number of pts with non-heart failure related first hospitalisations.

Pts hospitalized for CHF N (%)		Pts hospitalized for non-CHF N (%)		Pts hospitalized for All Cause N (%)	
D (n = 249)	Pl (n = 257)	D (n = 249)	Pl (n = 257)	D (n = 249)	Pl (n = 257)
73 (29.3%)	102 (40.0%)	52 (20.9%)	54 (21.0%)	125 (50.2%)	156 (60.7%)

Conclusion: In pts with AF/AFl and LV dysfunction, D therapy significantly reduced the requirement for hospitalisation mediated by an improvement in CHF.

3134 The effect of dofetilide on pharmacodynamics of warfarin and pharmacokinetics of digoxin

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Dofetilide (D) is a novel class III antiarrhythmic agent effective in treating a broad range of supraventricular tachyarrhythmias, including atrial fibrillation (AF) and atrial flutter (AFl). Warfarin (W) and digoxin (DIG) are drugs commonly used in the treatment of patients with AF/AFl. This study was performed to assess whether steady-state D treatment altered the pharmacodynamics of W or the pharmacokinetics of DIG.

Fourteen healthy men were randomly assigned to treatment with either D 750 mcg bid or placebo (P) in a two-way crossover design study with a washout period of ≥1 week. A single dose of W 40 mg was administered 2 hours after D or P on day 5 of an 8-day treatment period. Prothrombin time (PT) was measured at specified intervals to 96 hours. Compared with P, D did not significantly affect PT (D-P 0.04 sec; p = 0.69) or the area under the PT time curve (AUECt) [D-P = 13 sec•h; p = 0.78].

After a one-week washout period, 13 men received 250 mcg DIG daily (following loading doses of 1000 mcg on day 1 and 500 mcg on day 2). Serial measurements of plasma DIG concentration were evaluated for C_{trough}, C_{max}, T_{max}, AUC_{0-24}, and renal clearance on day 7. On day 8, subjects were randomly assigned to concomitant treatment with 250 mcg bid D (n = 8) or P (n = 5). DIG pharmacokinetic measurements were repeated on day 12 and compared with the baseline values. Compared with P, D did not affect C_{trough} (D-P = −0.02 nmol/l; p = 0.71), C_{max} (D-P = 0.0 nmol/l; p = 0.97), T_{max} (D-P = −0.7 hours; p = 0.06), AUC_{0-24} (D-P = 0.0 nmol•h/l; p = 0.99), or the renal clearance (D-P = −25 ml/min; p = 0.30) of DIG.

Conclusion: D does not significantly affect the pharmacodynamics of W or the pharmacokinetics of DIG, medications which are commonly prescribed in patients with AF/AFl.

3135 Pharmacokinetics and pharmacodynamics of dofetilide: daily versus intermittent dosing

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This randomized, single-blind, placebo-controlled, parallel-group study assessed the pharmacokinetics (PK) and dynamics (PD) of dofetilide (D). D (1 mg) was given bid for 24 days (daily) or as a single AM dose on days 1, 5, 10, 17 and 24 (int). Daily D resulted in initially rising plasma concentrations (conc.) with peak and steady-state conc. achieved by day 5. PK parameters were unaffected by int D and consistent with low inter- and intra-subject variability.

		Day 1	Day 5	Day 10	Day 17	Day 24
C_{max} ng/mL	Daily	4.79	7.10	6.93	7.08	6.99
	Int	4.61	4.74	4.48	4.69	5.01

Mean renal clearance was stable whether dosing was daily or int. Daily D resulted in increasing prolongation of the QTc interval for the first 2 days with no further increase despite increasing plasma D conc. This attenuation of QTc response stabilized after day 5 up to day 24, as represented by the change in slope of the plasma conc. versus change in QTc from baseline (Δ Slope of PK-PD effect). Int D dosing resulted in consistent changes in the QTc prolongation each time the drug was given.

		B/L	Day 1	Day 2	Day 3	Day 4	Day 5	Day 10	Day 17	Day 24
QTc Max	Daily	373	443	453	450	445	440	441	446	442
(msec)	Int	387	472	406	397	396	467	467	469	458
Δ Slope of	Daily						−5.15	−5.59	−5.38	−5.80
PK-PD	Int						−0.76	−0.69	−0.22	−1.40

In conclusion, this study demonstrates that D has predictable PK and PD when administered daily. The QTc interval prolongs for the first 2 days in response to increasing plasma conc. Thereafter, the QTc response to D is attenuated up to day 5 and does not progress further after day 5 up to day 24. QTc interval should be carefully monitored for the initial 3 days of D therapy.

3136 After one year treatment on dofetilide patients with longer post-cardioversion QT (QTc) interval are more likely to remain in sinus rhythm

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Dofetilide (D) is a new pure class III antiarrhythmic agent with a linear relationship between dose and QT interval. The relationship between QT interval and clinical efficacy has not been established for class III drugs.

Methods: EMERALD (European and Australian Multicenter Evaluative Research on Atrial Fibrillation – Dofetilide) assessed the efficacy and dose relationship of oral dofetilide (D) [125, 250, 500 mcg bid] and placebo (P), in 534 patients (pts) with atrial fibrillation (AF) in a double blind parallel group design. Patients with a QT interval > 500 msec or an increase over 20% from baseline after the first oral dose were excluded from the study.

Results: By day 3, 431 pts (81%) regained sinus rhythm (SR), pharmacologically or by DC conversion. D cardioverted significantly more pts (up to 29%) in a dose-dependent manner than P (<1%, $p < 0.05$ at all dose levels). At 3, 6, and 12 months, all doses of D maintained significantly more pts in SR than P ($p < 0.05$ at each time point). D was effective in converting patients with AF and maintaining up to 71% in SR at 6 months.

The post-cardioversion QT interval correlated linearly with the efficacy of D in maintaining SR after 12 months ($p = 0.04$). Patients with a QT interval after conversion > 425 msec had a 31% higher chance of staying in SR, compared to patients with a shorter QT.

In conclusion, the efficacy of D to maintain sinus rhythm after conversion of atrial fibrillation was related to the degree of QT prolongation by D.

3137 Dofetilide improves quality of life

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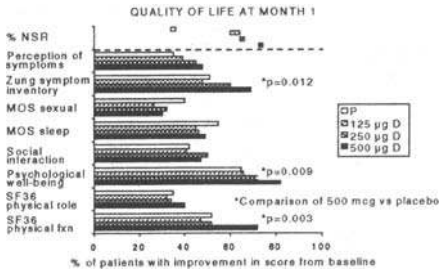
Quality of life (QOL) is significantly reduced in patients (pts) with atrial fibrillation or flutter (AF/AFl). The extent to which treatment of AF/AFl improves QOL depends on the effectiveness of the treatment and the side effects of the agents used. Dofetilide (D), a new class III agent has proven effective in the restoration and maintenance of sinus rhythm in pts with AF/AFl. The EMERALD (European And Australian Multicenter Evaluative Research on Atrial Fibrillation and Dofetilide) study was performed to assess the effect of D therapy on QOL.

Methods: Pts with AF/AFl were randomised to twice daily doses of 125 μg D (129 pts), 250 μg D (133 pts), 500 μg D (135 pts), or placebo (P) (137 pts) in a double-blind trial. QOL was assessed at baseline and at 1 month, independent of rhythm status, using MOS Short Form-36 (SF-36) physical function scale; SF-36 physical role limitation scale; Psychological General Well-Being Index; SQOLB Social Interaction Scale; MOS Sleep Evaluation Scale; MOS Sexual Functioning Scale; Zung Symptom Inventory.

Results: Symptom perception was assessed using a numerical scale. Compared to P, D resulted in significantly more patients with improvement in the SF-36 physical function scale, psychological well-being score, and the Zung symptom inventory. A dose response in improvement was also demonstrated for these instruments.



Conclusion: D significantly improves QOL in pts with AF/AFl.

3150 The ACE I/D polymorphism and mortality: a population-based study

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A previous report has suggested an association between the DD genotype of the ACE I/D polymorphism and an increased mortality rate in patients with chronic heart failure. To date, there is no epidemiological work looking at the effect of the ACE I/D polymorphism on mortality in the general population. We report on the association between the ACE I/D polymorphism and all cause mortality in a random sample of 1640 men and women aged 25–74 from a geographical urban population.

1640 attendees were studied in 1992/3. Left ventricular function was assessed by a left ventricular ejection fraction (LVEF) using the apical Biplane Simpson's Rule Method. A LVEF $\leq$ 30% was taken as significant systolic dysfunction (LVD). Ischaemic heart disease (IHD) as defined as a previous history of myocardial infarction or angina, use of nitrate drugs or the presence of a q wave or major ischaemia on the ECG. The ACE I/D polymorphism was determined according to the method of Rigat. The analysis below refers to all cause mortality at 4 years of follow up.

24% (322) of subjects were II, 48% (651) ID and 28% (385) of the DD genotype. These are in Hardy-Weinberg equilibrium. The 4 year all cause mortality rate in the whole cohort was 4.9% (80 deaths). DNA was available for analysis in 63 of these subjects.

Genotype	4 yr. mortality %	(n)	
II	3.1%	10	
ID	4.4%	29	p = 0.0.005 (II vs DD)
DD	6.2%	24	

A trend also existed for the DD polymorphism carrying a higher mortality rate in subjects with IHD (DD-12.4% vs II 7.8%) and in those with LVD (II 3% vs DD 25%). These were not statistically significant, most probably due to the small numbers of deaths.

We have demonstrated a significant association between homozygosity for the D allele of the ACE I/D polymorphism and all cause mortality in the general population

3151 Haemostatic parameters disturbances in patients with essential hypertension: the effect of ACE gene polymorphism

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The deletion (D) allele of the insertion/deletion (I/D) polymorphism of the angiotensin converting enzyme (ACE) gene has been implicated in the pathogenesis of a variety of cardiovascular disorders. This study examined the possible association of the ACE gene polymorphism with the fibrinogen (F), fibrinogen degradation products (FDP), D-dimer and plasminogen activator inhibitor-1 (PAI-1) levels in untreated hypertensive patients (pts).

Methods: The I/D polymorphism of ACE gene was determined in 104 hypertensives aged 56 ± 12 yrs. Forty-two pts had DD genotype (Group A), 30 pts had ID genotype (Group B) and 32 pts had II genotype (Group C). The three groups are matched for age, sex and body mass index. The F, FDP, D-dimer and PAI-1 levels were determined (ELISA method) in the whole population.

Results: The results and the comparison between the three groups are shown below:

Parameters	Group A	Group B	Group C
Fibrinogen (mg/dl)	342 ± 54	295 ± 49	298 ± 33
FDP (NV < 250 ng/ml	429 ± 167.5	263 ± 38.7	262 ± 64
D-dimer (NV < 400 ng/ml)	371 ± 73.6	244 ± 85	233 ± 88
PAI-1 (IU/ml)	13 ± 8.8	9.13 ± 6.6	8.84 ± 3.2

F	A–B, $p < 0.001$	A–C, $p < 0.001$	B–C, p = NS
FDP	A–B, $p < 0.0001$	A–C, $p < 0.0001$	B–C, p = NS
D-dimer	A–B, $p < 0.0001$	A–C, $p < 0.0001$	B–C, p = NS
PAI-1	A–B, $p < 0.05$	A–C, $p < 0.01$	B–C, p = NS

Conclusions: Our findings suggest that the DD genotype of the ACE gene polymorphism is associated with significantly increased levels of F, FDP, D-Dimer and PAI-1 in pts with EH, supporting the idea that ACE gene polymorphism plays a crucial role in the haemostatic balance hypertensives.

3152 The 825T-allele at the B3-subunit gene of heterotrimeric G proteins enhances adrenaline-induced platelet aggregation requiring simultaneous activation of gaq by 3′5′adenosine-2-phosphate

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We have recently identified a C825T polymorphism at the gene GNB3, encoding for the beta3 subunit of heterotrimeric G proteins, which is associated with enhanced PTX-sensitive G protein signalling, hypertension, and myocardial infarction (MI). Since platelet aggregation is crucial in the development of MI and involves activation of various G proteins, it is likely, that the 825T-allele, enforces the platelet responses to agonist stimulation.

Methods: Platelet rich plasma was obtained from 37 healthy, male volunteers. Aggregatory responses and changes in intracellular Ca^{2+} (delta$[Ca^{2+}]_i$) were compared according to genotype at GNB3 after stimulation with adrenaline, vasopressin, and thrombin- and thromboxane receptor agonists, respectively. Additionally, 3′,5′adenosin-2-phosphate (ADP), which activates PTX-sensitive (Galphai), and -insensitive (Gaalphaqq) G proteins, was removed from the suspending medium, and replaced by serotonin, which selectively activates Galphaq.

Results: While the response to agonists requiring PTX-insensitive G proteins was not affected, upon adrenaline stimulation, which involves mainly PTX-sensitive G proteins, slope and maximum of the secondary aggregation was higher in 825T-allele carriers, being significant at 1 μM, 2 μM and 10 μM and 2 μM, respectively ($p < 0.05$). The overall response rate to adrenaline, regarding secondary aggregation was throughout higher in 825T-allele carriers($p < 0.05$). Adrenaline induced aggregation was inhibited after removal of extracellular ADP, and restituted after addition of serotonin.

Conclusions: The 825T-allele at GNB3 significantly enhances the response to adrenaline stimulation in human platelets by a mechanism requiring simultaneous activation of Gaq by ADP. These findings may in part explain the observed association of the 825T-allele with MI.

3153 Genetic variants of the human endothelial nitric oxide synthase and hypertension

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A missense mutation of the human eNOS gene (Glu-298-Asp) has been reported to be associated in Japanese patients with essential hypertension (OR = 2.4, CI 1.4–4.0). In addition, the pathophysiological role of promoter variants of the human eNOS gene are discussed.

Hence, this study was undertaken to investigate if there is a similiar association in Caucasian and to search for new genetic variants in the promoter region of the eNOS gene.

We genotyped the BanII polymorphism (Glu-298-Asp) of the eNOS gene in a sample of 207 hypertensive probands and 137 normotensive controls. The same probands were screened for mutations using a non-radioactive SSCP-analysis method.

There is no significant difference in allele frequencies between patients and controls for the BanII polymorphism (0.66/0.34 vs 0.69/0.31).

We identified two new polymorphic sites in the eNOS promoter. At position −739 we found a C to T exchange, which is not associated with hypertension in our sample (0.43/0.57 vs 0.40/0.60), in addition we identified at position −794 a C to T substitution in one hypertensive patient.

Our results do not support the hypothesis that the human eNOS gene contributes essential to the development of hypertension in our Caucasian sample. But it remains the possibility that a genetic variant which is not yet identified, and which is not in linkage disequilibrium with Glu-298-Asp is associated with hypertension in Caucasian. Differences in ethnic background can explain such divergent results.

3154 How selected are families of myocardial infarction survivors? Implications for genetic analysis

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Family studies of myocardial infarction (MI) provide the basis to determine familial clustering of diseases and risk factors as a means for differentiating possible behavioural, environmental, and genetic causes and their interactions. Family structure, survival and emotional factors may influence recruitment of such families and may have great impact particularly on genetic analysis. The aim of this study was to examine the availability of family members (siblings) and the criteria for study participation in families recruited from a population-based MI registry (1985–95; 4,976 MIs plus 5,712 sudden cardiac deaths, age 25–75 years).

Methods: 1381 index probands (IPs) having experienced their incident transmural infarction prior to the age of 60 were selected and asked for participation in a family study and for information on survival and positive MI history of their first degree relatives. IPs and living siblings were invited for a standardized interview and an extensive cardiovascular examination.

Results: In 1996/7, 16.7% of the selected IPs were deceased. Of the remaining 1147 IPs, 15.6% had no brothers or sisters, 56% had ever had at least 1 natural sibling, 44% reported at least 1 living sib, and only 26% presented with at least 1 sib who participated in the study. Of these 536 siblings, only 31 were affected with prior MI. Survival of the IPs appeared to be determined by occurrence of anterior MI, diabetes mellitus and medication, but not by parental history of MI (deceased 26%, survivors 25%). IPs who had had a personal interview shortly after their incident MI were significantly more likely to participate in the family study than IPs without a personal interview. Participating IPs reported then significantly more often positive parental history than non-participating IPs (29% vs. 20%). 70% of the designated, non-participating siblings (n = 643) were deceased, located in distant area, or untraceable.

Conclusion: Due to high mortality and unfavourable family structures, only a small number of families can be recruited for a family study from a large MI registry. The actual study sample appears to be positively selected in terms of familial and genetic factors as a result of emotional determinants. For a study design such as an affected sib-pair study, recruitment of a sufficient number of families will depend on collaboration of multiple centers.

3155 The Acute Coronary Event DNA Library project: assesment of feasibility and demographics

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Background: The familial clustering of coronary artery disease (CAD) and acute myocardial infarction (AMI) have been recognised for some time.

Methods: We have initiated a linked marker approach to studying 2,500 sibling pairs affected prematurely with CAD before the age of 65 years, developing strategies for the identification of affected sibling pairs (ASP's) using hospital discharge coding databases, and local media in combination with a postal screening questionnaire. So far the two co-ordinating centres have identified 300 pairs of siblings affected by premature coronary artery disease (mean age 52 yr). DNA from ASP's is being extracted from whole blood and subjects screened with microsatellite markers (based on polymorphic di-/tri-/tetra-repeat sequences) spaced throughout the genome at an initial spacing of approximately 10 cM. Analysis of allele identity and frequency will then be undertaken using the 377 ABI PRISM Gene Scanner System and GENOTYPER software to seek regions of positive linkage.

Results: Demographic characteristics of the first 505 individuals to be identified are as follows: males 70%; females 30%, pairs 188, trios 20, myocardial infarction 65% (mean age of first event 51 yr), revascularisation 54%, angina 60%. *Historical evidence of risk factors:* current smoking 16%, ex-smoking 61%, type 1 diabetes 4%, type 2 diabetes 7%, hypertension 38%, dyslipidaemia 69%. *Parents:* no affected (CAD < 65 yr) parent 40%, one affected 48%, both parents affected 12%, one surviving parent 16%, two surviving parents 1%. *Siblings:* 1 or more dead affected sisters 8%, 1 or more dead affected brothers 23%.

Conclusions: We have demonstrated that it is possible to identify large numbers of affected sibling pairs through collaborative efforts. Furthermore, some of the demographic characteristics of individuals from families at increased risk of premature CAD have been described.

RISK FACTORS FOR CORONARY ARTERY DISEASE: NEW INSIGHTS

3166 Increased mortality over a 5-year follow-up in diabetics with coronary disease on combined metformin/sulphonylurea therapy

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Purpose. Adverse cardiovascular effects were described for oral antidiabetic drugs. The relationship between different types of antihyperglycemic therapy and mortality rates in non insulin dependent diabetes mellitus (NIDDM) patients with ischemic heart disease (IHD) is uncertain. We aimed to examine the survival in NIDDM patients with IHD receiving various types of oral antihyperglycemic regimens over a 5 year follow-up period.

Methods. The population consisted of 11440 patients aged 45–74 years with previous myocardial infarction or stable angina, including 9045 nondiabetics and 2395 diabetics. Diabetics comprised 4 groups, on the basis of their therapy upon screening: diet alone (n = 990), sulphonylureas (n = 1041), metformin (n = 78) and a combination of a sulphonylurea and metformin (n = 266).

Results. All NIDDM groups were similar with regard to age, gender, hypertension, smoking, heart failure, angina and prior myocardial infarction. Crude mortality rate was lower in nondiabetics (11.21% vs. 21.8%; $p < 0.001$). In diabetics mortality was 18.5% for patients on diet alone, 22.5% for those on sulphonylureas, 25.6% for patients on metformin, and 31.6% for the combined sulphonylurea/metformin group ($p < 0.01$). Analyzing age-adjusted mortality rate and actuarial survival curves, the lowest mortality was found in patients on diet alone and the highest in patients on combined metformin/sulphonylurea therapy. After multivariate analysis, the use of metformin and of combined therapy were associated with increased relative risk (RR) for all-cause mortality of 1.44 (95% CI 0.87–2.38) and 1.41 (95% CI 1.10–1.90), respectively, whereas the use of sulphonylureas alone was not [RR 1.11 (95% CI 0.90–1.36)].

Conclusions. NIDDM patients with IHD receiving metformin, especially in combination with sulphonylureas, exhibited a significantly increased mortality over a 5 year follow-up period Until the results of problem-oriented prospective studies on oral control of NIDDM become available, alternative therapeutic approaches should be investigated for these patients.

3167 Impaired functional and structural properties of saphenous vein conduits in diabetic patients undergoing coronary bypass surgery

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Diabetes (DB) represents a widely recognized risk factor for unfavorable outcome after coronary bypass surgery. Nonetheless, structural and functional properties of CABG conduits in DB patients have been poorly investigated, and represent the aim of this study

Methods: Seventy patients were evaluated fro this study. Diabetes was present in 38 patients (24 pts with NIDD, and 14 pts with IDD), whereas 32 patients had no DB and represented the control group. The excess segments of internal thoracic artery (ITA)and saphenou vein (SV) were collected during elective CABG. Vessel strips were immediately set up in isolated organ-bath and suspended under an isometric transducer. Contractile and vasodilative responses were assessed by infusion of Norepinephrine, Serotonine, and KCl, and subsequently antagonised (Nifedipine, Captopril, TNG). Endothelium-dependent vascular reactivity was also evaluated by Acetylcholine administration during Norepinephrine-induced contraction. Histology was carried out on formaline-fixed specimens, which were processed for light microscopy.

Results: No differences were found between groups in relation to functional and structural properties of ITA segments, which proved to be well preserved. In contrast, significant impairment of endothelium-dependent response of SV grafts was observed in DB patients. Indeed, a significantly reduced inhibitory response to SV graft contraction after Acetylcholine administration was shown (8.7% in DB pts vs 32% in non-DB pts). Histological assessment confirmed significant derangement of SV endothelium of DB patients as compared to control ones (15 DB pts with diffuse intimal hyperplasia vs 2 control pts).

Conclusions: Functional and structural properties of SV graft endothelium are impaired in DB patients undergoing coronary bypass surgery, and may negatively affect the postoperative outcome by enhancing SV graft degeneration.

3168 Hyperhomocysteinaemia is a novel, independent risk factor for coronary heart disease in UK Indian Asians

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Premature coronary heart disease (CHD) mortality is 2-fold higher in UK Indian Asians (IA), than European whites (EW), and is not explained by classic risk factors smoking, hypertension and cholesterol. We hypothesised that homocysteine (Hcy) levels are elevated in IA compared to EW, and may account for their increased CHD risk. We studied 551 male CHD patients (257 IA aged 52 ± 7 yrs, 294 EW aged 55 ± 5 yrs) and 1025 age-matched controls (518 IA, 507 EW). Hcy was measured fasting and after a methionine load (100 mg/kg). Subjects were characterised for CHD risk factors, red cell folate, and vitamin B_{12}.

Mean Hcy levels were higher in IA than EW (fasting, 11.2 ± 7.7 vs 10.5 ± 5.4 μmol/l, p = 0.001; post-load, 34.9 ± 12.8 vs 33.2 ± 12.1 μmol/l, p = 0.001). Fasting Hcy levels were elevated in CHD patients compared to respective controls (IA, 12.0 ± 4.5 vs 10.8 ± 3.5 μmol/l, p = 0.001; EW, 11.1 ± 3.9 vs 10.2 ± 2.9 μmol/l, p = 0.001). In contrast, post-load Hcy levels did not differ significantly between patients and controls (IA, 36.1 ± 11.1 vs 34.3 ± 9.5 μmol/l, p = 0.02; EW, 33.9 ± 10.6 vs 32.9 ± 8.8 μmol/l, p = 0.18). The association between fasting Hcy and CHD was independent of conventional risk factors including diabetes, cigarette smoking, hypertension, and hypercholesterolaemia in both racial groups. Hcy levels were inversely related to vitamin B12 (p = 0.001) and folate (p = 0.001). Compared to EW, IA had lower folate (349 ± 160 vs 384 ± 166 ng/ml, p = 0.001), and vitamin B_{12} (270 ± 143 vs 358 ± 158 pmol/l, p = 0.001). The differences in homocysteine concentrations between the two racial groups were explained by lower vitamin B_{12} and folate levels in Asians.

We conclude that elevated fasting Hcy may contribute to theexcess CHD risk in IA compared to EW, and may be amenable to modulation through dietary vitamin supplementation.

3169 Why do Afro-Caribbeans have a low incidence of ischaemic heart disease?

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Afro-Caribbeans have a greater prevalence of diabetes, hypertension, left ventricular hypertrophy and obesity compared with White Europeans. In spite of this, they have a lower prevalence of ischaemic heart disease. An increased carotid intima-media thickness (IMT) has recently been found to be associated with the majority of known cardiovascular risk factors, including left ventricular hypertrophy. It is widely believed that intima-media thickening may represent an early marker for the development of atheroma. Afro-Caribbean subjects with their clustering of cardiovascular risk factors may be expected to have an increased IMT compared with White Europeans. In order to test this hypothesis 32 age, sex and blood pressure matched Black and White hypertensives underwent bilateral common carotid and femoral ultrasonography and echocardiography.

The Afro-Caribbean group had a significantly greater left ventricular mass index compared with the White Europeans (mean ± SEM 137 ± 7.3 versus 115 ± 8.5 g/m^2, $p < 0.05$). In spite of this, there were no significant differences in common carotid or femoral IMT between the Black and White groups (0.77 ± 0.02 versus 0.78 ± 0.04 mm and 0.67 ± 0.03 versus 0.66 ± 0.03 mm).

In conclusion, in spite of having a significantly greater left ventricular mass index, the Black subjects had a similar large vessel intima-media thickness compared with Whites. This may indicate that, even though they have a greater clustering of risk factors, Afro-Caribbeans may not have the same propensity for the development of atherosclerosis. This might help explain their lower incidence of ischaemic heart disease.

3170 Characteristics, therapy and prognosis of 952 hypertensive and 1,903 normotensive men with coronary heart disease: long-term follow-up

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Between 1990 and 1992, 3122 CHD patients (pts) were recruited to participate in the multicenter placebo controlled BIP trial, including 2855 men. Among 952 hypertensive (HT) men, 438 were so classified on the basis of history alone and 514 by history as well as at least one measurement exceeding systolic and/or diastolic levels of 160 and 95 mmHg respectively. Among HT CHD pts so defined, 89% were taking medication at the time of screening. The mean ages were 60.7 among HT and 59.5 in normotensive (NT) pts. The mean screening blood pressure levels were 144/86 among HT and 127/79 in NT pts, respectively. At randomization, and on repeated medical visits after 4 and 8 months, these values changed little (to 141/84 and 128/79 mmHg respectively). Mean BMIs were 27.1 and 26.4 kg/M2 in HT and NT respectively and there were no appreciable lipid level differences. Diabetes was the only condition obviously in excess (12.8% vs. 7.9%) in HT, whereas fewer of them (9.9%) reported smoking than NT (13.5%). Calcium channel blockers (CCB) (56%), beta blockers (48%), ACE inhibitors (22%) and diuretics (19%) were the most common treatment modalities in HT CHD pts. Other than CCB, the above therapies were by far more prevalent among HT than NT. Through 1997 (mean follow up 6 yrs, maximum 7.5) no difference in all-cause mortality was observed between HT (10.4%) and NT (10.3%). Upon multivariate adjustment the adjusted HT mortality hazard was 0.96 (95% CI, 0.75–1.23). HT exhibited a small non-significant excess in incident recurrent MI, unstable angina and invasive cardiac procedures. Only the incidence of stroke (9.9% in HT "qualifying" by elevated BP, 5.5% in HT with controlled BP, 5.2% in NT) was significantly related to baseline hypertension. These results confirm recent findings, from other studies, of little or no excess in cardiac events and mortality among HT CHD patients. An explanation of this apparent paradox remains elusive.

3171 Blood pressure and long-term coronary heart disease mortality in different populations; results from the seven countries study

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It is unclear whether the strength of the relationship between blood pressure and mortality from coronary heart disease (CHD) varies among populations. We compared the relationship of systolic (SBP) and diastolic (DBP) blood pressure with CHD mortality in 6 different populations, and examined the effect of blood pressure measurement error.

Methods: Blood pressure was measured at baseline in 12,268 middle-aged men in the United States, Northern and Southern Europe, Serbia and Japan. During 25 years of follow-up there were 1,397 deaths from CHD.

Results: For a SBP of 140 mmHg, CHD mortality rates varied more than threefold between populations and for a DBP of 85 mmHg, there was a fivefold range. High rates were observed in the US and Northern Europe and low rates in Japan and Mediterranean Southern Europe. The relative risk (RR) for CHD mortality for a given increase in blood pressure was similar in all populations. The overall RR for CHD mortality per 10 mmHg increase in SBP was 1.15 (95% confidence interval: 1.13–1.19) and per 5 mmHg increase in DBP 1.13 (1.10–1.15), and became 1.26 and 1.29 respectively after adjustment for measurement error.

Conclusions: The relative increase in CHD mortality for a given increase in blood pressure is similar in different populations. After adjustment for measurement error, the RR of SBP increased by 40 to 80% while that of DBP more than doubled. However, the large difference in absolute risk among populations at a given blood pressure level indicates that other factors, such as diet and physical activity, are also of interest with respect to primary prevention of CHD.

DIAGNOSTIC VALUE OF ELECTROCARDIOGRAM COMPUTER ANALYSIS

3172 Atrial flutter detection by computer

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Interpretation of arrhythmias is recognised as one of the major problems in automated ECG analysis, and new methods are continuously being investigated to improve the accuracy of this section of the Glasgow Program. As part of this research, a new algorithm has been developed for the detection of atrial flutter.

Methods: The original approach to detecting atrial flutter involves checking for repeated occurrence of opposing gradients in the T-Q interval, in keeping with the saw-tooth configuration of F waves. The new method searches for a regular pattern of detected "P" waves with a high atrial rate. If flutter is not found, further checks are made for a regular pattern of peaks in the first difference of leads II and V1. In each case a regularity index is calculated which takes into account the possibility of undetected or spurious waves. This index, plus the number of detected waves and estimated atrial rate, are used as criteria for atrial flutter. The algorithm was developed using a training set of 422 ECGs including 49 cases of atrial flutter with a variety of flutter wave shapes and varying degrees of A-V block. The remaining rhythms were atrial fibrillation (AF) and sinus rhythm with supraventricular extrasystoles (SVES) and/or ventricular extrasystoles (VES). Optimisation was achieved using a trial and error approach, with various parameters in the algorithm being tuned to maximise sensitivity (84%) without sacrificing specificity (98.1%).

Results: The new algorithm was evaluated and compared to the existing algorithm using a test set of 462 ECGs including 75 showing complex forms of atrial flutter with the remainder having either AF or sinus rhythm with SVES and/or VES. There was a significant improvement in sensitivity (77%) compared to the existing flutter logic (25%) while achieving high specificity (98.4%). If both old and new algorithms were used in combination, a sensitivity of 84% was achieved, with a high specificity of 98.1% being maintained.

Conclusion: Computer interpretation of cardiac arrhythmias can still be improved through careful development and enhancement of basic methods.

3173 Wavelet analysis of subthreshold cardiac modulation in healthy subjects and ventricular tachycardia patients

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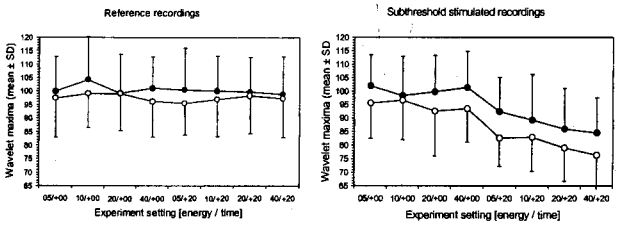
Subthreshold stimulation without capture reduces the stimulation threshold and changes the action potential of a subsequent stimulation with capture (Wedensky Phenomenon). Patients with EP documented ventricular tachycardia (n = 47, mean age 63 ± 13 years, 83% male) and healthy controls (n = 30, mean age 44 ± 16 years, 60% male) were subjected to a subthreshold external stimulation between precordial and left subscapular patches. Stimuli of 5, 10, 20, and 40 mA were delivered for 2 ms either simultaneously with the R wave or 20 ms after the R wave. 60 to 200 subthreshold stimulated QRS complexes were averaged and compared with non-stimulated complexes (reference). Vector magnitude wavelet decompositions (53 scales of Morlet wavelet, central frequencies 40–250 Hz) were obtained for both stimulated and non-stimulated complexes. Local maxima of the 3D spectral envelopes were counted in 50 ms windows following the subthreshold stimulation and compared in VT patients and controls. In non-stimulated recordings (left figure), they were no statistical differences between VT pts (filled circles) and controls (unfilled circles). In subthreshold stimulated recordings, the local maxima decreased (3D envelopes are more smooth). This decrease was greater in healthy controls and with stimulation after the R wave (right figure – all differences but in 10/00 experiment were significant – $p < 0.001$).



Hence, subthreshold external stimulation makes the depolarisation wave more uniform, mainly in healthy controls.

3174 Temporal changes in fractal and spectral characteristics of heart rate variability in patients with coronary artery disease

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Background: Spectral and fractal measures of heart rate (HR) variability are altered and provide prognostic information in patients with coronary artery disease (CAD), but there are no data from longitudinal studies on the determinants of temporal changes in HR behavior. This study evaluated changes in the 24-hour measures of HR variability in patients with CAD undergoing repeat Holter recordings 32 months after the baseline recordings.

Methods and Results: Non-spectral, spectral and fractal measures of HR variability were analyzed from the baseline 24-hour ECG recordings and from recordings performed 32 months later in 110 patients participating in the multicenter trial (LOCAT) evaluating the angiographic progression of CAD. Several laboratory variables, including lipid, glucose and insulin levels, exercise tests and quantitative computer-assisted analysis of coronary artery stenoses were also assessed at baseline and after 32 months's follow up. None of the traditional non-spectral or spectral measures of HR variability changed significantly during the follow-up. The power-law slope of R-R interval variability decreased from -1.28 ± 0.12 at baseline to -1.36 ± 0.23 ($p < 0.001$) and short-term fractal scaling exponent of R-R intervals from 1.29 ± 0.14 to 1.22 ± 0.19 ($p < 0.001$) during the time course. Changes in the measures of HR variability were not related to changes in any of the laboratory variables, exercise capacity, clinical ischaemic events or angiographic progression of CAD.

Conclusions: This longitudinal study shows that fractal analysis techniques are more sensitive than traditional analysis methods in documenting temporal changes in HR behavior of patients with CAD. Altered fractal characteristics of HR behavior are related to aging itself, but not to progression of CAD or to changes in the risk factors of CAD.

3175 No reduction of high frequency contents in power spectra of epicardial electrograms in regions with moderate contraction abnormalities in patients with chronic ischaemic myocardium

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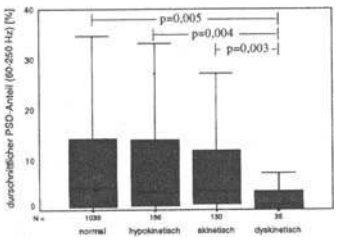
Purpose: The aim of the present study was to assess the influence of the severity of regional myocardial dysfunction on high frequency components of epicardial electrograms in patients with chronic myocardial ischaemia.

Methods: During elective coronary artery bypass surgery, intraoperative epicardial mapping was performed in 21 patients. Using a sock electrode, 102 bipolar electrograms were simultaneously recorded from the epicardial surface of the heart during sinus rhythm. In a 200 ms time window around center of local activation, the relative part of the power spectrum density [PSD] was calculated in a frequency band of 60–250 Hz. The severity und extent of regional myocardial dysfunction was assessed from preoperative biplane angiograms. The results were projected to the grid and intraoperative position of the sock electrode.

Results: Epicardial electrograms and regional contractile function were analysed in 1390 left ventricular segments (n = 186 hypokinetic, n = 130 akinetic, n = 35 dyskinetic). In contrast to previous studies describing a significant decrease of high frequency PSD-components in acute myocardial ischemia, we found a significant decrease of PSD components only in electrograms of dyskinetic areas ($p < 0.01$) Hypo- and akinetic areas, however, showed normal or almost normal PSD-deviations.



Conclusion: The findings indicate differences in the electrical characteristics of acute vs. chronic ischaemic myocardium. Areas of chronic ischaemic myocardium and moderate dysfunction show normal electrical behaviour, possibly indicating myocardial viability.

3176 Comprehensive assessment of QT dispersion in various at risk groups including acute myocardial infarction, unstable angina, hypertrophic cardiomyopathy, idiopathic dilated cardiomyopathy, and healthy controls

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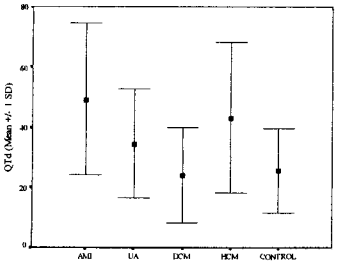
Background: QT dispersion (QTd) has been proposed as a risk marker of ventricular tachyarrhythmias. However, inconsistent results had been shown on various at risk groups due to various methods used. No comprehensive study has been done to compare QTd in various cardiac conditions using a consistent method to determine its clinical value.

Aim: We compared and determined the value of QTd in various at risk patients and healthy control using a fully automated method.

Methods: We performed QTd on 81 acute myocardial infarction (AMI) patients on the first day *after* AMI (61 male, age 63.1 ± 12.3), 22 unstable angina patients (UA) (17 male, age 62.7 ± 12.8) on the first day *after* admission, 76 hypertrophic cardiomyopathy patients (HCM) (43 male, age 39.6 ± 14.0), 27 idiopathic cardiomyopathy patients (DCM) (18 male, age 48.9 ± 15.7), and 69 healthy controls (30 male, age 50.6 ± 7.4), using Marquette MAC VU equipped with QT Guard software which automatically analysed QTd on digitally stored ECGs.

Results: 1) Using student's t-test, AMI, UA, HCM patients but not DCM had significantly higher QTd than control (AMI: 49.3 ± 25.1 vs. 25.7 ± 14.1, $p < 0.0001$; UA: 34.7 ± 18.1 vs. 25.7 ± 14.1, $p = 0.041$; HCM: 43.3 ± 25.0 vs 25.7 ± 14.1, $P < 0.0001$; DCM: 24.1 ± 15.8 vs. 25.7 ± 14.1, p = N.S.). 2) AMI patients had significantly higher QTd compared with UA (49.3 ± 25.1 vs. 34.7 ± 18.1, $p = 0.004$) and DCM patients (49.3 ± 25.1 vs. 24.1 ± 15.8, $p < 0.001$) but not with HCM patients (p = N.S.). 3) UA patients had significantly higher QTd than DCM patients (34.7 ± 18.1 vs. 24.1 ± 15.8, $p = 0.038$) but not with HCM patients (p = N.S.) 4) HCM patients had higher QTd than DCM patients (43.3 ± 25.0 vs. 24.1 ± 15.8, $p < 0.0001$).



Conclusions: 1) QTd is most increased in AMI and HCM patients, less so in UA patients but no difference in DCM patients compared with controls. 2) Different cardiac condition has different degree of ventricular repolarisation manifested by different QTd values. 3) QTd is useful as a risk stratification tool in most cardiac conditions assessed here but not all. 4) The underlying cardiac condition must be considered when QTd is compared.

3177 ECG detection of acute myocardial infarction by artificial neural networks

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Recent reports have demonstrated that artificial neural networks can be used for interpretation of ECG. The purpose of this study was to compare the performance of artificial neural networks, an experienced cardiologist and an intern in detecting acute myocardial infarction in the 12-lead ECG. **Methods:** A total of 960 ECGs from patients with acute myocardial infarction and 11750 control ECGs recorded at an emergency department with computerized ECG were studied. Artificial neural networks were trained to detect acute myocardial infarction by use of measurements of the ST-segments of each ECG together with the correct diagnosis. After the training process the neural networks, an experienced cardiologist and an intern reviewed 200 ECGs from patients with acute myocardial infarction and 800 control ECGs, with and without access to earlier ECGs for comparison. Receiver-operating characteristic (ROC) curves were obained and the area under each curve was calculated. A high value signifies good performance. **Results:** Area under the ROC-curves

	With earlier ECG	Without earlier ECG	p-value
Intern	0.777	0.712	<0.001
Cardiologist	0.805	0.791	0.17
Neural Networks	0.833	0.846	0.07

Conclusions: Neural Networks are able to diagnose acute myocardial infarction in the 12-lead ECG at least as well as an experienced cardiologist and definitely better than an unexperienced ECG reader. Availability of an earlier ECG for comparison is of doubtful help to an experienced ECG reader.

ELECTRICAL CARDIOVERSION OF ATRIAL FIBRILLATION

3178 The sequential application of two different paddle positions in external atrial defibrillation

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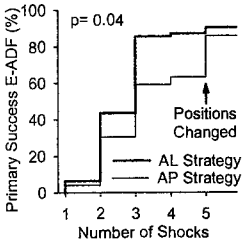
External atrial defibrillation (E-ADF) is a generally accepted method to restore sinus rhythm (SR). Either anterior-posterior (AP) or anterior-lateral (AL) paddle positions are used in E-ADF. However, the effect of application of both techniques sequentially is unknown.

Methods: We investigated primary (SR immediately after E-ADF) and secondary success (SR after 1 month) of E-ADF in 111 consecutive patients with persistent (>24 hours duration) atrial fibrillation (AF). Patients were randomized to either AL (n = 62) or AP (n = 49) positions, with paddle diameters 9 + 9 cm and 8 + 12 cm respectively. Monophasic DC-shock energy was increased stepwise until successful (100; 200; 360 Joules). If this failed, another 360 Joules were delivered. If still ineffective, 360 Joules in the other paddle positions were finally applied.

Results: After the third shock (maximal energy) 85% of the patients in AL strategy were in SR vs. only 59% in AP strategy (p = 0.04; see figure). As to be expected, the fourth shock (maximal energy, same positions) was rather ineffective (AL + 2%, AP + 4%). However, the fifth shock (maximal energy, *positions changed*) was not very effective in AL strategy, but highly effective in AP strategy (AL + 3%, AP + 23%). Eventually, strategies were comparable for primary (AL 90%, AP 86%) and secondary (AL 38%, AP 45%) success of E-ADF. Multivariate analyses confirmed that strategy was neither related to primary nor to secondary success. No heart failure or ventricular (pro-) arrhythmia was observed immediately after E-ADF.



Conclusions: Without a sequential change of positions, AL positions are most effective. A 2nd delivery of 360 Joules in the same positions is rather ineffective. A sequential change of positions should be considered when AP positions are ineffective at 360 Joules.

3179 External cardioversion of atrial fibrillation: a randomized comparative study on efficacy of biphasic versus monophasic waveform shocks

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Biphasic waveform shocks were found to decrease energy requirements as compared to monophasic waveform in terminating ventricular fibrillation. We compared the efficacy of external cardioversion of atrial fibrillation (AF) using biphasic versus monophasic waveform in a prospective study.

Methods and results: Thirty nine patients (Pts) were randomized to undergo cardioversion using antero-lateral approach either with a defibrillator using a monophasic waveform. (Hewlet Packard, Codemaster) or a defibrillator which delivers an impedance-compensating biphasic waveform (Forerunner, Heartstream Inc). The energy of the first shock with the Codemaster (monophasic waveform) was set at 150 J to match with the energy delivered by the Forerunner (biphasic waveform) and if needed followed by a second 360 J.

Characteristics of patients

	Monophasic (Group I)	Biphasic (Group II)
Number of Pts	19	20
Chronic/Paroxystimal	18/1	19/1
Heart disease	14	12
Size of left atrium (mm)	45 ± 5.2	46 ± 4.8
Duration of treated episode (months)	4.1 ± 7.8	4.3 ± 7.6
Antiarrhythmics	9	12

Sinus rhythm was restored with the first shock in 11 out of 19 Pts (58%) in group I and 18 out of 20 Pts (90%) in group II ($p < 0.05$) However after completion of the protocol the success rate was 94% in group I and 90% in group II. Myocardial enzymes did not show any significant change in both groups. No complication was observed.

Conclusion: This study demonstrates that at an energy at 150J external cardioversion of AF is more effective using biphasic than monophasic shock waveform.

3180 Randomised comparison of electrode pad size and position for transthoracic cardioversion of atrial fibrillation

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Transthoracic impedance (TTI) is a major determinant of intramyocardial current flow during external countershock. It has been suggested that TTI is lower with larger pad sizes and in anteroposterior (AP) electrode position. We prospectively randomised 119 patients (pts) undergoing transthoracic cardioversion of atrial fibrillation to 3 different pad sizes – standard (S; area 106 cm^2, n = 39), medium (M; area 140 cm^2, n = 40), and large (L; area 221 cm^2, n = 40) and 2 pad positions – anteroapical (AA n = 58) and anteroposterior (AP n = 61). TTI and peak current were measured.

TTI was significantly lower with larger pads (S; 74.8 ± 14.6 Ω, M; 64.9 ± 17.3 Ω, L; 48.5 ± 6.8 Ω, p = 0.0001) with a corresponding increase in the peak current (S; 35.7 ± 10.6 A, M; 40.6 ± 10.7 A, L; 47.9 ± 11.3 A p = 0.0001). Cardioversion success rate was similar in all the 3 different pad sizes (S; 34/39–87%, M; 34/40–85%, L; 36/40–90% p = 0.79). Similarly success rate at low energy shocks (≤200 J) was similar in all the 3 groups (S; 20/39–51%, M; 23/40–58%, L; 23/40–58% p = 0.81). TTI was lower in the AP position (AP 65.8 ± 19.0 Ω, AA 59.4 Ω ± 15.1, p = 0.05). However there was no significant differences in the total success rate (AA 85%, AP 85% p = 0.47) or rate of success at low energy shocks (AA 57%, AP 54% p = 0.76) between the 2 pad positions. Twenty pts crossed over to the alternate route if cardioversion failed in one position and 50% (3/6) succeeded in the AP position and 36% (5/14) in the AA positions (p = 0.55).

TTI is lower with larger pad sizes and AP pad position with corresponding increase in the current. However cardioversion success rate for atrial fibrillation is not related to electrode pad size or position.

3181 Chronic atrial fibrillation: a 3-month course with low-dose amiodarone before electrical cardioversion reduces early recurrences

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Electrical cardioversion (ECV) is a an effective and safe procedure to restore sinus rhythm in patients (pts) with atrial fibrillation (AF). However, the high rate of recurrences constitutes a limitation of the procedure. In this study we tested the hypothesis that a low-dose of amiodarone (Amd) before ECV is helpful in order to mantain sinus rhythm after successful ECV

Methods. 106 pts with chronic AF (6 months to 5 years) were randomized to ECV following 3 months of Amd therapy (group A) or to ECV without specific antiarrhythmic therapy (group B). Amd was administered at a loading dose of 100 mg/kg for a week, followed by a maintenance dose of 200 mg daily. All pts were anticoagulated with warfarine, at least for 4 weeks before ECV. After successful ECV, pts in group B initiated Amd therapy (low maintenace dose following a loading dose) while group B pts were mantained in the low-dose regime. All pts were revaluated 3 months after the procedure.

Results. Baseline characteristics (age, % of structural cardiopathy, ejection fraction, left atrium dimension, AF duration, and % of AF longer than 3 years) were similar in both groups. At the time of planned ECV, 7 (13%) Pts of group A had achieved sinus rhythm for none in group B (p = 0.01). The rate of successful ECV was similar in both groups (65% and 75%, respectively). At 3 months follow-up there were 2 (6.7%) recurrences of AF in group A vs 11 (27.5%) in group B (p = 0.03); thus, the RR for recurrences in group A, compared to group B, was 0.2 (95% CI, 0.06 to 1.01). Adverse reactions were seen in 31 (29%) pts; most of them were not serious and were reversed with a dose reduction. Withdrawal of Amd was necessary in 8 (7.5%) pts.

Conclusion. In pts with chronic AF, a low dose of Amd during the 3 months going before ECV, significantly reduces early recurrences. In addition, some 13% of pts can achieve pharmacologic sinus rhytm, making unnecessary the ECV.

3182 Left ventricular dysfunction of chronic atrial fibrillation with controlled ventricular rate is reversed or greatly ameliorated after one year in sinus rhytm

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Atrial fibrillation (AF) with fast ventricular rate can be associated with left ventricular systolic dysfunction (LVSD). It has been shown that the control of ventricular rate or the sinus rhythm restoration can greatly improve the LV function. However, it is not yet proved if a similar benefit could be attained in patients (pts) with chronic AF and controlled ventricular rate. Therefore, we designed an observational study to asses the hypothesis that cardioversion is also advantgeous for pts with chronic controlled AF and moderate or severe LVSD.

Methods: Serial assessment of echo ejection fraction (EF) was performed in 30 pts with chronic AF (>6 months) and baseline EF $\leq$ 0.50 who underwent electrical cardioversion. The ventricular rate was pharmacologically controlled to <100 bpm (Holter assessment) before baseline determination of EF. All pts were anticoagulated for one month prior to cardioversion. A low-dose amiodarone (200 mg daily) was prescribed for all pts who achieved sinus rhythm. This therapy was maintained for one year or until the recurrence of AF.

Results: Cardioversion was successful in 25 (83%) pts and 20 of them (67%) were still in sinus rhythm after one-year follow-up. In these, EF increased from 0.42 $\pm$ 0.7 at baseline to 0.56 $\pm$ 0.11 at one year follow-up ($p < 0.0001$). A normal EF ($\geq$0.55) was achieved in 14 pts (47% of the entire cohort). In contrast, EF did not change (0.38 $\pm$ 0.8 at baseline vs 0.41 $\pm$ 0.9 at one year follow-up) in pts that did not achieve sinus rhythm or have AF recurrence.

Conclusions: Intention to treat analysis of pts with chronic AF and controlled ventricular rate shows that restoration and long-term maintenance of sinus rhythm can completely reverse the associated LVSD in about a half of the pts. Therefore, we firmly advise to attempt sinus rhythm restoration, in spite of a good control of the ventricular rate, in all pts with chronic AF and LVSD.

3183 No cerebral circulating microemboli in patients undergoing electrical cardioversion due to permanent atrial fibrillation

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Introduction: Electrical cardioversion (CV) in patients (pts.) with atrial fibrillation is known to be associated with an increased periprocedural risk for thromboembolic events. This is due to mobilisation of pre-existent atrial thrombotic material during CV but also to an increased risk for thrombus-formation after CV because of impaired atrial contractility ("stunned atrium"). We analysed pts. undergoing electrical CV for circulating cerebral microemboli (ME), which are known to be predictive for thromboembolic events.

Methods/Results: Pts. admitted for CV were included if they had been on effective anticoagulation with phenprocoumon (INR 2.0–3.0) for at least 3 weeks and gave full written informed consent. They underwent duplex sonography of the carotid arteries and were excluded if a stenosis of $\geq$50% was detected. Finally, 29 pts (22 men, age 54 $\pm$ 13 yrs) were included. Concomitant cardiac anomalies were mitral valves defects (n = 5), coronary heart disease (n = 9) and cardiomyopathies (n = 2), in 13 pts no structural anomaly could be identified. All underwent transthoracal and -esophageal echocardiography without detection of intracardiac thrombotic material. Additionally, 10 pts. with prosthetic left heart valves on phenprocoumon without CV were examined as controls. Unilateral transcranial Doppler (TCD) sonography was performed of the middle cerebral artery through the temporal skull with a two-channel 2 MHz probe using a system from EME/Nicolet. Five one-hour TCD monitorings for ME were performed: (a) 24 h before CV, (b) during and directly after CV, (c) 4–6 h, (d) 24 h, as well as (e) 2–4 weeks after CV. All monitorings were analysed offline in a blinded matter by an experienced investigator. None of the pts. neither with CV nor with prosthetic valves showed any symptoms characteristic for thromboembolic events. No ME were detected before CV and during a total of 115 h of post-CV-monitoring. In contrast, in 6 out of the 10 pts. with prosthetic valves, ME were detected with a frequency of 2 to 15/h.

Discussion: In 29 pts. with effective anticoagulation for at least 3 weeks undergoing electrical CV, no circulating cerebral ME could be detected before, during or after CV, although sensitivity of this technique was confirmed in controls. With regard to the well-known potential of ME to indicate increased thromboembolic activity, large-scale studies are warranted to evaluate the prognostic relevance of this method to improve the peri-procedural management of patients undergoing CV.

MARKERS OF INFLAMMATION, COAGULATION AND MYOCARDIAL DAMAGE IN ACUTE CORONARY SYNDROMES

3188 Inflammation markers and adhesion molecules in acute coronary syndrome: culprit or consequence?

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Introduction: Many studies demonstrated increased levels of C-Reactive Proteine (CRP) and Tumor Necrosis Factor a (TNF-a) in acute coronary syndrom (ACS). Recently elevation of soluble Intracellular Adhesion Molecule 1 (sICAM-1) in ACS could be evidenced. However it remains unclear whether these markers of inflammation and adhesion react as sensitive but unspecific acute phase reactants or if they play a pathogenetic role in development of unstable coronary lesion.

Methods: In 321 patients (pts) with ACS levels of Troponin I (TNI) [ng/ml], high sensitive CRP (hsCRP) [mg/l], TNF-a [pg/l], and sICAM (ELISA technique) [ng/ml] were determined on admission to hospital. Considering TNI as a marker for myocardial injury with subsequent acute phase reaction we divided pts with ACS in TNI+ and TNI− groups (>0.5 = TNI+).

Results: 156/312 (48.6%) pts with ACS had a TNI+ level.

ACS: inflammation markers and ICAM-1

Mean (sem)	TNI−	TNI+	p
hsCRP [mg/l]	13.9 (1.7)	40.4 (3.7)	<0.0001
TNF-a [pg/ml]	26.1 (4.9)	47.8 (5.5)	0.003
sICAM-1 [ng/ml]	298.4 (11.2)	306.9 (13.6)	0.628

Conclusion: We could demonstrate that in pts with ACS levels of hsCRP and TNF-a are significantly higher in TNI+ group than in TNI−. Elevated levels of sICAM-1 in ACS do not differ between both TNI groups. These results suggest that elevated levels of hsCRP and TNF-a in ACS are mainly due to myocardial injury and subsequent acute phase reaction whereas endothelial inflammation documented by elevated sICAM levels are indepently of myocardial injury and are likely to play a causative role in pathogenesis of unstable lesion.

3189 C-reactive protein and fibrinogen in unstable coronary artery disease are related to long-term cardiac mortality

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Previous studies, including the FRISC substudy, have shown an association between short-term mortality and markers of inflammation such as C-reactive protein (CRP) and fibrinogen, in patients with unstable coronary artery disease (UCAD). The follow-up in FRISC have been extended and we therefore are able to report the long-term influences of CRP and fibrinogen on mortality.

Methods: The patients were participating in FRISC – a double blind, randomised, placebo controlled trial of l.m.w. heparin (dalteparin) in UCAD. Blood samples were obtained at inclusion. CRP was analysed turbidimetrically and fibrinogen by rate nephelometry. The patients were stratified into tertiles based on fibrinogen levels and CRP levels, respectively. Information about death and cause of death during the extended follow-up period was obtained from the national registry on mortality.

Results: The median age at inclusion of the 917 patients were 70 years (25^{th}–75^{th} perc. 63–75) and 65% were males. After 3 years there were 114 (12.4%) deaths of which 91 (9.9%) were cardiac in origin. Cardiac mortality (%) in relation to time and level of the markers:

CRP, mg/L	<2.0	2–9.9	≥10.0	RR (95% CI)†	RR (95% CI)*
1 month	0.6	0.4	3.9	0.6 (0.1–6.4)	10.5 (1.4–80.1)
1 year	3.2	3.3	11.1	1.1 (0.4–2.5)	3.3 (1.6–6.8)
3 years	6.4	6.3	16.2	1.0 (0.5–1.8)	2.6 (1.5–4.3)
Fibrinogen, g/L	<3.4	3.4–3.9	≥4.0	RR (95% CI)†	RR (95% CI)*
1 month	0.3	1.0	4.0	3.1 (0.3±30.0)	4.0 (1.1–13.9)
1 year	4.1	6.3	7.9	1.5 (0.8–3.0)	1.3 (0.7–2.2)
3 years	6.1	11.0	12.9	1.8 (1.1–3.1)	1.2 (0.8–1.8)

†relative risk, second vs first group; *relative risk, third vs second group

Conclusion: Elevated levels of markers of inflammation are associated with both an increased short- and long-term cardiac mortality. Especially high levels of CRP seem to be associated with an increasingly high risk of cardiac death by time after an episode of unstable coronary artery disease.

3190 C-reactive protein and troponin T independently predict mortality in patients with unstable refractory angina

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Elevated levels of C-reactive protein (CRP) and Troponin T (TnT) are predictive for short and long term cardiovascular outcome in patients (pts) with acute coronary syndrome. We investigated whether elevation of CRP provides prognostic information beside the TnT status with respect to cardiac events (death, AMI) during 6 months follow-up. Included were 561 pts with refractory unstable angina enrolled in the placebo arm of the CAPTURE trial.

Results: CRP was higher among pts who died compared with survivors (25.4 vs 8.6 mg/L, p = 0.003). The probability of elevated TnT levels rose with increasing CRP concentrations (p < 0.0001). Among TnT negative pts, CRP measurements identified a subgroup of high risk patients (CRP > 10 mg/L; 2.7% mortality). In TnT negative pts with CRP levels < 10 mg/L no death was documented during 6 months follow-up (p = 0.003). TnT positive pts with CRP levels > 10 mg/L were at highest risk relative to TnT positive patients with CRP level < 10 mg/L (5.9 vs. 3.6% mortality; p = 0.008). In contrast, CRP measurements did not provide independent predictive value for the incidence of AMI during 6 months follow up (logistic regression analysis; p = 0.32).

Conclusions: Elevated CRP at presentation in pts with unstable angina is correlated with short term mortality and identifies TnT negative pts with increased risk. A combination of CRP and TnT testing more reliably stratifies high risk patients with regard to mortality but not to incidence of AMI.

3191 Long-term cardiac mortality in relation to troponin T level and ECG findings in unstable coronary artery disease

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The FRISC troponin T-substudy in unstable coronary artery disease (UCAD) showed that maximal levels of tnT < 0.06, 0.06–0.6 and ≥0.6 μg/L identified low, intermediate and high risk groups, respectively, regarding short-term risk of cardiac death. However, no previous study has evaluated the long-term risk. We therefore report the long-term influences of tnT and, in additon ECG findings, on cardiac mortality after extension of the follow-up in FRISC.

Methods: The patients were participating in FRISC – a double blind, randomised, placebo controlled trial of l.m.w. heparin (dalteparin) in UCAD. ECG was obtained at admission, blood samples at inclusion and after 12 and 24 hours. Information about death and cause of death during the extended follow-up period was obtained from the national registry on mortality.

Results: The median age of the 917 patients were 70 years and 65% were males. After 3 years there were 114 deaths of which 91 were cardiac in origin. Cardiac mortality (%) in relation to time and level of the markers:

Max. tnT, μg/L	<0.06 n = 173	0.06–0.6 n = 367	≥0.6 n = 377	RR (95% CI)†	RR (95% CI)*
1 month	0	0.6	3.4	–	4.2 (1.2–14.7)
1 year	0.6	4.4	10.3	7.5 (1.0–56.4)	2.4 (1.4–4.2)
3 years	1.7	9.3	14.3	5.3 (1.7–17.2)	1.5 (1.0–2.3)

†relative risk, second vs first group; *relative risk, third vs second group Both markers provided independent prognostic information in muitiv. analysis.

ST-segment depr.	No (n = 358)	Yes (n = 559)	RR (95% CI)
1 month	0.8	2.3	2.8 (0.8–9.7)
1 year.	2.5	8.4	3.3 (1.7–6.7)
3 years	4.7	13.2	2.8 (1.7–4.6)

Conclusion: Both elevated tnT and presence of ST-segment depression are associated with an increased short- and long-term risk of cardiac death after an episode of UCAD. On the other hand, a normal maximal tnT is associated with a favourable long-term prognosis regarding cardiac mortality.

3192 Antibodies to Chlamydia pneumoniae in unstable angina: results from the CAPTURE trial

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Patients with coronary heart disease frequently have elevated antibody titers against Chlamydia pneumoniae (CP). Whether CP has a causal role in coronary heart disease or is activated as a secondary phenomenon remains unclear.

We examined the sera of 422 patients with unstable angina regarding their titers of CP-IgG, -IgM, C-reactive protein (CRP)- and Troponin-T (TnT) at admission and prior to discharge. CP-titers were measured with specific CP-antibodies by means of rELISA, CRP- and TnT-titers by means of ELISA.

CP-IgG-titers were elevated with average values of 1.6 ± 1.9 (index 1 = titer 1:100) in 42% of the cases at admission and with 1.9 ± 2.2 in 49% of the cases at discharge. CP-IgM-titer were elevated with average values of 0.2 ± 0.3 (index 1 = titer 1:50) and 0.3 ± 0.5 in 2% respectively 4% of the cases. IgG-titers in patients with consecutive events (myocardial infarction or death) had 19% higher titers at admission than patients without subsequent events. IgM-titers were 39% lower in patients with subsequent event. In both groups, titers increased during hospitalization, IgG from 1.8 resp. 1.5 to 2.2 resp. 1.9, on average 21%, IgM from 0.09 resp. 0.15 to 0.23 resp. 0.22, on average 44% (p < 0.01). Patients with an increase of IgG- or IgM-titer of >100% had no increased frequency of consecutive events. IgG- or IgM-titer did not correlate with titers of CRP (r = 0.02/−0.05) or TnT (r = 0.03/−0.05).

Our data indicate that patients with unstable angina have elevated C. pneumoniae-IgG-titers. However, there is no individual correlation between increased Chlamydia titers and coronary events, CRP- or TNT-titers. Patients with myocardial infarction or death during follow-up have higher titers that further increase during hospitalization.

3193 The prognostic value of fibrinopeptide A, cardiac troponin I, myoglobin and myosin light chain in patients presenting to the emergency department with chest pain

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Background: Although cardiac troponin I (TnI), myoglobin (Myo), and myosin light chain (MLC) have been used to risk stratify patients with acute MI or unstable angina, their role in predicting future cardiac events in a general patient population presenting with chest pain is less clear. Fibrinopeptide A (FPA), a marker of thrombin activity, has not been previously evaluated as a predictor of ischemic events. We sought to determine which myocardial markers would accurately predict major adverse events in patients who presented to the Emergency Department (ED) with possible acute coronary syndromes.

Methods: Serial measurements of urinary FPA, serum TnI, Myo and MLC were analyzed from 247 consecutive patients during the first 8 hours after their presentation to the ED. Major adverse clinical events (MACE) were defined as death of any cause, myocardial infarction, unstable angina, and myocardial revascularization. Events during the initial week and at 6 month follow-up were determined. Sensitivity (Sens), specificity (Spec), positive (PPV), and negative predictive values (NPV) were calculated.

Results: All markers predicted MACE at one week by univariate analysis (all p < 0.01). However, by multivariate logistic regression, only an elevated FPA (odds ratio (OR) 4.82, confidence intervals (CI) 1.78, 13.03, p = 0.002) and an elevated TnI (OR 9.41, CI 2.84, 31.17, p < 0.001) were independent significant predictors of adverse outcomes. At six months, excluding the index events, FPA was the only significant marker to predict MACE (OR 9.57, CI 3.29, 27.80, p < 0.001) and was the only marker to determine a shorter event free survival (p < 0.001). The marker predictive values are listed below.

	1 Wk				6 Mon			
	Sens	Spec	PPV	NPV	Sens	Spec	PPV	NPV
FPA	36	83	71	53	51	82	51	82
TnI	34	91	82	52	30	81	39	75
Myo	33	84	71	50	31	77	34	74
MLC	49	68	63	52	38	59	28	72

Conclusion: In this heterogeneous patient group, TnI and FPA were the most significant markers to predict MACE at one week. An elevated FPA was the most accurate marker in detecting events and predicting decreased survival at 6 months.

ARTERIAL HYPERTENSION: AMBULATORY MONITORING AND THERAPEUTIC ASPECTS

3194 The smoothness index, but not the trough-to-peak ratio, predicts changes in carotid artery morphology during antihypertensive treatment

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Objective: It has been recently demonstrated that the "Smoothness Index" (SI) [the ratio between the average of the blood pressure (BP) changes computed for each hour of the recording and its standard deviation, High Blood Press 1997], a new, reproducibile and clinically relevant measure of the homogeneity of BP reduction by antihypertensive treatment, has evident advantages over Trough to Peak ratio (T/P) in the prediction of the regression of left ventricolar hypertrophy (J Hypertens 1998). Therefore we considered worthwhile to compare the ability of SI and T/P to predict changes in the carotid artery morphology in patients with essential hypertension.

Design and methods: In 90 patients with essential hypertension [WHO I–II, age range 45–71 years, clinic supine diastolic BP ranging between 95 e 115 mm Hg], 24-hour ambulatory BP and Carotid artery intima-media thickness (IMT) (BIOSOUND 2000 II) were measured after 3 weeks of therapeutic wash-out and after 12 months of antihypertensive treatment (calcium antagonists, diuretics, ACE inhibitors or β-blockers). The homogeneity of the effect of treament over BP was evaluated by computing T/P and SI.

Results:

Correlations vs. (r)	Δ av comm car art IMT	Δ av comm car art IMT far	Δ av bif IMT	Δ max comm car art + bif IMT
SI of systolic BP	−0.25*	−0.28**	−0.38***	−0.32**
SI of diastolic BP	−0.21*,	−0.25*,	−0.34***	−0.27**
T/P of systolic BP	0.16	0.19	0.06	0.11
T/P of diastolic BP	−0.005	−0.18	−0.058	0.03
Δ24-hour systolic BP	−0.12	−0.14	−0.16	−0.15
Δ24-hour diastolic BP	−0.11	−0.12	−0.17	−0.17

*p < 0.05, **p < 0.01, ***p < 0.001. Δ = changes (therapy − basal), av = average, max = maximum, comm = common, car = carotid, art = artery, far = only far wall, bif = carotid bifurcation].

Twenty-four hour BP was significantly reduced by therapy (from 137/86 ± 12.1/9.20 mm Hg to 129/81 ± 9.89/9.05 mm Hg p < 0.001) while, on average, no significant change of indices of carotid artery wall thickness was observed, although in some cases IMT was clearly reduced. Statistically significant correlations were observed between changes in the 4 indices of carotid artery IMT during therapy and SI. No significant correlation was observed between indices of carotid artery morphology and T/P, basal 24 hour BP or changes in BP during therapy.

Conclusions: SI seems to be a better predictor of changes in carotid artery wall thickness than T/P. The information provided by SI is independent from basal BP values. For carotid artery morphology the smoothness of BP reduction is more important than its absolute change.

3195 24-hour ambulatory pulse pressure and left ventricular structural changes in patients with mild to moderate essential hypertension

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The aim of this study was to evaluate the relationship between 24-h blood pressure (BP) profile parameters and left ventricular (LV) structural changes in patients (pts) with mild to moderate essential hypertension (EH).

Methods: We investigated 70 hospitalized males with mild to moderate EH, aged between 30 and 62 (mean age 48 ± 1.0 y). Noninvasive 24-hour BP recordings (SL-90207) was performed with intervals of 15 min in day- and 30 min in nighttime. LV mass was assessed by echocardiography (Devereux) and normalized by body surface area (LVMI). LV remodeling was assessed by the relative wall thickness (RWT), which was calculated as the sum of the posterior wall thickness and interventricular septum, divided by the end-diastolic dimension. The relationship between LVMI and parameters of BP profile was established by: 1) using multiple stepwise linear regression (MSLR) analysis; 2) Pts were divided into two groups (Gr) according median value of pulse pressure (PP): Gr. A (PP > 45 mm Hg, n = 35) and Gr. B (PP≤45 mm Hg, n = 35).We compared the group A with the group B regarding BP profile parameters. Differences in estimated parameters(M ± SE) were tested by Student t-2 test, the prevalence of normal structure of the LV (LVMI≤125 g/m^2 with RWT ≤ 0.45) – by Fisher's exact test. P < 0.05 was considered as statistically significant.

Results: (1) Awake and sleep systolic, diastolic, pulse pressures entered multiple regression analysis to evaluate their ability to influence LVMI. Multiple R was 0.62 (p < 0.0001). A MSLR analysis identified nighttime PP as a significant predictor of LVMI, which was correlate more closely than other parameters (b = 0.78, partial R = 0.37, p < 0.002).

(2) No significant differences was observed between Gr by mean age, body mass index and duration of arterial hypertension. LVMI (134 ± 5 vs 116 ± 3 g/m^2, p < 0.03) and RWT (0.48 ± 0.01 vs 0.43 ± 0.01, p < 0.01) were significantly higher in the Gr.A, comparatively with Gr.B. The prevalence of normal LV structure was significantlty higher in the Gr with nighttime PP < 45 mm Hg (46% vs 14%, P < 0.008).

Conclusion: Our findings demonstrate that nocturnal ambulatory pulse pressure is a powerful and independent risk factor for left ventricular structural changes in patients with mild to moderate essential hypertension.

3196 Dichotomous age-related effect of ambulatory diastolic blood pressure on morbidity and mortality in essential hypertension

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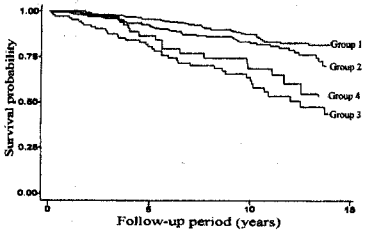
Population studies have demonstrated age-related changes in diastolic blood pressure. This study compared the prognostic significance of 24 hour ambulatory diastolic blood pressure (DBP) in hypertensives above and below 60 years of age. We followed up 688 patients who underwent pretreatment 24 hour intra-arterial ambulatory BP monitoring, a mean of 9.2 ± 4.1 years earlier; 157 first morbid events were recorded. Patients were divided into 4 groups as follows: group 1 = age < 60 years, DBP < 95 mmHg; group 2 = age < 60 years, DBP ≥ 95 mmHg; group 3 = age ≥ 60 years, DBP < 95 mmHg; group 4 = age ≥ 60 years, DBP ≥ 95 mmHg. Kaplan Meier survival curves after adjustment for sex, race, diabetes, smoking and previous history of cardiovascular disease are shown below:



Whereas DBP ≥ 95 mmhg was associated with reduced survival in the <60 years age group, in those aged ≥60 years, DBP < 95 mmhg was associated with the most adverse outcome. In conclusion, 24 hour diastolic BP has a dichotomous age-related effect on subsequent morbidity and mortality in essential hypertension.

3197 Evaluation of long-term effects of amlodipine and lisinopril on left ventricular mass and diastolic function in elderly, previously untreated hypertensive patients (the ELVERA trial)

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Meta-analyses by Dahlöf and Cruickshank suggest that ACE-inhibitors reduce echocardiographic left ventricular mass more effectively than diuretics, beta-blockers and calciumantagonists. Little is known about the effects of drug treatment in the elderly hypertensive patient. The ELVERA trial was designed to evaluate the long term effects of the long-acting calciumantagonist amlodipine and the ACE inhibitor lisinopril on left ventricular mass and diastolic function in elderly, previously untreated hypertensives.

Methods: From a population survey 166 newly found, elderly hypertensives (aged 60–75 years) were randomized to amlodipine 5–10 mg or lisinopril 10–20 mg in a two year double-blind randomised comparative trial. Before and after one and two years of treatment left ventricular mass, indexed by body surface area (LVMI) was estimated by 2-D mode echocardiography according to Devereux with use of Penn convention. Early to atrial filling ratio (E/A) was assessed by transmitral flow. Change from baseline of LVMI and E/A ratio was evaluated by repeated measurement analysis of the treatment effect in an intention to treat analysis.

Results: At the end of the study period, in the amlodipine group LVMI decreased by -21.8 g/m^2 (95% CI: -25.3, -18.3) and E/A ratio increased by 0.08 (95% CI: 0.05, 0.11). In the lisinopril group LVMI decreased by -22.4 g/m^2 (95% CI: -25.8, -19) and E/A ratio increased by 0.07 (95% CI: 0.04, 0.10). Blood pressure reduction was equal for both treatment regimens.

Conclusion: The ELVERA trial proves that the long term effects of amlodipine and lisinopril are equipotent with respect to reduction of left ventricular mass and improvement of diastolic function in elderly hypertensive patients.

3198 Effect of angiotensin-converting enzyme inhibitor on fibrogenic activity in hypertensive patients

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This study was conducted to evaluate fibrogenic activity in patients with hypertension by measuring serum concentrations of procollagen type I peptide (PIP) and procollagen type III peptide (PIIIP) as biochemical markers of tissue synthesis of collagen type I and type III. Also, to assess the relation between their serum concentrations and left ventricle (LV) structure and functions, and to demonstrate the effect of reduction of blood pressure by captopril on their serum concentrations. We studied 79 hypertensive patients and 50 normotensive control subjects. After clinical evaluation, echocardiography (M-mode, 2D, and pulsed Doppler) was done to evaluate left ventricle structure and function. Serum PIP and PIIIP were estimated by radioimmunoassy. All hypertensives received captopril for 6 months, after which, echocardiograhic and biochemical studies were repeated. Posterior wall thickness, septal thickness, left ventricular mass and mass index were significantly higher in patients than in control. Serum concentrations of PIP and PIIIP were significantly higher in patients than in control (258 ± 57.1 & 3.7 ± 2.2 vs. 167.4 ± 69.8 & 1.91 ± 1.36 μgm/L respectively). In addition PIP and PIIIP were significantly higher in hypertensives with LVH than in those without LVH (270.6 ± 56.8 & 4.03 ± 2.3 vs. 223.4 ± 42.2 & 2.9 ± 0.91 μgm/L respectively). After treatment with captopril for six months left ventricle hypertrophy regressed in 13 out of 68 patients, LV mass index and diastolic dysfunction were normalized in 17 out of 58 patients and in 10 out of 44 patients respectively. Serum concentrations of PIP and PIIIP were diminished significantly after treatment (258.1 ± 57.1 and 3.73 ± 2.16 versus 168.4 ± 62.6 and 2.51 ± 2.19 μgm/L respectively). We concluded that, biochemical monitoring of collagen fibril turnover might provide a potential non-invasive method of assessing myocardial fibrosis and elevated serum PIP and PIIIP may be useful markers of increased collagen synthesis in those patients. Circulating procollagen derived peptides may reflect ongoing myocardial fibrosis in essential hypertension. ACE-I may reduce the excessive synthesis of collagen type I and type III in hypertension.

3199 Effect of losartan on human platelets activation

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Previous studies have demonstrated that losartan could block the receptor of thromboxane A_2 (TXA_2) on the vascular wall. The aim of present study was to assess the effect of losartan on human platelet activation.

Design and Methods: Platelets were obtained from 15 healthy men with ages between 26 and 40 years. Platelet activation was measured by the changes in the light transmission of platelet-rich plasma stimulated by the TXA_2 analogue, U46619 (5×10^{-6} mol/L) or ADP (10^{-5} mol/L).

Results: U46619-stimulated platelet aggregation was significantly inhibited by losartan in a dose-response manner. Only a high dose of EXP3174 (5×10^{-5} mol/L), the in vivo active metabolite of losartan, was able to attenuate U46619-induced platelet activation. Captopril (5×10^{-5} mol/L) an angiotensin I-converting inhibitor failed to modify U46619- induced platelet aggregation. Furthermore, the binding of [^{3}H]-U46619 to platelets was competitively inhibited by losartan, whereas only a high dose of EXP 3174 (5×10^{-5} mol/L) reduced the binding of [^{3}H]-U46619. Captopril failed to modify the binding of [^{3}H]-U46619 to platelets. The effect of losartan on platelet activation induced by ADP (10^{-5} mol/L), a platelet agonist partially dependent on TXA_2, was also tested. Losartan reduced ADP-induced platelet activation. In addition, blocking of thromboxane A2 generation by aspirin inhibited ADP-induced platelet aggregation to a similar magnitude as losartan. Exogenous angiotensin II did not elicit any modification of either U46619-or ADP-stimulated platelet aggregation.

In conclusion: Losartan decreased platelet aggregation by a TXA_2-dependent mechanism. EXP3174 showed a lesser potency than losartan to reduce TxA_2-platelet activation. Captopril and exogenous angiotensin II had no effect on human platelet activation. These results suggest that losartan reduced TXA_2-dependent platelet activation independently of Ang II involvement.

NEW DEVELOPMENTS AND APPLICATIONS OF THREE-DIMENSIONAL ECHOCARDIOGRAPHY

3204 Improved accuracy of transthoracic three-dimensional echocardiography with harmonic imaging for assessment of left ventricular volumes: comparison with magnetic resonance imaging

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Background: Three-dimensional transthoracic echocardiography (3D ECHO) eliminates geometrical assumptions in estimation of left ventricular (LV) volumes and harmonic imaging may improve accuracy because of improved delineation of endocardial borders. We compared 3D ECHO with multislice magnetic resonance imaging (MRI) which is considered a gold standard for LV volume measurement.

Methods: Thirteen consecutive patients undergoing coronary angiography because of heart failure and impaired LV function (11 males, 12 with ischemic heart disease and one with cardiomyopathy) were included in the study. LV volumes were measured independently by MRI and 3D ECHO (GE-VINGMED,System V) using fundamental B-mode and tissue harmonic imaging. Volume calculations were performed by two of the authors in order to assess interobserver variability.The agreement between 3D ECHO and MRI, and interobserver variability for determination of EDV, ESV, and EF were estimated. Thus, the mean difference between the two measurements $\pm$ 2 SD of the differences expressed as a percentage of the average values were calculated.

Results: According to MRI, EDV = 278 ± 82 ml, ESV = 202 ± 82 ml and EF = 0.29 ± 0.08%. Compared with fundamental imaging, tissue harmonic imaging showed closer agreement with MRI and less interobserver variability in estimation of left ventricular volumes (see table).

	Harmonic imaging		Fundamental imaging	
	MRI-3D ECHO	Interobs. variability	MRI-3D ECHO	Interobs. variability
EDV	-1.9 ± 9.7	-0.3 ± 5.6	-10.8 ± 17.5*	5.5 ± 13.9*
ESV	0.4 ± 9.3	0.7 ± 10.8	-6.3 ± 22.0*	0.5 ± 18.7
EF	-1.5 ± 6.3	$-0.7 \pm 0.6.4$	-2.8 ± 12.1	2.6 ± 13.7*

*$P < 0.05$ Harmonic vs. fundamental imaging. Mean $\pm$ 2 SD(%).

Conclusion: Tissue harmonic imaging with 3D ECHO shows low interobserver variability and is a very accurate method for assessment of LV volumes in patients with heart failure and LV dilatation.

3205 Flow quantification with digital three-dimensional Doppler: a potential tool for monitoring cardiac output

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The accuracy of conventional Doppler methods for measuring stroke volume is highly variable especially if the flow in the area of measurement deviates from a circular fixed cross-section and uniform velocity profiles. We have developed a Gauss's Theorem based digital three-dimensional (3D) Doppler method for resolving volume flow rates with minimal angle dependence. We tested the method *in vitro* using a simulated ascending aortic flow model.

Method: 8 pulsatile flows (peak flows 85–200 cm^3/sec, verified with an ultrasonic flowmeter) were pumped through each of three curved, oval-shaped compliant tubes (cross-sectional area 1.75–3.5 cm^2). A rotational 3D scan at 5° intervals was performed with a multiplane transesophageal probe oriented in 2 distinctive views (20° and 40° oblique to the flow direction). ECG triggered digital color Doppler images were obtained synchronized to peak flow. Doppler velocity vectors normal to a selected spherical surface projected within the 3D data (Fig.) were integrated to yield flow rate.

Results: The 3D derived flow rates correlated well to the references for all three tubes at all settings (n = 48, Table). Stroke volume derived from multiple samplings integrated within the pulse cycle (at one flow rate) also yielded results comparable to true stroke volume (56 vs. 50 cm^3).

Tube	Regression (n = 8 each)		r		SEE (cm^3/s)		p	
	20° Oblique	40° Oblique	20°	40°	20°	40°	20°	40°
1	Y = 0.94X + 6.1	Y = 1.25X − 35.2	0.99	0.96	5.6	14.0	<0.001	<0.001
2	Y = 0.99X + 0.2	Y = 0.97X − 4.2	0.98	0.99	8.2	5.5	<0.001	<0.001
3	Y = 0.92X + 10.2	Y = 0.97X − 3.4	0.97	0.99	9.0	3.4	<0.001	<0.001

Conclusion: Our digital 3D Doppler method provides laminar flow volume quantification with little angle dependence and could be applicable clinically for measurements of stroke volume and cardiac output.

3206 Real-time three-dimensional stress echocardiography in assessment of patients with ischaemia; comparison with two-dimensional stress echocardiography

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Real-time 3D ultrasound (RT-3D, VOLUMETRICS) displays multiple views from a single acquisition, a major advantage in assessment of LV wall motion (WM). RT-3D images were obtained within a minute of 2D images at baseline and at peak Dobutamine stress echo (DSE) in 179 patients (pts); RT-3D and 2D images were reviewed independently by 2 different observers.

Results: Imaging time per stage ranged from 45 to 60 secs. for RT-3D and 60 to 90 secs. for 2D. Out of 179 pts, technically satisfactory studies for comparisons were obtained in 158 pts. At baseline 41 of 158 pts had abnormal LV WM by RT-3D and 43 of 158 by 2D (84.8% concordance). At peak DSE 62 of 151 pts had abnormal WM by RT-3D compared to 55 of 149 pts by 2D (81.6% concordance, 11 were non-diagnostic by RT-3D and 14 by 2D). WM scores in pts with abnormal WM at peak DSE were 1.52 ± 0.36 by RT-3D and 1.22 ± 0.22 by 2D ($p < 0.0001$). Mean ± SD (ml), LV end diastolic volume (EDV), LV end systolic volume (ESV) and ejection fraction (%) by RT-3D at baseline were 110.9 ± 33.2, 49.3 ± 17.6, 56.1 ± 5.2 and at peak DSE were 101.8 ± 28.7, 34.9 ± 15.4 and 66.5 ± 7.1. LV volume measurements by RT-3D were validated against biplane LV Cine-angiograms in 9 pts with r = 0.9 for EDV and 0.8 for ESV.

In 56 pts with coronary angiographic data, the sensitivity of RT-3D in detection of coronary artery disease was 81.1% compared to 67.6% by 2D.

Conclusions: RT-3D DSE is sensitive in detection of coronary artery disease, provides rapid measurements of LV volumes and offers promise in delineating the extent of ischemia.

3207 Initial experience with real-time three-dimensional echocardiography using ultrafast rotating transthoracic scanner: preliminary human and experimental studies

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Background: Real-time data acquisition for three-dimensional echocardiography (3DE) has been accomplished using a dedicated system with pyramidal scanning capability. The study was designed to determine the feasibility of real-time data acquisition using a newly developed ultrafast rotating transthoracic scanner (URS) in humans and in experimental contrast echocardiographic studies.

Methods: Studies were performed using URS connected to Vingmed System FiVe. 3DE was performed in 3.3 MHz fundamental or 2.9/5.8 MHz harmonic mode with image settings optimized for high 2D frame rates. Data were collected in a digital cine loop during a fast (160–480 rpm) rotation of the URS array without ECG or respiratory gating. After transfer to EchoPAC-3D environment, off-line data analysis was performed. Studies were performed in 4 patients and 2 porcine experiments with imaging before and after the bilateral coronary injection of a deposit agent, Myomap™.

Results: A total of 29 successful acquisitions was performed. Variable rotational speed resulted in datasets collected at 3–15 degree interval with temporal resolution of 6–14 volumes per heart cycle. Successful, geometrically correct datasets were obtained both in fundamental and second harmonic mode. Anyplane and volume-rendered views could be reconstructed. Resolution was sufficient to display anatomical details such as valve orifices or coronary arteries. The deposit contrast agent provided a consistent myocardial opacification, reliably reproduced within 3DE datasets. The main problems were cardiac motion artifacts and resolution limitations resulting from insufficient 2D frame rate.

Conclusions: 3DE real-time data acquisition can be performed with an ultrafast rotating scanner connected to a standard echo system. Resulting datasets are suitable for clinical analysis and may be used for perfusion contrast studies. Increase in maximal 2D frame rate is desirable to improve resolution and widen the imaging sector.

3208 Evidence of reduced regression of left ventricular mass one year after valve replacement for pure aortic stenosis in patients with small prosthetic valves: a three-dimensional echocardiographic study

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We sought to assess the impact of prosthetic valvular size on the regression of left ventricular mass (LVM) in patients with pure aortic stenosis one year after mechanical valve replacement. In 20 patients (mean age 63 ± 10 years) without concomitant coronary artery disease, hypertension or diabetes mellitus LVM was measured using transesophageal three-dimensional echocardiography (3DE) 2 ± 1 days before and 12 ± 1 months after aortic valve replacement. Results of LVM regression were compared for patients with a small prosthetic valve size (23 mm; group I = 10 pts) to those with a valve of >23 mm (range 25 to 31 mm; group II = 10 pts.). 3DE image acquisition was performed in 3° increments using ECG and respiratory gating (HP Sonos 5500). LVM was measured using a previously validated software (Echo-View, TomTec). In addition, regression of LVM was also assessed by M-mode echocardiography according to ASE standards.

Results: Preoperative mean valve area was 0.7 cm^2 in both groups. Before surgery LVM by 3DE averaged 116.9 ± 37.0 g/m^2 in group I and 140.7 ± 33.9 g/m^2 in group II ($p = 0.01$). One year after valve replacement there was a significant difference in the regression of LVM between the two groups (18.5 ± 5.7 g/m^2 or 16.7% in group I vs. 38.7 ± 11.8 g/m^2 or 27.6% in group II; $p < 0.003$). There was no significant association between the regression of LVM and mean transvalvular Doppler gradient after surgery (mean pressure gradient 8.0 ± 4.0 mmHg versus 7.7 ± 2.1 mmHg for group I and II; p = ns). Despite comparable baseline mass values for M-mode (126.0 ± 34.8 g/m^2 and 147.3 ± 23.4 g/m^2; p = ns versus 3DE) no significant difference in LVM regression between groups I and II could be detected (25.8 ± 16.5 g/m^2 or 19.6% vs. 28.9 ± 16.1 g/m^2 or 19.6%; p = ns).

Conclusion: 1) In pure aortic stenosis the regression of LVM is lower for prosthetic valves sized 23 mm as compared to valves > 23 mm at one year. 2) M-mode is an insensitive tool to detect subtle mass changes in patients with small prosthetic valves.

3209 Measurement of mitral valve area using three-dimensional echocardiography: in vitro validation

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Two-dimensional echocardiography (2DE) is an imperfect tool for the measurement of mitral valve area (MVA) due to limitations of beam alignment and difficulty in locating the precise short axis plane of the orifice at the leaflet tips. Three dimensional echocardiography (3DE) allows careful selection of the optimal plane for planimetry thereby offering a more accurate method for quantitation of mitral stenosis. This technique has yet to be validated.

Methods: 20 porcine mitral valves were isolated and the commissures glued to simulate mitral stenosis over a range of severity. The valves were scanned in a water bath using a 7.5 MHz transoesophageal probe and a rotational 3D data set acquired using Tomtec Echoscan. During off-line analysis a line of intersection was positioned at the tips of the mitral leaflets in the plane of the orifice and a series of parallel cross sections through the valve were generated at 1 mm intervals (paraplane echo). The optimum 2D short axis slice was selected and the orifice area measured by planimetry. 'Actual' mitral valve area was determined by pixel intensity measurement of a digitally scanned image of the valve which had been angulated to project the maximum orifice size.

Results: The digital scanner technique had been validated using 14 cylindrical phantoms of known cross-sectional area, the mean difference between phantom area and area measured by the digital scanner was 0.05 $cm^2 \pm 0.12$ cm^2 (mean $\pm$ 2 SD, Bland Altman), $r = 0.99$, $p < 0.001$. MVA of the prepared porcine valves ranged from 0.3 to 3.6 cm^2. MVA measured by 3DE correlated very well with MVA measured by digital scanning with mean difference 0.1 $cm^2 \pm 0.15$ cm^2, $r = 0.99$, $p < 0.01$.

Conclusions: This invitro study demonstrates that 3DE is very accurate in the measurement of MVA. If these findings are confirmed in clinical studies transoesophageal 3DE could become the gold standard for measurement of MVA

MECHANISMS OF PROGRESSION OF VALVULAR HEART DISEASE

3210 Abnormal aortic elastic properties in patients with bicuspid aortic valve

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Bicuspid aortic valve (BAV) is frequently associated with abnormalities of the aorta suggesting that this association may reflect a common developmental defect, namely intrinsic medial weakness. Aortic dilatation has been considered to be a clinical correlate of aortic medial weakness, and it has been shown to be present in patients with BAV independently from hemodynamic abnormalities of the aortic valve. In order to evaluate the presence of abnormal aortic elastic properties in patients with BAV, we consecutively studied 42 young male patients with BAV and no or mild aortic regurgitation by means of 2D-echocardiography to assess aortic distensibility and stiffness. We compared our results with data obtained in 44 consecutive normal young males, matched for age and blood pressure. Patients with BAV showed significantly larger aortic root dimensions at annulus (24 $\pm$ 2 mm *vs* 22 $\pm$ 2 mm, respectively, $P = 0.00126$), sinuses of Valsalva (32.6 $\pm$ 3.6 mm *vs* 26 $\pm$ 2.7 mm, respectively, $P < 0.001$), sinotubular junction (28.3 $\pm$ 2.8 mm *vs* 24.7 $\pm$ 1.8 mm, respectively, $P < 0.001$) and ascending aorta (28 $\pm$ 23 mm *vs* 24.9 $\pm$ 1.9 mm, respectively, $P < 0.001$) in comparison with controls. The difference between systolic and diastolic aortic diameters in patients (2.07 $\pm$ 1.24 mm), was significantly lower than the one in controls (2.76 $\pm$ 1 mm, $p = 0.002$). Systolic and diastolic blood pressure and pulse pressure were comparable in patients and controls. Aortic distensibility in patients ($2.61 \pm 1.5 \times 10^{-6}$ $cm^2/dyne^{-1}$) was significantly lower than in controls ($4.6 \pm 2.2 \times 10^{-6}$ $cm^2/dyne^{-1}$, $P < 0.001$), while aortic stiffness index was higher in patients with BAV (10.43 $\pm$ 5.4) than in controls (5.63 $\pm$ 2.9, $P < 0.001$).

In conclusion, patients with BAV and no or mild aortic regurgitation, present larger aortic root dimensions and abnormal elastic properties of the ascending aorta, confirming that aortic dilatation is a morphological correlate of intrinsic medial weakness.

3211 Role of endothelial adhesion molecules in the pathogenesis of degenerative aortic valve disease

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The presence of activated T lymphocytes in degenerative aortic valve (AV) disease suggests that immunnological mechanisms may be important in the pathogenesis. Adhesion molecules play a key role in recruitment of leukocytes to sites of inflammation. We studied the valvular expression of the endothelial adhesion molecules intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin in patients with degenerative AV disease and the relation between endothelial expression and soluble adhesion molecule levels.

Methods: Aortic valves from 23 (adequate endothelium in 22) patients undergoing elective AV replacement were stained for the 3 adhesion molecules by immunohistochemistry. Staining intensity was graded 0–4 independently, a grade of 2 or more was considered positive. Soluble adhesion molecule levels were measured by enzyme linked immunosorbent assay in 16 of the patients without other inflammatory illnesses. Levels of soluble adhesion molecules were correlated with endothelial staining intensity (Spearman's correlation). Six autopsy AV (4 normal, 2 thickened)were also studied.

Results: A high proportion of the diseased valves stained positive for the 3 adhesion molecules (Table 1)while the normal autopsy valves were negative. There was no significant difference between the proportions of valves staining positive between the bicuspid and trileaflet groups. There was a strong association between the intensity of endothelial staining and the soluble molecule levels for E-selectin ($R = 0.724$, $p = 0.002$) but not for ICAM-1 ($R = -0.130$, $p = 0.631$)or VCAM-1 ($R = -0.367$, $p = 0.162$).

Table 1. Adhesion molecule expression on aortic valve endothelium

	ICAM-1 +	VCAM-1 +	E-selectin +
Surgical – trileaflet (n = 16), n (%)	12 (75)	11 (69)	12 (75)
Surgical – bicuspid (n = 6), n (%)	4 (67)	3 (50)	5 (83)
Autopsy – normal (n = 4), n	0	0	0
Autopsy – thickened (n = 2), n	2	2	2

Conclusion: The increased expression of adhesion molecules ICAM-1, VCAM-1 and E-selectin supports an inflammatory component in the pathogenesis of degenerative AV disease. Soluble E-selectin levels may be useful markers of endothelial activation in this condition, while soluble ICAM-1 and VCAM-1 may be derived from sources other than valvular endothelium.

3212 Is Chlamydia pneumoniae aetiologically linked to aortic stenosis?

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Background: The etiology of nonrheumatic calcified valvular aortic stenosis is unknown. Recent work suggests a possible link to infection with *Chlamydia pneumoniae*. Therefore we tested the evidence for *C. pneumoniae* in calcified aortic valves, and as control in non-calcified aortic and mitral valves.

Methods: We studied 23 patients (pts.) (mean age 68 $\pm$ 13 years, 13 males) undergoing valve replacement because of severe calcified aortic stenosis (AS, n = 17), aortic regurgitation (AR, n = 2) and mitral regurgitation caused by mitral valve prolapse (MR, n = 4). Resected valve tissue was investigated by culture, by immunohistochemistry (IHC) using 2 different monoclonal antibodies (RR-402, CF-2) and by PCR (amplification A and B). In addition IgG serum antibodies against *C. pneumoniae* were analysed by ELISA in 21 pts.

Results: Outcome of serological and non-serological testing differed markedly.

	% positive in pts. with AS	% positive in pts. with AR or MR
IgG serum antibodies	94	100
Immunohistochemistry RR-402	29	0
CF-2	41	0
PCR amplification A	44	33
PCR amplification B	88	67
culture	0	0

Uniformly positive results with both IHC methods and both PCR amplifications were obtained only in 3 pts. (all with AS), and uniformly negative results in only 1 patient (with AR), the latter despite a positive serum IgG titer.

Conclusions: Serological evidence of *C. pneumoniae* is commonly present in pts. with calcified aortic stenosis. However, the only partial detection of *C. pneumoniae* antigen in aortic stenosis by immunohistochemistry, the presence of DNA even in non-calcified valves in pts. with aortic and mitral regurgitation, and the failure to culture *C. pneumoniae* in any of the resected valves cast doubt on a specific causative role of *C. pneumoniae* in calcified valvular heart disease.

3213 Haematological investigation of suspected hypercoagulability in patients with aortic valve disease

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Patients with aortic valve (AV) disease have an increased risk of thromboembolism which may in part be due to increase in coagulopathy. To investigate this we studied indices of platelet activation, endothelial dysfunction and coagulation in 54 patients (20 males, mean age 68 years) with AV disease and 54 age and sex-matched controls. Blood samples were taken from a peripheral vein atraumatically. We measured levels of the soluble adhesion molecule P selectin (sP-sel, ng/ml, an index of platelet activation) von Willebrand factor (vWf, IU/dL, marker of endothelial dysfunction) by ELISA and plasma fibrinogen (g/L) by modified Clauss method. Results, expressed as mean (standard deviation) are as follows:

Index	Controls	Patients	P
Number	n = 54	n = 54	
Age in years (sd)	68.1 (9.8)	67.8 (9.8)	0.46
sP-sel	102.7 (45)	78.1 (40)	0.028
vWf	101.0 (30)	125.6 (32)	0.0001
Fibrinogen	3.0 (0.7)	3.7 (1.0)	0.001

The plasma levels of vWf and fibrinogen were significantly higher in patients with AV disease compared to healthy controls suggesting increased endothelial dysfunction and coagulation in these patients. Conversely, the plasma levels of sP-sel were significantly lower in patients with AV disease. From the total cohort 26 patients underwent mechanical aortic valve replacement (AVR). There was a significant increase in sP-sel ($p < 0.01$) and vWf ($p < 0.01$) but not fibrinogen 3 months post surgery compared to before surgery in these patients.

Conclusions: AV disease is associated with increased endothelial dysfuntion and coagulation but not platelet activation. Following mechanical AVR there is increased endothelial dysfunction and platelet activation. This may contribute to the increased risk of thromboembolism in such patients.

3214 Sudden death in mitral regurgitation due to flail leaflets: when is it unexpected?

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Background: Sudden death (SD) is a catastrophic complication of mitral regurgitation (MR), and its incidence and predictability are undefined.

Methods: To address this issue, we analyzed the occurrence of SD under conservative management in 350 patients (Pts) with MR due to flail leaflets diagnosed echocardiographically from 1980 through 1994.

Results: At diagnosis, patients were age 67 ± 12 years, 74% male, EF 63 ± 10%, and had NYHA class I(61%), II(24%), III(11%), and IV(3%). During a mean medical follow-up of 48 ± 41 months 25 SD death occurred accounting for the 24% of total number of death. Linearized SD rate was overall 1.8%/year. In proportional hazards analysis, independent baseline predictors of SD were NYHA Class ($P = 0.006$), EF ($P = 0.0001$) and atrial fibrillation (AF) ($P = 0.058$). However, among Pts who had SD 9/25 (36%) were in NYHA class I or II (remained so during follow-up) and had an EF > 60%. Moreover, 5 of these 9 were in sinus rhythm and remained so, leading to 5 (20%) completely unpredictable SD. When post-surgical follow-up was considered, multivariate analysis adjusting for NYHA Class, EF, and AF showed surgery performed any time to be independently associated with a reduced incidence of SD (adjusted Hazard Ratio [95% C.I] = 0.22 [0.08–0.58], $P = 0.002$).

Conclusions: 1) Sudden death is a relatively common mode of death in Pts with MR due to flail leaflets. 2) Patients either with severe symptoms, reduced LV function, and AF, are at higher risk of SD, but 3) a notable number of SD are completely unpredictable; 4) Correction of MR appears to reduce the incidence of SD and this effect should be weighed in considering early surgery for MR due to flail leaflets.

3215 Mitral annulus calcification as cause of structural and functional abnormalities in mitral valve and left atrium

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Background: Idiopathic mitral annulus calcification (MAC) is one of the most common cardiac abnormalities found at autopsy. It has also been reported that severe MAC causes mitral regurgitation (MR). This study investigates the consequences of MAC on mitral valve (MV) and left atrium (LA) in the ederly.

Methods: LA diameter, LA mean surface, MV orifice and MR were measured in 55 patients aged over 60 yrs with MAC by 2D Echo, pulse and color Doppler technique. Patients were classified in three groups according to the severity of MAC: Group A (n = 28, mean age: 72.6 ± 7.1 yrs) with calcification under the posterior leaflet, Group B (n = 17, mean age: 74.7 ± 6.9 yrs) with total MAC and Group C (n = 10, mean age: 75.1 ± 7.9 yrs) with calcification extending to the basal part of the leaflets. Patients with atrial fibrilation, hypertension, aortic stenosis, rheumatic disease and chronic renal failure were excluded from our study.

Results: Echocardiographic study showed that mean LA diameter and surface were in group A 4.2 ± 0.4 cm and 22.7 ± 3.1 cm^2, in group B 4.49 ± 0.6 cm and 25.5 ± 4.2 cm^2 ($p = 0.02$) and in group C 5.1 ± 0.7 cm and 27.2 ± 4.1 cm^2 ($p = 0.01$), respectively. Additionally, there was a minor degree of MV stenosis (mean surface: 1.67 ± 0.7 cm^2) in all patients of group C and two patients of group B (1.68 cm^2 and 1.66 cm^2 respectively). Finally, MR 1^+ was found in 50% of patients of group A, 29% of group B and 30% of group C, while MR 2^+ in 25% of group A, 70% of group B and 60% of group C.

Conclusions: MAC is accompanied by minor to moderate MR in ederly. When calcification invades the basal part of the leaflets, there is a restriction of the MV orifice. Furthermore, LA dilatation is a significant consequence related with the severity and extension of MAC in ederly.

HYPERTROPHY IN RODENTS

3225 AT1 receptor blockade prevents cardiac hypertrophy and myocardial damage in bradykinin B2 receptors knockout mice

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Transgenic mice lacking bradykinin (BK) B2 receptor develop mild hypertension, cardiac hypertrophy and several foci of replacement fibrosis in the left ventricle similar to that seen in hypertensive cardiomyopathic hearts of humans. These effects have been attributed to the hypertrophying and damaging action of angiotensin II(Ang II) in the absence of balancing protection of BK. To verify this hypothesis pregnant BK knockout (KO) mice were treated orally with a non-peptide antagonist of AT1 receptors (170 μg/kg, A81988, Abbott Laboratories) and the offsprings after weaning continue to receive the same drug in the drinking water until 180 days of age. An additional group of wild type mice was similarly treated. Untreated KO mice served as controls. Arterial blood pressure was monitored by the tail cuff method at regular intervals starting at 40 days of age. At the end of the experiment hearts were arrested in diastole with cadmium chloride. After the measurements of left ventricular chamber length, middle transverse diameters and ventricular wall thickness, the right and left ventricles and septum were dissected free and separately weighted. Transverse slices of the left and right ventricles were embedded in paraffin and examined quantitatively to determine the amount of myocardial damage. No effect on body weight gain, heart rate and arterial pressure was seen in wild type mice with the treatment. In contrast, in KO mice AT1 receptor blockade decreased arterial blood pressure to control values until 3 months of age with no changes in heart rate. Thereafter arterial pressure was similar in treated and untreated mice. At 180 days of age both left ventricular and cardiac weights of treated KO mice were 20% ($p < 0.05$) lower than in untreated KO. No statistically significant differences were seen in left ventricular wall thickness and chamber volume between treated and untreated mice. Interestingly, myocardial damage was almost abolished by AT1 blockade indicating that local Ang II may play a significant role in the genesis of myocardial scar through AT1 receptor. In conclusion, Ang II receptor blockade prevents functional, anatomical and structural alterations characteristic of BK B2 receptors KO mice implying that the balance between Ang II and BK is essential for the maintenance of a normal heart with age. Moreover, the absence of myocardial damage and myocardial hypertrophy in transgenic mice with AT1 blockade in the presence of mild hypertension suggests that local production of Ang II is the major responsible for myocyte death and growth.

3226 The effects of nitric oxide donor, sodium nitroprusside, on the immediate growth response to load in intact adult rat hearts

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Nitric oxide (NO) inhibits smooth muscle cell growth *in vitro*, but effects on adult cardiac growth are poorly understood. We have previously shown that the imposition of systolic load in isolated perfused adult hearts induces the acute growth response of new cardiac protein synthesis and proto-oncogene expression. Thus, we used this model to test the hypothesis that the NO donor, sodium nitroprusside (SNP) inhibits the induction of new cardiac protein synthesis and the immediate early gene *c-myc*.

Isovolumic perfused adult rat hearts with constant flow were subjected to the growth stimulus of an acute increase in systolic wall stress for 1 hr by an increment in LV balloon volume. New protein synthesis was measured by the rate of [^{3}H] phenylalanine (Phe) incorporation into LV proteins. LV message levels of *c-myc* were measured by Northern blot analysis. To eliminate confounding effects of changes in coronary flow during SNP infusion, all hearts were studied in the presence of maximal vasodilatation with adenosine (10^{-6} M) at identical coronary perfusion pressure. In the control hearts subjected to elevated systolic load (n = 9), the rate of Phe incorporation was 720.5 ± 65.3 nmol/g protein/hour. Treatment with SNP (10^{-3} M, n = 8) decreased load-induced protein synthesis by 28 ± 6% ($p < 0.05$ vs load alone). In addition, SNP inhibited load-induced LV *c-myc* expression by 55 ± 13% ($p < 0.05$ vs load alone). These effects were associated with an increase in left ventricular cyclic GMP content (7.2 ± 1.1 vs 3.8 ± 0.6 10^{-12} M/g dry weight, $p < 0.01$).

These results demonstrate that the NO donor, sodium nitroprusside, suppresses the acute effects of systolic load on proto-oncogene expression and new cardiac protein synthesis in the intact adult heart.

3227 Angiotensin II increases GLUT-1 mRNA gene expression in rat myocardium

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Background and Methods: Indirect evidences suggest that Angiotensin II (Ang II) is involved in development of hypertrophy of surviving myocardium after myocardial infarction. We have previously observed that postinfarction hypertrophy is associated with alterations of the expression of a number of regulatory proteins of metabolism. To study the possible role of Ang II on the expression of regulatory proteins of glucose and fatty acid metabolism, 500 ng/kg/min Ang II was infused in rats for 3 and 7 days by osmotic mini-pumps. mRNA levels of metabolic genes were determined by Northern blot in the left ventricle of hearts.

Results: Blood pressure was increased in Ang II-treated rats (+8%, p = NS and +33%, $p < 0.01$ at 3 and 7 days, respectively) compared to the control group. Hypertrophy of the left ventricle in Ang II-treated rats was detectable at 3 and 7 days with an increase of the left ventricular weight (+21%, p = 0.01 and +12%, $p < 0.05$ at 3 and 7 days, respectively). mRNA expression of both atrial natriuretic factor (+500%, $p < 0.001$ at 3 and 7 days) and α smooth muscle actin (+32%, $p < 0.05$ at 3 days and +27%, $p < 0.001$ at 7 days) was increased during Ang II infusion.

Ang II induced a change in the mRNA expression of the isoform of the glucose transporter with an up-regulation of the foetal isoform GLUT-1 (+25%, p = NS at 3 days and +41%, $p < 0.05$ at 7 days) and a down-regulation of the adult isoform GLUT-4 (−29%, $p < 0.05$ at 3 days and −3%, p = NS at 7 days). Conversely, no alteration of mRNA expression of genes involved in fatty acid metabolism was detected after 3 or 7 days of Ang II infusion.

Conclusion: Development of left ventricle hypertrophy in response to Ang II infusion is associated with an up-regulation of GLUT-1 in rat hearts.

3228 Acute haemodynamic stress induces growth promoting and inhibitory signaling pathways in adult rat heart

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A role of several parallel extracellular signal-regulated (MAPK) and stress-activated protein kinase (SAPK) pathways in the growth response of cardiac myocytes examined *in vitro* are established, but their importance in response to abrupt changes in hemodynamic load *in vivo* in the adult rat heart is less clear. To address this, we examined the activation of the MAPKs and SAPKs i.e. $p54^{JNK}$ and $p38^{MAPK}$ in left ventricular muscle immediately following aortic banding (AoB) in rat heart. In AoB systolic blood pressure increased from 130 ± 4 to 212 ± 6 and 188 ± 9 mmHg at 15 and 30 min, respectively ($p < 001$ vs SHAM).

Active kinases were immunoprepitated with specific antibodies and we found that AoB increased MAPK phosphorylation by only ~2-fold at 30 min, but increased $p54^{JNK}$ by 5-fold, and $p38^{MAPK}$ activity by 41-fold ($p < 0.01$ vs SHAM). The increase in $p38^{MAPK}$ activity was accompanied by a 2.5- and 6.5-fold increase in the phosphorylation of the p38 substrate MAPKAPK2/3 at 15 and 30 min, respectively ($p < 0.05$ vs SHAM).

Activation of these kinases was accompanied by an increase in phosphorylation of c-Jun and ATF-2 and enhanced DNA binding of activator protein-1 in nuclear extracts, as detected by gel-shift analysis and by phospho-specific antibodies (6.3 ± 2 vs 24 ± 2 arbitrary units vs SHAM; $p < 0.05$). This response to hemodynamic load was also followed by significant increases in mRNA abundance in Northern analysis and protein levels of the MAP kinase phosphatase 1 (MKP-1) in immunoblots at 15 and 30 min following banding (3.9 ± 0.1 vs 14.3 ± 7.0 and 7.3 ± 0.2 vs 24.9 ± 2.9, respectively; $p < 0.05$).

Thus, hemodynamic stress of the adult rat heart results in rapid activation of several parallel kinase cascades, particularly the SAPKs as well as mRNA and protein abundance of a principal counterregulatory phosphatase, MKP-1.

3229 Cell stretch induces the release of growth-promoting factors from cardiomyocytes and fibroblasts

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Background An increased workload of the heart stretches the myocardium passively and induces a growth response in myocardial cells. We investigated whether unstretched cells undergo a growth response via paracrine effects of stretched cells.

Methods Myocytes and fibroblasts derived from neonatal rat hearts were subjected to stretch (20%, 1 Hz) for 0 (control), 2, 4, and 6 h. Subsequently, the stretch-conditioned medium (CM2h, CM4h and CM6h, resp) was collected and transferred to unstretched myocytes for 6 h. Protein synthesis induced by CM in unstretched myocytes was assessed by adding ^{3}H-leucine during the final 2 h of incubation. Furthermore, CM of stretched myocytes and fibroblasts (CMmyo and CMfibro, resp) were analysed using size exclusion HPLC.

Results In myocytes incubated with CMmyo, the rate of protein synthesis was increased by 8 ± 8% and by 4 ± 4% versus control (CM4h and CM6h, resp) ($p < 0.05$). The rate of protein synthesis also increased upon incubation of myocytes with CMfibro2h (by 6 ± 4% over control, $p < 0.01$). Furthermore, CMmyo and CMfibro stimulated the expression of ANPmRNA in myocytes. Therefore, these results indicate that CMfibro and CMmyo induce a hypertrophic response in myocytes.

In CMmyo as well as in CMfibro, HPLC detected 6 peaks with molecular weight < 10 kDa, representing proteins released upon stretch. By comparing the chromatograms of CMmyo and CMfibro, two peaks appeared identical, one of which may represent endothelin-1. We found no peak that could represent angiotensin II.

Conclusion Upon stretch of myocytes and fibroblasts factors are released which exert a hypertrophic response in myocytes in a paracrine way. Very likely, one of these growth promoting factors is endothelin-1.

3230 Molecular characterization of myocardial fibrosis during hypothyroidism

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The purpose of this study was to gain insights into the underlying mechanism of myocardial fibrosis during hypothyroidism. We evaluated the effect of hypothyroidism on the biological responses of rat cardiac fibroblasts in a defined in vitro system. Treatment of cardiac fibroblasts with a medium lacking thyroid hormone led to a 47% increase in [^{3}H] thymidine incorporation into the cell nuclei compared with that in untreated cells. Northern blot analysis of RNA from cardiac fibroblasts grown in a thyroid hormone depleted medium resulted in a 38% increase in the abundance of mRNA for pro-α1(I) collagen. At the protein level, the amount of type I collagen, as determined by immunoprecipitation, was increased either in the cell lysate (46%) of cardiac fibroblasts grown in a thyroid hormone depleted medium or in the medium (44%). Transient transfection experiments were performed to more precisely define the mechanism whereby thyroid hormone affects type I procollagen gene transcription. The chimeric plasmid, ColCAT 3.6, contains the 5′-flanking region of the rat pro-α1(I) collagen gene (from bases −3520 to +115) fused to the chloramphenicol acetyltransferase (CAT) gene. The plasmid was cotransfected with thyroid hormone receptor (TR) expression plasmid into rat cardiac fibroblasts and COS-1 cells (monkey mesangial cells). Cells transfected with the ColCAT plasmid in the presence of thyroid hormone (100 nmol/L T3) had a significant decrease (39% in fibroblasts, $P < 0.01$; 52% in COS-1 cells, $P < 0.001$) in CAT activity when compared to cells not exposed to thyroid hormone. Transient cotransfection of TR with various pro-α1(I) collagen/CAT deletion constructs showed that T3-dependent repression was preserved with the deletion from 3520 bp of the flanking sequence to a 5′ end point at position −224, indicating that a thyroid hormone- response element (TRE) was localized at the region −224 to +115. The TR-DNA binding assays demonstrated binding of the human TR β 1 to a fragment containing a proposed TRE located between position −35 and +115 in the 5′-flanking region of the rat pro-α1(I) collagen gene.

GENETIC DETERMINANTS FOR RESTENOSIS

3247 Polymorphism of glycoprotein IIb of the platelet fibrinogen receptor and risk of thrombosis and restenosis after coronary stent placement

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Platelet glycoprotein (GP) IIb/IIIa receptor plays a central role in platelet aggregation. While the association between the HPA-1 polymorphism of GP IIIa and thrombosis and restenosis has already been studied, there are no data about the significance of the HPA-3 polymorphism of GP IIb in the outcome of patients undergoing percutaneous coronary interventions.

Methods: The study included 2178 consecutive patients (pts) with successful coronary stent placement with 1-year clinical follow-up in all and a 6-month angiography in 1731 patients (80%). HPA-3 genotype was determined with the aid of polymerase chain reaction. Angiograms were assessed quantitatively.

Results: Of the 2178 pts, 789 (36%) were HPA-3 a/a, 1023 (47%) HPA-3 a/b, and 366 (17%) HPA-3 b/b. There were no significant differences between these groups with respect to clinical, angiographic and procedural parameters. Stent vessel occlusion occurred in 1.7% of the HPA-3 a/a pts, 1.7% of the HPA-3 a/b pts and 1.6% of the HPA-3 b/b pts ($P = 1.0$). Angiographic restenosis (≥50% diameter stenosis at follow-up) was encountered in 37.7% of the HPA-3 a/a pts, 36.2% of the HPA-3 a/b pts and 34.6% of the HPA-3 b/b pts ($P = 0.72$). Late lumen loss was also comparable. In addition, no significant differences were recorded between these 3 groups in the incidence of death, myocardial infarction and target lesion revascularization at 1 year after the intervention. Event-free survival one year after stent placement was 76.1% in HPA-3 a/a pts, 76.5% in HPA-3 a/b pts and 76.4% in HPA-3 a/a pts ($P = 0.97$). One-year survival free of myocardial infarction was 95.8% in HPA-3 a/a pts, 96.9% in HPA-3 a/b pts and 95.5% in HPA-3 b/b pts ($P = 0.32$). No significant difference among the groups was noted either for overall survival one year after stent placement. It was 97.8% in HPA-3 a/a pts, 98.2% in HPA-3 a/b pts and 96.9% in HPA-3 b/b pts ($P = 0.36$).

Conclusions: HPA-3 polymorphism of the platelet membrane GP IIb is not associated with an increased risk of vessel thrombosis or restenosis after coronary stent placement.

3248 The PI A1/A2 polymorphism of the platelet glycoprotein IIIa is not associated with coronary stent restenosis

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Background: platelet glycoproteins IIb/IIIa have a role in platelet aggregation. A common polymorphism of glycoprotein IIIa (PI A1/A2) has been associated with a higher risk of myocardial infarction, and coronary stent thrombosis and restenosis.

Methods: a prospective study to investigate the association between PI A1/A2 and angiographic restenosis (DS ≥ 50% at QCA) at follow-up in non-diabetic patients (pts) after successful placement of a single stent in a single de novo lesion in a native coronary vessel. Seventy-five consecutive pts with restenosis (R) were matched for age, sex, and extent of coronary artery disease, with 75 controls without restenosis (NR). No significant difference was found between R and NR as to conventional risk factors for coronary artery disease, frequency of the D allele of the ACE gene, history of myocardial infarction, left ventricular ejection fraction, focal/diffuse pattern of the original lesion, clinical presentation at PTCA, indication for stent placement, and type of stent used.

Results: overall, in the 150 R and NR pts the PI A2 allele frequency was 0.14, with the following distribution of the 3 genotypes: PI A1/A1 = 73.3%, PI A1/A2 = 25.4%, PI A2/A2 = 1.3%. The PI A2 allele frequency was 0.166 and 0.113 (ns) in the R and NR cohorts, respectively. The distribution of the genotypes PI A1/A1, PI A1/A2 and PI A2/A2 in R vs NR was 68% vs 78.7%, 30.7% vs 20%, 1.3% vs 1.3%, respectively (ns).

Conclusions: our data suggest that, in non-diabetic patients treated with a single coronary stent for a single de novo lesion in a native vessel, restenosis is not associated with significant differences in the distribution of the PI A1/A2 polymorphism of the platelet glycoprotein IIIa.

3249 The 5A6A polymorphism in the promoter of the stromelysin-1 gene as a risk factor for restenosis

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Intracoronary utrasound studies in humans show that chronic remodeling rather than neointimal hyperplasia is the mechanism of restenosis. Stent implantation limiting this remodeling process has been shown to significantly reduce restenosis. Stromelysin-1 (MMP3), a member of the matrix metalloproteinase family may play a role in this remodeling. A 5A/6A MMP3 promoter polymorphism allowed us to estimate the possible contribution of MMP3 in restenosis.

The 5A/6A MMP3 genotypes were determined in a series of 287 consecutive patients who underwent coronary angioplasty (Balloon) and in a series of 198 consecutive patients who underwent coronary angioplasty successful implantation of a Palmaz-Schatz stent (Stent). All the patients had systematic 6 month angiographic follow-up (fu). Restenosis was estimated with quantitative computer assisted angiography measurements.

Minimal luminal diameters before and after the procedures did not differ significantly among genotype groups. At follow-up, subjects with the 6A6A genotype had an increased risk of restenosis after balloon angioplasty, while stented patients had not.

	5A5A	5A6A	6A6A
Balloon	n = 60	n = 156	n = 71
Diameter stenosis at fu (%)	44 (18)	46 (20)	52 (21)*
Loss index	0.34 (0.69)	0.34 (0.71)	0.53 (0.61)+
Stent	n = 56	n = 92	n = 50
Diameter stenosis at fu (%)	39 (20)	33 (24)	31 (19)
Loss index	0.46 (0.37)	0.42 (0.39)	0.41 (0.37)

means (SD), *p = 0.012, +p = 0.038

Thus, the 6A6A MMP3 genotype (~25% of the population) is a genetic susceptibility factor for restenosis after PTCA without stenting, suggesting an involvement of MMP3 in the remodeling process after angioplasty.

3250 Association between transforming growth factor β polymorphism and coronary in-stent restenosis

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Following coronary angioplasty (PTCA) and stenting, some patients developed in-stent restenosis and may require further revascularisation procedures. Transforming growth factor beta-1 (TGF) affects vascular remodelling and neointimal formation. Its infusion is known to accelerate neointimal proliferation in animal studies. TGF gene polymorphism influences TGF production with individual being either high or low TGF producers. This study examined the association between TGF polymorphism and the incidence of in-stent restenosis after PTCA. DNA extraction, PCR and subsequent electrophoresis identified TGF genotype. The study population consisted of 77 patients with follow up coronary angiograms after PTCA and 107 control patients with no coronary disease. Restenosis was defined angiographically as >70% renarrowing of the stented coronary segment. Signicantly more of the 36 patients with in-stent restenosis are high TGF producers (High producers 35 patients [97%], Low 1 [3%]) when compared to control patients (87 [81%], 20 [19%] $p < 0.05$). No significant difference was observed between the 41 patients without restenosis (36 [88%], 5 [12%]) and the control patients (p = NS).

Conclusions: High TGF producers are at an increased risk of developing in-stent restenosis. Inhibitions of TGF production may reduce the incidence of in-stent restenosis.

3251 Long-term clinical outcome of coronary stenting: role of the D allele of the ACE gene, and importance of the angiographic pattern of restenosis

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The D allele of the angiotensin-converting enzyme (ACE) seems to be a risk factor for restenosis after stent placement. A genetic marker may have a priori predictive value, and a permanent interaction with the mechanisms of restenosis, which may influence the prognosis, beyond the conventional 6-month follow-up period.

Methods: we analyzed the angiographic pattern of restenosis of patients treated with coronary stents in our Centre according to their I/D ACE genotype, and the long-term clinical outcome according to the pattern of restenosis. Restenosis (%DS > 50) was observed in 137 (23%) out of 593 patients (pts). After exclusion of pts with total occlusion (19) and focal restenosis at the articulation site of the Palmaz-Schatz 153 stent (5), 113 pts were analyzed. The length and the severity of the restenotic lesion was significantly different for each genotype, as the distribution of a focal (<10 mm) or diffuse (>10 mm) type of restenosis (table).

Restenosis data	DD (56)	ID (48)	II (9)	p
Restenosis length (mm)	14.6 ± 10.5	9.3 ± 11.2	4.5 ± 4.2	0.005
DS% at follow-up	71.4 ± 11.9	65.5 ± 10.5	61.3 ± 7.2	0.004
Focal restenosis (48)	15 (31%)	26 (54%)	7 (15%)	
Diffuse restenosis (65)	41 (63%)	22 (34%)	2 (3%)	0.001

At six months, 27/48 (56%) and 35/65 (54%) pts with focal and diffuse restenosis had a 2° PTCA respectively (p = ns). Subsequent reinterventions on the target lesion were as follows:

Events	Focal restenosis (48)	Diffuse restenosis (65)	p
3° PTCA (8)	0	8/35 (22.8%)	0.01
3° PTCA or CABG (23)	3/48 (6.3%)	19 (29.2%)	0.002

The Kaplan Meier analysis at a 40 months follow-up period showed that 93.7% of pts with focal restenosis and 61.5% with diffuse restenosis were free from new target lesion revascularization, log rank = 9.75, p = 0.001.

In conclusion, the I/D polymorphism is a determinant of the pattern of restenosis, and the latter predicts the long-term outcome after coronary stent placement.

3252 Insertion/deletion polymorphism of the angiotensin I-converting enzyme gene and 1-year angiographic and clinical outcome after coronary stent placement

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The renin-angiotensin system is thought to play a role in coronary thrombosis and restenosis. Plasma angiotensin I- converting enzyme (ACE) activity is associated with an insertion/deletion (I/D) polymorphism in the ACE gene. This prospective study was performed to test the hypothesis that the D allele of the gene encoding ACE is associated with a higher risk for thrombotic and restenotic events over one year after coronary stent placement.

Methods: This prospective study included 1254 consecutive patients with coronary artery disease who underwent intracoronary stent implantation. The determination of ACE I/D polymorphism was performed using polymerase chain reaction amplification. Angiographic control at 6 months was achieved in 80% of the patients and coronary angiograms were assessed with QCA. Clinical follow-up was extended up to 1 year after the procedure. Primary endpoints of the study were 1-year event-free survival and angiographic restenosis; secondary endpoint was the angiographically proven stent thrombosis.

Results: The observed distribution of the ACE genotypes was 19.8% for II, 53.0% for ID and 27.2% for DD. Stent thrombosis occurred in 2.4% of II patients, 1.2% of ID patients and 0.9% of DD patients (P = 0.248). Restenosis rate at angiographic follow-up was 32.3% for II patients, 34.0% for ID patients and 36.0% for DD patients (P = 0.715). Event-free survival one year after stent placement was 78.1% in patients with genotype II, 77.8% in patients with genotype ID and 76.0% in patients with genotype DD (P = 0.737). No independent role for the D allele could be demonstrated also by multivariate analysis.

Conclusions: The ACE DD genotype or D allele does not influence the 1-year clinical and angiographic outcome of patients undergoing coronary stent placement. These data suggest that routine determination of the ACE genotype may not help to identify patients who are at higher risk of thrombosis and restenosis after coronary stent placement.

EXPERIMENTAL RESTENOSIS AND MODULATION OF PROLIFERATION

3253 Temporal and spatial pattern of VEGF and KDR/FLK expression in reendothelialization and neovascularizations after coronary angioplasty

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Background: Time to complete reendothelialization has been suggested as determinant of neointimal proliferation after coronary angioplasty. VEGF may play a central role in this process.

Methods and Results: Coronary angioplasty was performed in minipigs and injured arterial segments were analyzed after 24 hrs (n = 4), 72 hrs (n = 3), 96 hrs (n = 3), 7 days (n = 4) and 2 weeks (n = 4).

In paraffin embedded tissue we performed in-situ hybridization (ISH) using a probe generated from minipig ovary tissue mRNA by rtPCR (19- and 17-mer sense/antisense primers, chosen to fit the known VEGF- and the human KDR/flk sequence). VEGF ISH for the VEGF receptor showed positive signals beginning 48 hrs after angioplasty in periluminal cell layers. The number of positive cells increased until day 7 after angioplasty in areas of deep arterial injury. ISH for the VEGF receptor KDR/flk showed positive signals with a maximum on day 4. Absolute numbers of positive cells were 198 ± 35/mm^2 (mean + SEM, VEGF day 7) and 38 ± 6/mm^2, (KDR/flk day 4). None of the normal control segments showed a positive signal for either VEGF or KDR/flk. ISH using a probe for the VEGF receptor flt-1 showed no positive signal. Immunostaining with a rabbit polyclonal VEGF antibody was positive in periluminal cells (maximum after 2 wks) and in areas of deep arterial injury, where it co-localized with lectin-positive neovascularizations.

Conclusion: These data support the hypothesis that locally expressed VEGF and ist receptor KDR/flk are involved in reendothelilization and the formation of neovascularizations in deeply injured coronary arteries.

3254 Early spontaneous re-endothelialization does not reduce late intimal thickening

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Introduction: Early re-endothelialization after PTCA or stenting has often been put forward as an important parameter in enhancing vascular repair and subsequently in attenuating neointimal growth. Most experimental models that study this phenomenon compare denuded to non-denuded segments using Fogarty balloons for de-endothelialization prior to PTCA or stenting. However, Fogarty balloons not only remove the endothelium, but also the basement membrane. As a result, Fogarty denudation induces more intimal hyperplasia than balloon angioplasty. Without the confounding factor of Fogarty denudation, we studied the effect of early spontaneous endothelial regrowth on late intimal hyperplasia in swine coronary arteries, using two different stainless steel stent designs.

Methods: Implantation of stainless steel Palmaz-Schatz (PS) and divYsio (D) stents was performed in normal swine coronary arteries under guidance of QCA to match stent and artery size. The metal to surface area is ± 20% and >15% for expanded PS and D respectively. All animals received aspirin during follow-up. The animals were sacrificed at 5 days (n = 10) for assessment of endothelial regrowth using planimetry of scanning electron microscopy images, and at 12 weeks (n = 8) to assess intimal hyperplasia using light microscopy and morphometry. Only stent struts were taken into consideration for assessment of endothelialization and not the area between the stent struts.

Results: Planimetric analysis showed an endothelial coverage of 60 ± 27% for PS and 91 ± 12% for D ($p < 0.05$) at 5 days after stenting. Morphometric analysis at 12 weeks after stenting showed an intimal thickness of 0.2 ± 0.1 mm for PS and 0.2 ± 0.2 mm for D (p = NS).

Conclusion: Despite a significant difference in the percentage re-endothelialization at 5 days after stenting, there is no significant difference in intimal hyperplasia at 3 months follow-up. Therefore dysfunction of the regrown endothelium or non-endothelium dependent factors are likely responsible for ongoing tissue growth.

3255 Effect of angiotensin II type I receptor antagonist on the remodelling after vascular injury

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Vascular remodeling is one of the main cause of restenosis following PTCA. Angiotensin II (AT-II) is a major factor to contribute to vascular remodeling, namely to migration and proliferation of smooth muscle cells in the early phase and to extracellular matrix production in the late phase. Although extensive studies have focused on the effect of AT-II on migration and proliferation of smooth muscle cells, little attention has paid to matrix production. Therefore, we first investigated the expression of AT-II and angiotensin II type I receptor (AT1R) in the rat carotid balloon injury model, especially in the late phase, and next examined the effect of AT1R antagonist to vascular remodeling.

Methods: Rat carotid arteries were denuded three times with a 2F Fogarty balloon catheter. Carotid arteries were removed at 2, 5, 7 days and 2, 4, 8, 16 and 24 weeks after vascular injury. Specimens were subjected to immunohistochemistry with AT-II and AT1R antibodies, and to in situ hybridization (ISH) for AT1R mRNA. Rats were divided into three groups. Group A is control (just denudation without treatment). Rats were administrated a AT1R antagonist (TCV-116, 10 mg/kg/day) from one day before denudation for 8 weeks (group B), and from 4 days after denudation for 8 weeks (group C), in which smooth muscle cells (SMC) were allowed to migrate into the intima. At 8 weeks after denudation, they were sacrificed, the carotid arteries were removed and morphometric analysis was performed.

Results: Immunohistochemical analysis showed that immunoreactivity of AT-II were hardly detected in the media of uninjured arteries. Vascular injury induced AT-II immunoreactivity in the intima with a peak at 7 days and returned to the medial level by 4 weeks. On the other hand, ATIR were little stained in the medial SMC of uninjured arteries, however after injury they were well stained in the intimal SMC, even at 24 weeks after injury. Furthermore, ISH revealed that mRNA of AT1R were detected much in the intimal SMC even at 8 and 16 weeks after vascular injury. Treatment with AT1R antagonist (group B) significantly decreased the neointimal area compared to group A (5.0 ± 1.8 square mm vs 8.2 ± 2.2 square mm, $p < 0.001$). In group C, neointimal formation was also significantly inhibited in comparison with group A (5.2 ± 2.7 square mm vs 8.2 ± 2.2 square mm, $p < 0.05$).

Conclusion: Angiotensin II type I receptor was upregulated in the intimal smooth muscle cells even in the late phase after vascular injury and was suggested to play an important role in the remodeling via matrix production in the late phase after vascular injury.

3256 Local photodynamic therapy in stented porcine vessels

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Photodynamic therapy using local drug delivery (LPDT) was examined in porcine vessels before stent implantation.

Methods: The photosensitizer, Photofrin® (5 mg = 2 ml; QLT, Canada) was delivered with a needle injection catheter (NIC) and activated subsequently by light application (630 nm; 100 J/cm^2). 46 arterial segments from pigs (mean weight 34 kg) underwent stenting (Palmaz-Schatz stents, 16 atm in 3 mm coronary and femoral vessels). Subsequently local photodynamic therapy was performed (therapeutic group 1). The tissue was removed at different time points after the intervention (7, 14 and 21 days). 16 further vessel segments were only stented (control group 2). 12 segments received local drug delivery or monochromatic light exposure after stenting (Group 3 and 4). After explantation, the vessel segments of all groups were embedded in methymetacrylate, serially cut (100 μm) and stained (Lazko-Levai).

Results: *Group 1, therapeutic group:* the stented vessels treated with LPDT showed no inflammation and/or proliferative response (area of tissue hyperplasia 0.3 mm^2). *Group 2, control group:* after substantial vessel injury only, polymorphonuclear leukocyte infiltration and subsequent proliferation of myofibroblasts (maximum after 7d, +365% vs. control) was seen. A myoproliferative response resulted in tissue hyperplasia of 1.8 ± 1 mm^2. *Group 3 and 4:* results did not reveal significant differences to group 2.

In conclusion: LPDT led to a marked reduction of proliferation and tissue hyperplasia in porcine stented vessels.

3257 Reduction of in-stent restenosis in pig coronary arteries by adenovirus-mediated GAX gene transfer

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Intima hyperplasia is the dominant factor in the development of restenosis after coronary stenting. Inhibition of vascular smooth muscle cell (VSMC) proliferation should theoretically reduce neointima formation. Previous work in our lab has shown that over expression of the GAX transcription factor inhibits VSMC proliferation (Smith et al. Genes and Devel, 1997; 11: 1674–1689), and induces apoptosis in cells that are chronically stimulated with mitogens (Perlman et al. EMBO J 1998, in press). Therefore, we investigated the effect adenovirus mediated GAX overexpression, in a porcine model of coronary in-stent restenosis.

Eighteen male Yorkshire pigs underwent coronary angiography. All pigs received 10.000 units of heparin at the beginning of the procedure, and were treated with 325 mg aspirin and 250 mg ticlopidine daily starting two days before. Nir stents (Boston Scientific; Boston, MA) were placed in a straight segment of the left anterior descending artery (balloon vessel ratio 1.1–1.3). This was followed with delivery (Chanelled balloon; Boston Scientific) of the active drug adenovirus (GAX; n = 9) or control vehicle (CON; n = 9). After 4 weeks a coronary angiogram was performed and analysed off line using the CMS system (Medis; Leiden the Netherlands).

Treatment with GAX significantly reduced in-stent restenosis: GAX 24.4 ± 5.6 versus CON 55.2 ± 7.9% (mean ± SEM p = 0.006). Histologic data of the stented vessels will be presented at the meeting.

Treatment with adenoviral GAX significantly reduces in-stent restenosis in a pig model. Allthough systemic dissemination may pose an important problem, the gene therapeutic approach with GAX is a succesfull approach to prevent restenosis after coronary stenting.

3258 Drug effects after local paclitaxel delivery with different catheter types on experimental atherosclerosis in the rabbit

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The microtubule stabilizing compound paclitaxel has proven to have potent antiproliferative effects on smooth muscle cells both in vitro and in vivo. It induces cellular modifications that result in reduced proliferation, migration and signal transduction by shifting the cellular microtubule equilibrium towards assembly. We therefore reasoned that a visualization of the altered cytoskeleton could enable an evaluation of the drug effects following local drug delivery.

3 catheters – the porous balloon, the microporous balloon and the double balloon catheter – were chosen for this study representing the spectrum from passive to active, pressure-driven delivery. After the induction of a defined plaque in the right carotid arteries of 40 New Zealand rabbits by electrical stimulation, 32 animals underwent balloon dilatation and 8 animals served as pre-interventional control group with electrostimulation only. In 24 animals (n = 8 in each group) subsequent local paclitaxel delivery (10 μmol/L) was performed. 8 animals served as control with angioplasty only. Vessels were excised 1 week following intervention. Immunohistochemistry with antibodies against bromodeoxyuridine, alpha-actin, macrophages, von Willebrand factor and α-tubulin was performed. Cytoskeletal changes were analyzed by electron microscopy. Tubulin staining and electron microscopy revealed changes with distinct staining patterns for the different catheters. Specific catheter-induced injuries could be identified for the porous and double balloon catheter. Intimal proliferation, percentage of macrophages and extent of injury favor the double balloon catheter for local paclitaxel delivery.

Conclusions: The alterations of the cytoskeleton induced by paclitaxel allowed for the detection of drug action by staining of tubulin and electron microscopy. This enables an evaluation of transfer, distribution and drug effects directly in the vasculature without marker substances. The double balloon catheter appears to be best suited for local paclitaxel therapy.

ADVANCES IN STENT TECHNOLOGY

3259 Effects of stent coatings on platelets and endothelial cells

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Background: Selectins and intercellular adhesion molecule-1 (ICAM-1) are important molecules in endothelial cell and platelet functions. Previous studies have documented that particularly P-selectin is a marker of subsequent stent thrombosis after stent placement. The aim of this study was to compare the effects of intracoronary placement of phosphoryleholine-coated (PC), heparin-coated and uncoated stents on platelets and endothelial cells.

Methods: Thirty patients (age 55 ± 10, 27 male) with significant LAD stenosis with Type A or Type B1 lesions were randomized to elective implantation of heparin-coated (Jo-stent), PC-coated (Divysio) or uncoated (AVE stent) stents. After stent placement, intravenous heparin infusion was administered only for 24 hours and aspirin + ticlopidine treatment was applied for one month. Venous blood samples were drawn before stent placement and, repeated 24 and 48 hours after the procedure. Patients were excluded if they had recent myocardial infarction, unstable angina pectoris, CABG surgery within last 6 months, total occlusion, or any illness known to influence platelet function.

Results: None of the patients had stent thrombosis. Platelet activity was uninfluenced in uncoated stents and decreased in PC-coated and heparin-coated stents (p = 0.04). Endothelial activation was present only in uncoated stents (p = 0.04).

	Before procedure	24 hr after procedure	48 hr after procedure
Heparin-coated stent (n = 10)			
sP-selectin (ng/ml)	242.60 ± 45.0	184.3 ± 64.7*	177.0 ± 77.3*
sEselectin (ng/ml)	31.8 ± 14.0	38.8 ± 13.8	27.6 ± 8.19.0
sICAM-1 (ng/ml)	199.5 ± 10.6	208.8 ± 42.1	231.6 ± 84.1
PC-coated stent (n = 10)			
sP-selectin (ng/ml)	255.3 ± 96.1	196.0 ± 65.9*	178.0 ± 72.0*
sE-selectin (ng/ml)	29.1 ± 9.5	26.3. ± 8.9	27.50 ± 9.9
sICAM-1 (ng/ml)	216.3 ± 72.4	233.1 ± 59.7	232.8 ± 54.8
Uncoated stent (n = 10)			
sP-selectin (ng/ml)	242.0 ± 98.8	205.5 ± 105.8	200.9 ± 122.3
sE-selectin (ng/ml)	30.4 ± 6.8	38.80 ± 16.9	43.8 ± 9.4*
sICAM-1 (ng/ml)	213.9 ± 92.9	228.5 ± 105.3	207.5 ± 108.7

*p < = 0.04, vs preprocedure parameters.

Conclusion: PC-coated and heparin-coated stents were found to decrease platelet activity without activating endothelial cells whereas uncoated stents led to endothelial activation without changing platelet activity. These results show that PC-coated and heperin-coated stents can be adventageous in decreasing thrombatic complications and restenosis.

3260 Heparin-coated stents and restenosis

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Despite the promising results with coronary stenting, sub-acute thrombosis and complications due to intensive anticoagulation are still restrictive problems. There are recent studies reporting the positive effect of heparin coated stents on restenosis by decreasing the cellular proliferation on long term. This study was designed to evaluate the effect of heparin coated Jo-stents on restenosis.

Seventy-eight patients (pts) were enrolled in the study and randomized into two groups according to the implantation of heparin coated or non-coated Jo-stents. There was no difference between the mean ages, risk factors, clinical characteristics, lesion morphologies, and ejection fractions of the groups. Primary procedural success was also similar. After stent implantation, all pts received heparin (IV 10000 U bolus+ infusion 4–6 hours), ticlopidine (500 mg/day), and aspirin (100 mg/day). All pts were controlled with quantitative coronary angiography after 5.7 ± 1 months. All data was compared with Student t-test. Angiographic restenosis (defined as diameter stenosis >50%) was seen in 16 (41%) pts with heparin coated and in 11 (28%) pts of the uncoated group (p > 0.05).

Results: (1) The early angiograph ic results of heparin coated stents were found similar to the results of uncoated stents. (2) There was no appreciable impact of heparin coating on stent restenosis. (3) These data suggest that compared to uncoated stents, heparin coating does not provide additional benefit to restenose rates.

Comparison of the groups

	Heparin coated (n = 39)	Non-coated (n = 39)	P
Refence luminal diameter (mm)	3.16 ± 0.18	3.12 ± 0.22	ns
Minimal luminal diameter (mm)			
– Preprocedure	0.84 ± 0.26	0.58 ± 0.32	<0.05
– Postprocedure	2.85 ± 0.31	2.80 ± 0.30	ns
– Control	1.73 ± 0.71	1.64 ± 1.02	ns
Acute Gain (mm)	1.96 ± 0.60	2.18 ± 0.43	ns
Late Loss (mm)	1.09 ± 0.76	1.06 ± 0.90	ns
Relative gain (mm)	0.64 ± 0.15	0.69 ± 0.15	ns
Relative loss (mm)	0.36 ± 0.23	0.34 ± 0.30	ns
Gain Index (mm)	0.27 ± 0.28	0.34 ± 0.30	ns

3261 Acute interventional success demonstrates no differences between gold-coated and standard stainless steel stents: first data from a multicentre, randomized trial

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Gold coated stents (G) seem to have various advantages compared to standard high quality steel stents (S): Higher visibility during fluoroscopy, less thrombogenicity and potentially less neointimal proliferation. To compare acute angiographic and clinical outcome as well as the angiographic longterm effects of both, G and S, a prospective, randomized multicenter trial (5 centers in Germany) was initiated. Primary endpoint is the amount of neointimal proliferation after 6 month measured by intracoronary ultrasound and quantitative angiography.

Methods: Monitored acute data of 196 pts are available at this time. Baseline characteristics (78% male, 19% previous PTCA, 6% previous CABG, 44% previous MI; 55% hypertension, 16% diabetes, 41% family history, 61% dyslipidemia) were not different. All patients underwent routine PTCA, indication for stent implantation was a visually suboptimal result after PTCA in both groups.

Results: Mean stent length G versus (vs) S was 13.0 ± 2.9 vs 12.3 ± 3.3 mm. Additional stent implantation was necessary in 7.5 vs 8.5%. Implantation pressure was 12.6 ± 2.8 vs. 13.8 ± 2.6 atmospheres. Angiographic success (<30% residual stenosis) was obtained in 98% (96 G, 96 S). In cathlab complications occurred in 4 cases: Two stent (S) could not be placed in the lesion, 2 stents slipped off the balloon and could be safely removed (G and S). There were no in-hospital infarctions, CABG, or deaths in both groups. One subacute stentthrombosis was observed within 60 days follow up (G).

Conclusion: These preliminary data indicate no significant difference between the safety and acute clinical outcome in pts receiving G or S. Better visibility did not result in shorter stents used to treat the lesion. Intravascular ultrasound at 6 month will demonstrate the impact off different stent surfaces on neointimal proliferation.

3262 Influence of stent design on one-year outcome after coronary stent placement: a multicentre randomized trial with five stent types

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There is experimental evidence demonstrating that stent design may have an impact on the stent-vessel interaction. The objective of this randomized study was to assess whether differences in stent design are translated into different clinical outcomes in patients undergoing coronary stent placement.

Methods: The study included 1147 patients who were randomly assigned to receive one of 5 types of stainless steel stents: Inflow (n = 231), MULTI-LINK (n = 227), NIR (n = 229), Palmaz-Schatz (n = 233) and PURA-A stent (n = 233). Six-month angiography was carried out in 82.7% of the eligible patients. Primary endpoint of the study was event-free survival at 1 year. Secondary endpoints of the study were the incidence of stent thrombosis at 30 days and quantitative angiographic indexes of restenosis such as diameter stenosis, late lumen loss and restenosis rate (≥50% diameter stenosis). All annalyses were performed according to the intention-to-treat principle.

Results: Event-free survival at 1 year was significantly different between the groups (P = 0.003). It varied from 69.0% for patients in the NIR stent group to 82.4% in MULTI-LINK patients. Similarly, freedom from myocardial infarction was also significantly different (P = 0.007) with values between 88.6 to 96.5%. There were no significant differences in the incidence of stent thrombosis. Diameter stenosis at 6 months varied from 38.1 ± 25.0% to 45.6 ± 27.7% (P = 0.046), late lumen loss ranged from 1.01 ± 0.70 mm to 1.20 ± 0.82 mm (P = 0.085) and the incidence of restenosis varied between 25.3 to 35.9% (P = 0.145).

Conclusions: This study demonstrates that stent design has a significant impact on the long-term results after coronary stent placement. These results suggest that optimization of stent design should be the target of future efforts to improve the outcome of patients undergoing coronary stent placement procedure.

3263 A randomized trial comparing a gold-plated stent with a conventional steel stent: angiographic and clinical results after 1-year follow-up

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Stent coating with various agents has frequently been investigated as a strategy for reducing thrombosis and restenosis. We report here the final angiographic and clinical results of the randomized trial that assessed the effects of plating steel stents with a pure gold surface.

Methods: Before the procedure, 731 patients (pts) were randomly assigned to receive either a conventional, non-coated steel stent (SS: 364 pts) or a steel stent with a complete gold surface, 5 μm in thickness (GS: 367 pts). Both stent types were slotted tube stents with identical design. Follow-up angiography at 6 months was performed in 78% of the eligible patients. All angiograms were evaluated with an automated quantitative system. Restenosis was defined as a diameter stenosis ≥ 50% at follow-up angiography. Subacute stent thrombosis, death, myocardial infarction, repeat PTCA or CABG were recorded.

Results: There were no differences in baseline clinical, angiographic and procedural data. The follow-up results are displayed in the table.

	GS	SS	P
Stent thrombosis, %	2.5	0.8	0.08
Diameter stenosis, %	52.3 ± 31.9	44.8 ± 29.3	0.005
Minimal lumen diameter, mm	1.48 ± 1.05	1.70 ± 1.00	0.011
Late lumen loss, mm	1.59 ± 0.97	1.33 ± 0.90	0.002
Restenosis rate, %	48.6	37.8	0.011
Death, %	6.5	4.7	NS
Myocardial infarction, %	2.7	1.1	NS
Repeat PTCA, %	26.4	15.9	0.001
CABG, %	3.0	3.0	NS

Conclusions: This randomized trial demonstrates that plating the steel stent with a gold surface exacerbates the hyperplastic response of the vessel wall after stenting. These findings underscore the relevant impact of stent surface on the process of restenosis after this intervention.

3264 Nickel allergy in patients with in-stent restenosis

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In-stent restenosis may be triggered by allergic reactions to nickel, chromate, manganese or molybdenum which are components of stainless steel stents. The purpose of this study was to investigate the incidence of allergic reactions to 316L stainless steel components in patients with in-stent restenosis.

In 131 patients (63 ± 9 years) with 171 stainless steel stents (33 Palmaz-Schatz, 70 AVE, 68 other types) coronary angiography was performed 6.1 ± 2.7 months after stent implantation. The percentage diameter stenosis within the stent was analyzed by quantitative coronary angiography. All patients underwent epicutaneous patch tests using Finn chamber technology for nickel-II-sulfate 2.5% and 5%, potassiumdichromate 0.5%, molybdenum-V-chloride 0.5%, manganese 0.5% and 316L stainless steel platelets. Results of the patch tests were evaluated by independent investigators after 48 h, 72 h and if necessary after 96 h of contact with the potential allergen.

Quantitative coronary angiography revealed in-stent restenoses (≥50% diameter stenosis) in 89 pts; 42 pts had no restenosis. In the group *without* restenosis there was *no* patient with an allergic reaction. *All* pts with positive patch tests (n = 9) were in the group *with* restenosis. In this group the overall incidence of positive reactions was 10%. In 3 pts we observed positive reactions to molybdenum and in 6 pts (3 male, 3 female) to nickel. However, none of the pts with allergic reactions to the standardized test solutions had a positive reaction to the 316L stainless steel platelets.

Conclusions: Patients *with* in-stent restenosis had a higher incidence of patch test reactions to nickel than those without restenosis. These results from this small group of patients suggest that allergic reactions to nickel may trigger in-stent restenosis.

CORONARY INTERVENTIONS IN DIABETICS

3265 Is Doppler-guided balloon angioplasty with conditional stenting a viable option in diabetic patients? A subanalysis of the DESTINI trial

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The DESTINI trial is a prospective randomized evaluation of primary stenting (PS) compared to Doppler-guided balloon angioplasty with conditional stenting (OP/CS). The population of this analysis consisted of all randomized patients who had a single lesion treatment and who had 6 mo clinical follow-up (87% of the total study population). This population was divided to diabetics (DM = 96 pts) and nondiabetics (NoDM = 435 pts). There were more females in the diabetic group (36% vs 22%, p = 0.004). Each group was divided into its two randomized arms.

Angiographic findings and follow-up data are shown below:

	DM		No DM	
	OP/CS N = 52	PS n = 44	OP/CS N = 219	PS n = 216
Baseline				
RD (mm)	2.96 ± 0.39	3.07 ± 0.49	3.08 ± 0.46	3.11 ± 0.45
MLD (mm)	0.90 ± 0.30	0.97 ± 0.32	0.95 ± 0.33	0.95 ± 0.33
Lesion length (mm)	12.96 ± 5.66	12.8 ± 5.86	12.55 ± 5.28	12.53 ± 4.99
Post-procedure				
RD (mm)	2.96 ± 0.42	3.15 ± 0.45	3.11 ± 0.47	3.23 ± 0.43
MLD (mm)	1.98 ± 0.58*	2.94 ± 0.49*	2.05 ± 0.56*	2.93 ± 0.54*
6-mo Follow-up				
Death	1 (1.9%)	0 (0%)	1 (0.5%)	2 (1%)
MI	1 (1.9%)	2 (4.5%)	6 (2.7%)	3 (1.4%)
TLR	8 (15%)	6 (14%)	27 (12%)	25 (12%)

*P < 0.05; RD, reference diameter; MLD, minimum lumen diameter; TLR, target lesion revascularization.

Conclusions: 1) Doppler-guided BA with conditional stenting in diabetic pts yield similar intermediate-term outcome to primary stenting; 2) Furthermore, with similar baseline lesion characteristics, diabetics faired as well as nondiabetics in the first 6-month. Whether there will be a divergence in outcome after 6-month will be determined after the completeness of 1-year follow-up.

3266 Clinical outcome of stent placement compared to balloon angioplasty in diabetic patients with coronary atherosclerosis

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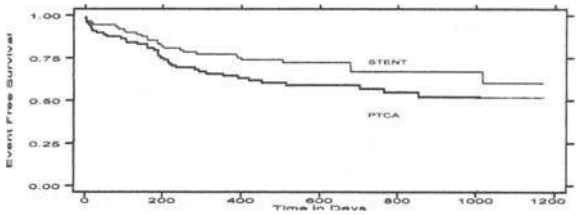
Although coronary stenting reduces angiographic restenosis in diabetic patients, its impact on clinical outcome and place in management remains undefined.

Methods: The Angioplasty vs Stenting in Diabetics with Angina (ASDA) study compared the clinical effectiveness of these treatments using a observational historically prospective cohort design. Over 30 months, 176 of 433 diabetics who underwent an intervention, met the inclusion criteria and were enrolled. The 88 patients in each group had similar baseline characteristics and were followed up 22 (8) months later. Assuming an alpha error of 0.05 and a treatment difference of 1.75, a sample size of 176 gave a power of 80%.

Results: Post-procedure MLD was greater with stent placement (2.97 (0.44) *v* 2.24 (0.53) mm; $p < 0.001$). Event-free survival for the composite primary clinical endpoint (death, MI, repeat revascularization, clinical restenosis) favoured stenting (hazard ratio 1.57; 95%CI, 0.95–2.58; $p = 0.08$; see graph). A similar trend was seen for the composite secondary endpoint of target vessel revascularization and clinical restenosis (hazard ratio 1.72; 95%CI, 0.99–2.99; $p = 0.05$). After adjusting for covariates using Cox regression analysis, the results for both primary (hazard ratio 1.62; 95%CI, 0.97–2.69; $p = 0.06$) and secondary (hazard ratio 1.64; 95%CI, 0.94–2.86; $p = 0.08$) endpoints changed only slightly.



Conclusion: A strong and consistent trend favoured stenting for both endpoints, and persisted after adjusting for covariates, Diabetics requiring coronary revascularization who are not surgical candidates should be considered for stent placement rather than PTCA.

3267 The increased restenosis rate after stent implantation in diabetics is independent of the treatment modality for diabetes

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The long-term success of coronary stenting in diabetic (DM) pts is impaired by an increased restenosis rate compared to non-DM pts. The influence the treatment modality for DM (insulin vs. oral antidiabetic agents or diet) has not been sufficiently elucidated. We retrospectively analyzed the long-term angiographic outcome after coronary stenting in DM pts treated with insulin (ITDM pts) versus DM pts treated without insulin (non-ITDM pts) and compared the results with those in non-DM pts. The study cohort comprised 1444 pts with a total of 1963 lesions.

Angiographic results:

	Non-DM	Non-ITDM	ITDM	p
Patients (lesions)	1220 (1657)	178 (251)	46 (55)	
Intervention				
Ref. diameter (mm)	2.87 ± 0.44	2.83 ± 0.43	2.72 ± 0.53	0.026
MLD (mm)	0.67 ± 0.42	0.68 ± 0.37	0.73 ± 0.41	0.578
MLD post stent (mm)	2.80 ± 0.37	2.75 ± 0.39	0.65 ± 0.46	0.0032
Stenosis pre stent (%)	77 ± 14	76 ± 13	73 ± 14	0.152
Stenosis post stent (%)	2 ± 12	2 ± 12	2 ± 13	0.771
Follow-Up				
Ref. diameter (mm)	2.79 ± 0.47	2.80 ± 0.46	2.62 ± 0.46	0.024
MLD (mm)	1.80 ± 0.79	1.60 ± 0.80	1.38 ± 0.75	<0.0001
Stenosis (%)	36 ± 25	43 ± 26	48 ± 27	<0.0001
Restenotic lesions	430 (26%)	89 (35%)	22 (40%)	0.0008
Loss index	0.49 ± 0.36	0.57 ± 0.39	0.66 ± 0.42	<0.0001

Conclusions: DM pts have a less favorable angiographic outcome after coronary stenting than non-DM pts, regardless of the treatment modality for DM.

3268 Stenting the coronary vessel in a diabetic: are outcomes comparable with the non-diabetic?

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Coronary intervention in the diabetic patient has historically been associated with discouraging outcomes: a) high incidence of restenosis, b) increased need for target lesion revascularization and c) increased long-term mortality. Limited data is available on the impact of diabetes on long term clinical outcomes and restenosis rates following stenting (ST) of coronary lesions. We retrospectively compared procedural, in-hospital and 12-month clinical outcomes following intracoronary ST implantation in diabetic (DM) and nondiabetic (non-DM) patients who underwent transcatheter intervention at our center. From 1/96 to 1/99, 1197 STs were implanted in 1075 native coronary arteries of 934 patients, 199 (21.3%) DM and 735 (78.7%) non-DM. Clinical presentation included acute MI in 25.6%, unstable angina in 47.6% and positive stress test in 22%. Additional co-morbid risk factors included: age > 70, 33.8%; prior MI, 34%; prior CABG, 25.7%; LV dysfunction (EF < 40%), 20.3%; and multivessel disease, 28.7%. The target vessel distribution was the LAD in 38.1%; 7% lesions were ostial. Both groups were well-matched for clinical and angiographic variables. Stented vessels were ≥3.0 mm in diameter. Post-ST high pressure dilatations were performed (mean 16.7 atm). Adjunctive IABP support was used in 19.5%. All patients received oral antiplatelet therapy post-procedure.

Results: Procedural success (≤20% residual stenosis; TIMI 3 flow) was obtained in 98.0% DM and 98.5% non-DM ($p = 0.16$). Acute re-closure occurred in 2.1% of DM and 0.1% non-DM ($p = 0.21$). One non-DM died of worsening heart failure ($p = 0.72$).

	12-Month Follow-Up (96.7% complete; mean 6.72 ± 5.02 mos.)				
	TLR-PTCA	CABG	Death	Event-Free Survival	Mean rise in LVEF (%)
DM	32 (16.1%)	7 (3.5%)	5 (2.5%)	155 (77.9%)	+1.35
Non-DM	38 (5.2%)	19 (2.8%)	12 (1.6%)	668 (90.9%)	−0.95
'p'	*0.019**	0.188	*0.03**	*0.03**	0.89

* 'p' value significant at ≤ 0.05; TLR: target lesion revascularization

Conclusions: (1) In this series of patients treated with ST implantation in obstructed native coronary vessels, acute procedural success was similar in DM and non-DM patients. (2) In-hospital complications were low and infrequent in both populations. (3) The incidence of in-stent restenosis requiring TLR-PTCA showed a *statistically significant* increase and event-free survival was *significantly* lower in the diabetic group. (4) This translated into lower absolute survival rates in the diabetic group, which was *statistically significant.* Our data suggests that stenting is associated with similar acute procedural and clinical success in DM and non-DM patients. DM patients, however, demonstrate increased mortality and a greater need for revascularization for in-stent restenosis, in the long-term. These findings merit further study.

3269 Influence of diabetes mellitus on initial and long-term outcome of stented patients with multivessel coronary disease

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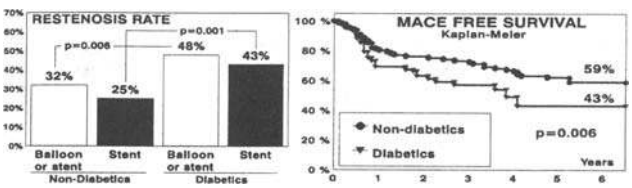
To assess the influence of diabetes mellitus (DM) on restenosis and long-term prognosis after coronary stenting (CS) of pts with multivessel disease, we compared the clinical and angiographic evolution of 94 multivessel pts with DM versus 489 non-diabetic pts.

Diabetics were older (64 ± 8 vs 62 ± 10 yr, $p < 0.01$) and had more number of diseased vessel (2.5 ± 0.5 vs 2.3 ± 0.5, $p < 0.05$) and a higher rate of female gender (23 vs 13%, $p < 0.001$), hypertension (51 vs 40%, $p = 0.01$) and previous heart failure (14 vs 6%, $p < 0.01$). No other clinical or angiographic differences were found. Clinical follow-up (FU) was completed for 94% of pts at 33 ± 18 months.

Coronary stenting was the only revascularization method in 70% of pts, whereas additional ballooning was required in 30% of pts, without differences between diabetic and non-diabetics. Initial clinical success (absence of death, AMI, new revascularization or hospital admission due to angina at 30 days) was similar in both groups (87 vs 87%, p = NS). Likewise, diabetics and non-diabetics had similar long-term survival (84.5 vs 86.4%, p = NS). Nevertheless, diabetics had a higher rate of restenosis and lower rate of freedom from events during FU (figures.).



Thus CS provides similar procedural result and initial outcome in diabetic and non-diabetic pts with multivessel disease. In terms of mortality, late prognosis is also similar. However, events during FU are more frequent among diabetics.

3270 Influence of diabetes in saphenous vein graft stenting: immediate and late outcomes

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Background. Patients with diabetes mellitus have a greater incidence of procedural complications and higher restenosis rates after stenting in native coronary arteries. However the effect of diabetes on immediate and late outcomes in saphenous vein graft (SVG) stenting has not been determined.

Methods. We studied 906 consecutive patients with 1366 SVG lesions treated with Palmatz-Schatz stent implantation. In-hospital and one year major adverse cardiac events (MACE) including death, MI, and any repeat revascularisation were compared among non-diabetics (non-DM, n = 616), and diabetics (DM, n = 290).

Results. DM group had more hypertensives (75.2% vs 60.6%, p = 0.001) and women (28.4% vs 15.6%, p = 0.001). Angiographic findings included similar vessel size (3.3 mm vs 3.4 mm) and lesion length (9.8 mm vs 10.0 mm). Angiographic success (99.5% vs 100%) and final diameter stenosis (7.5% vs 6.1%) were similar between the groups.

	Non-DM (n = 610)	DM (n = 290)	p
In-hospital MACE	1.6%	4.7%	0.04
1 year death	8.6%	12.6%	0.05
1 year MI	0.6%	1.3%	0.27
1 year TLR	18.7%	22.2%	0.14
Late MACE	32.5%	40.7%	0.01

p = NS between NIDDM vs. IDDM; MACE = any death, MI, TLR; TLR = target lesion revascularisation.

Conclusion: As in native coronary arteries, SVG stenting in diabetes is associated with higher in-hospital complications and late cardiac events, mainly due to increased mortality. Potential mechanisms, such as diffuse atherosclerosis and comorbidity, should be further investigated.

BENEFICIAL EFFECTS OF STATIN THERAPY FOLLOWING PERCUTANEOUS INTERVENTIONS

3271 Reduction of atherosclerosis by adoptive transfer of protective immunity in apoE knockout mice

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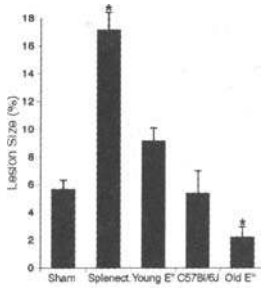
Atherosclerotic plaques contain macrophages and T lymphocytes, many of which are immunoreactive against oxidized low density lipoprotein (oxLDL) and immunization with oxLDL reduces lesion in atherosclerotic apoE knockout (E°) mice. However, the role of immune response in atherosclerosis has not been clarified, yet.

Methods: E° mice were immune depressed by splenectomy followed by intavenous transfer of spleen cells deriving from young E° mice that had not yet developed disease, atherosclerotic, old E° mice, wildtype C57BL/6J mice, or buffer alone. Mice were fed a proatherogenic diet for 20 weeks. Lesion size and composition and oxLDL specific cell and antibody immune response were analyzed.

Results: Splenectomized E° mice had three-fold greater aortic root lesions than sham operated mice (*p < 0.01). Transfer of spleen cells from young E° mice or C57BL/6J mice was able to rescue the aggravating effects of splenectomy. As shown in the figure, transfer of spleen cells from diseased mice reduced lesions to half as compared to sham operated mice (*p < 0.01).



Protection was associated with an increase in antibody titers and T cell responses to oxLDL but fewer CD4+ T cells in lesions.

Conclusion: Our data demonstrate that spleen-associated protective immunity in atherosclerotic mice inhibits disease progression.

3272 Statin therapy blocks the excess risk of coronary stent restenosis associated with the NADPH p22 phox polymorphism

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Background: Oxidative stress in the vasculature has been implicated in the pathogenesis of restenosis after coronary interventions. The NADH/NADPH oxidase system plays a central role for the generation of superoxide anions in vascular smooth muscle cells. A genetic mutation in the gene encoding for the electron transfer element p22 phox, the CC-genotype, has been suggested to increase the susceptibility to coronary artery disease. Statins reduce oxidative stress in the vasculature by lipid lowering, and, in addition, possess antiproliferative and antiinflammatory properties, thereby, potentially interfering with the major processes of stent restenosis.

Methods: We investigated the effects of the p22 phox polymorphism in presence or absence of statin therapy on angiographic outcome in 494 patients following successful coronary stent implantation.

Results: (6 month follow-up)

Stent-Restenosis (≥50%)	No Statin N = 245	Statin N = 249	p-value
TT or TC-genotype	43/132 (31.8%)	34/132 (25.8%)	0.3
CC-genotype	50/113 (44.2%)*	35/117 (29.1%)	0.01

*p = 0.04 vs. TT/TC genotype

Multivariate analysis identified the CC-genotype (p = 0.048), statin therapy (p = 0.02), the minimal lumen diameter immediately post stenting (p = 0.001) and stent length (p = 0.001) as independent predictors for subsequent restenosis development.

Conclusion: Statin therapy substantially reduces the excess risk of coronary stent restenosis associated with the CC genotype of the NADPH p 22 phox polymorphism and thereby may counteract the deleterious effects of oxidative stress on stent restenosis.

3273 The benefit of aggressive lipid lowering: Atorvastatin Versus Revascularization Treatments (AVERT)

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The AVERT study is the first trial to determine the effect of aggressive lipid lowering with atorvastatin on clinical outcome in patients with stable coronary artery disease (CAD).

Methods: In this open label, multicenter study patients with LDL-C levels > 3.0 mmol/L (115 mg/dL) and ≥1 major coronary artery with at least 50% stenosis were randomized to atorvastatin (80 mg/day) or PTCA followed by usual care (including lipid-lowering therapy if prescribed). The primary endpoint was any documented ischemic event (defined as myocardial infarction, CAD death, unstable angina, CABG or PTCA) over an 18-month period. The major secondary endpoint was the time to the first ischemic event for each patient.

Results: A total of 341 patients were randomized, 164 to atorvastatin and 177 to the PTCA group. The use of anti-anginal drugs did not differ between the two groups. After 18 months, 22 (13%) atorvastatin patients versus 37 (21%) angioplasty patients had experienced ≥1 ischemic event, a 36% reduction (p = 0.048). Furthermore, the time to the first ischemic event was significantly longer (p = 0.027) for the atorvastatin than the PTCA group. Compared with baseline, LDL-C fell 46% from 3.75 to 2.0 mmol/L (145 to 77 mg/dL) with atorvastatin and by 18% from 3.8 to 3.1 mmol/L (147 to 120 mg/dL) with PTCA/usual care. The reduction in the PTCA/usual care group was associated with a lipid-lowering drug, 69% taking a statin by the end of the study. There was a significant correlation between LDL-C reductions and cardiovascular event rates in favour of atorvastatin therapy. Atorvastatin was generally well tolerated. Four patients on atorvastatin 80 mg/day (2.4%) had elevated ALT or AST to values 3× ULN. No patient experienced myopathy during the study.

Conclusions: Atorvastatin not only resulted in a reduction in ischemic events but also a significant delay in the time to first event and was generally well tolerated. AVERT supports the benefits of aggressive cholesterol lowering with atorvastatin in stable CAD patients.

3274 Statin therapy in diabetic patients dramatically reduces proliferation and clinical events after coronary stenting

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Background: After intracoronary stenting, patients with diabetes mellitus [D] show an augmented proliferative response as compared to non-diabetic patients [ND]. Data on clinical outcome and restenosis rates in D vs. ND are ambiguous and may be confounded by differences in baseline variables and co-medication. Besides effective lipid lowering, statins [S] exhibit antiproliferative, antiinflammatory and antithrombotic properties; thus potentially interfering with all three major processes that initiate in-stent restenosis.

Methods: We performed a comparison of clinical and angiographic outcome at 6 months between 122 D (50 S and 72 /S) and 244 ND matched for statin treatment (100 /144 /S) and also matched for minimal lumen diameter [MLD] post stenting and reference diameter at baseline, two important predictors of restenosis following stent implantation.

Results: (6 months follow-up)

		Baseline Cholesterol	Follow-Up Cholesterol	Restenosis Rate	Diameter Stenosis	Combined Endpoint*
D	S:	256 ± 54	209 ± 37	13 (26%)	35 ± 23%	16 (33%)
	/S:	215 ± 40	204 ± 38	28 (39%)	45 ± 26%	37 (51%)
ND	S:	243 ± 53	209 ± 44	19 (19%)	35 ± 23%	27 (28%)
	/S:	219 ± 37	218 ± 41	50 (35%)	41 ± 24%	53 (37%)
P		<0.001	n.s.	<0.05	<0.05	<0.05

*: Comb. Endpoint: death or myocardial infarction or target lesion revascularization.

Conclusions: In diabetic patients, who constitute a population at high cardiovascular risk, statin therapy dramatically reduces restenosis rates and improves clinical outcome after coronary stent implantation. This beneficial effect of statins is, at least in part, independent of the cholesterol lowering property.

3275 HMG-CoA reductase inhibitor simvastatin inhibits smooth muscle cell proliferation *in vitro* and prevents the neointimal formation after stenting

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Vascular smooth muscle cell (VSMC) proliferation in response to local stimuli as stent implantation is the major determinant of neointima formation and restenosis. It's well known that Ras proteins are key transducers of mitogenic signals from membrane to the nucleus and Ras farnesylation is essential to activate these proteins. The statins are powerfull inhibitor agents of Ras farnesylation. We tested the effects of Simvastatin (S) on *in vitro* VSMC proliferation and on neointima formation after stent implantation in rat common carotid arteries. S (40 mg/kg/daily) was administered in drinking water from 14 days before the procedure until the animals' sacrifice. NIR 7 cells stents were implanted in common carotid arteries using 1.5 mm PTCA balloon catheter inflated at high pressure (10 Atm) in 12 animals divided into subgroups of 6 rats treated with S or placebo (C). 21 days after stent deployment the arteries were removed. A statistically significant reduction of both neointima (N) (from 0.508 ± 0.035 to 0.362 ± 0.047 mm^2 $p < 0.05$) and neointima-media ratio (N/M) (from 2.00 ± 0.136 to 1.360 ± 0.180 $p < 0.05$) after S administration was found. No difference in the rate of stent thrombosis was observed in the two groups.

fig53475.eps

Thus Simvastatin inhibits VSMC proliferation *in vitro* and markedly reduce the neointima formation after arterial stenting *in vivo*.

3276 Time-dependent changes of arterial distensibility induced by cholsterol and balloon injury: an in vivo intravascular ultrasound study

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Hypercholesterolemic feeding of rabbits induces formation of early atherosclerotic and stenotic lesions. Balloon injury leads to development of advanced stenotic plaques. The aim of our study was, to analyze changes in arterial distensibility in rabbit aortas revealiing different stages of atherosclerotic plaque formation during cholesterol diet and after balloon injury at different points of time. Newzealand White rabbits (3.5–4.3 kg) received normal chow (I, n = 15) or 1% cholesterol rich diet for 10 weeks (II, n = 14). Balloon injury of abdominal aortas was performed after 4 weeks. 10 segments of the aorta of each animal were evaluated pre and directly post injury, 2 and 6 weeks after trauma with intravascular ultrasound (30 MHz 3.5-F-catheter, introduced via right femoral artery). Acetylcholine was applicated i.a. over 5 minutes to assess arterial reactivity pre and post injury. Corresponding, perfusion fixated segments identified through anatomical landmarks were gained after 2 (n = 49) and 6 weeks (n = 99) for histomorphology. Systolic-diastolic changes of luminal areas of segments served for assessment of vascular pulsatility (vascular pulsatility = [maximum − minimum luminal diameter]/maximum luminal diameter). The inimal index was calculated as follows: plaque area/(luminal + plaque area).

Pre injury vascular pulsatility of aortas of normal fed animals was significantly higher compared to cholesterol fed rabbits (9.0 ± 3.1% vs. 6.7 ± 2.2%; $p < 0.01$). Directly after trauma, there was significant decrease of vascular pulsatility in both groups of 38.4% in I and 42.8% in II ($p < 0.01$ compared to pre injury; p = n.s. for I vs. II directly after injury). After 2 weeks pulsatility was reduced to 3.0 ± 2.2% in I and 3.8 ± 2.6% in II (I vs. II: n.s.), after 6 weeks to 2.2 ± 1.9% in I and 0.7 ± 0.1% in II ($p < 0.05$). There was a significant reduction of vascular pulsatility in both groups after 2 and 6 weeks compared to directly post injury ($p < 0.01$). The intimal index increased from 0% in I and 1.4 ± 0.01% in II pre injury to 1.9 ± 0.02% in I and 17.9 ± 1.8% in II after 6 weeks ($p < 0.01$).

The reduction of arterial distensibility assesed via intravascular ultrasound reveals functional and structural alterations of the arterial wall and corresponds to the depth of vascular injury and plaque development.

CLINICAL PROBLEMS IN ANTITHROMBOTIC THERAPY

3281 Acute effects of high-dose heparin administration on ischaemic threshold in patients with coronary artery disease

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Heparin is commonly used as an antithrombotic agent in patients with acute coronary syndromes. However, recent studies indicate that its administration at doses achieved in acute coronary syndromes might decrease endothelial nitric oxide (NO) (nitrite/nitrate) production. In order to investigate the effect of heparin on ischemic threshold, we studied 12 patients (age 63 ± 7 yrs) with a positive exercise test and angiographically documented coronary artery disease. All patients were submitted to a randomized, placebo-controlled trial using i.v. 0.9% NaCl as placebo and i.v. heparin (5000 IU bolus + 1000 IU hour). After both saline and heparin bolus, the infusion was started and, after 10 minutes, treadmill exercise test performed (Bruce protocol). Blood samples for No and free fatty acids (FFA) determination were withdrawn before, at peak exercise and at ECG recovery.

Compared to placebo, heparin significantly decreased time to 1 mm ST segment depression (241 ± 160 vs 303 ± 175 sec, p = 0.003) and prolonged exercise recovery (573 ± 177 vs 441 ± 195 sec, p = 0.003), while total exercise duration was similar. Accordingly, rate-pressure product (RPP) at 1 mm ST depression was lower after heparin (23035 ± 6624 vs 25466 ± 7304 mmHgxbpm, $p < 0.01$), while it was similar at peak exercise. No significant differences were found for basal and peak heart rate, systolic-diastolic blod pressure and plasma NO levels. Conversely, FFA levels immediately increased after heparin administration and remained significantly higher, compared to placebo, throughout the study period. In conclusion, this preliminary report indicates that in patients with stable coronary disease, heparin may significantly decrease the ischemic threshold. Since RPP at onset of ischemia was lower than that recorded during placebo in spite of similar NO levels, the effect of heparin may be mediated by its known positive action on free fatty acid release which can adversely influence the metabolism of ischemic myocardium.

3282 Low rate of bleeding during oral anticoagulant treatment in a prolonged follow-up of elderly patients attending an anticoagulation clinic

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Over the last few years, there has been a world-wide increase in oral anticoagulant treatment (OAT). The evaluation of risk/benefit ratio of this treatment is of great importance. A recent large prospective multicenter Italian study (ISCOAT) has demonstrated a lower frequency of bleeding and thrombotic complications in outpatients attending anticoagulation clinics in comparison to that reported in previous observational studies. In ISCOAT 2745 patients were enrolled and followed up for a mean time of 8.8 months (2011 pt-yrs).

The aim of this study was to evaluate if in a more prolonged follow-up a low incidence of OAT complications can be maintained in a population attending an anticoagulation clinic, which uses the same procedures of ISCOAT participating centers.

We studied the frequency of bleeding and thromboembolic events in 530 patients followed at Florence anticoagulation clinic for a mean time of 18.9 months (835 pt-yrs). 76% of patients were receiving warfarin for the first time. Patients were aged as follows: 58% <70 yrs and 42% >70 yrs (ISCOAT: 64.8 and 35.2, respectively), among whom 24.4% were over 75 yrs (ISCOAT 16.8). The time spent within, below and above therapeutic range was 64%, 19% and 17% respectively (ISCOAT: 68, 26.1 and 5.9)

The frequency of major bleeding was 0.84% pt-yrs (ISCOAT: 1.1) and no fatal event was observed (ISCOAT: 0.25). Only in two of seven major events the INR was above therapeutic range. Minor bleedings were 6.34% pt-yrs (ISCOAT: 6.2). The rate of major thromboembolic events was 2.98% pt-yrs and 1.32% pt-yrs were fatal (ISCOAT: 2.9 and 1, respectively). Minor events were 2.64% pt-yrs (ISCOAT: 0.6)

In conclusion, a low incidence of complications was maintained during a prolonged follow-up. The older age of the patients assessed in our study in comparison to ISCOAT may provide an explanation for the slightly higher rate of minor thromboembolic events. These data indicate that also elderly outpatients treated routinely in an anticoagulation clinic may have a very low rate of bleeding complications.

3283 Comparative effects of triflusal and aspirin on cardiovascular inflammatory mediators upregulated by NF-kappaB

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The nuclear transcription factor NF-kappaB regulates the activation of cytokine and adhesion molecule genes that might be involved in the pathogenesis of atherosclerosis, acu- te coronary disease or stoke. Triflusal (2-acetoxy-4-trifluorome-thylbenzoic acid) is an antiplatelet drug displaying structural analogy to aspirin, but showing distinct pharmacological and pharmacokinetic properties. Since salicylates have been found to inhibit NF-kappaB activation, the objective of this study was to test triflusal and its deacetylated metabolite 2-hydroxy- 4-trifluoromethylbenzoic acid (HTB) as inhibitors of NF-kappaB activation and related events.

Methods: Peripheral blood mononuclear cells (PBMC) from healthy human donors and human umbilical vein endothelial cells (HUVEC) were used. TNF-alpha production was assayed by ELISA. Vascular cell adhesion protein (VCAM-1) expression was assayed by RT-PCR amplification. Activation of NF-kappaB was quantified in nuclear extracts by electrophoretic mobility shift assay (EMSA) using a double-stranded 32P-oligonucleotide containing consensus kappaB-binding sites.

Results: Incubation with 3 mM triflusal or HTB inhibited NF-kappaB activation in lipopolysaccharide(LPS)-activated PBMC (87 ± 3 and 85 ± 7%, respectively), whereas aspirin and salicylate produced 48 ± 5% and 35 ± 12% inhibition. Similar results were obtained using TNF-alpha-activated HUVEC (triflusal 85 ± 3%, HTB 81 ± 7%, aspirin 52 ± 12% and salicylate 21 ± 12% inhibition). Incubation of HUVEC with 2 mM triflusal or HTB completely blocked VCAM-1 mRNA expression elicited by TNF-alpha, whereas the inhibition produced by 2 mM aspirin and salicylate was lower than 20%. Triflusal and HTB also inhibited TNF-alpha release by LPS-activated PBMC in a concentration-dependent manner (0.01–1 mM), as compared to a 24 ± 9% and 35 ± 11%inhibition by 1 mM aspirin and salicylate, respectively.

In conclusion, triflusal and its metabolite HTB are more potent inhibitors of NF-kappaB than aspirin and salicylate, thus blunting the induction of both cytokine and adhesion molecule gene products at therapeutic concentrations.Studies are undertaken to assess the therapeutic utility of triflusal on cardiovascular diseases where genes under NF-kappaB control are upregulated.

3284 Triflusal may offer a safer alternative to aspirin in the treatment of acute phase of myocardial infarction: results from the TIM study

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Background: There is firm evidence that treatment with aspirin (ASA) improves the prognosis of patients with acute myocardial infarction (AMI) receiving or not thrombolytic therapy. Triflusal is an irreversible platelet cyclooxygenase inhibitor with negligible effect on PGI2 synthesis.

Objective: To compare the effectiveness of triflusal and ASA in the prevention of cardiovascular events following an AMI.

Methods: In this double-blind, multicentre, sequential design study, patients younger than 80, who had not received ASA or any other antiplatelet drug during the previous 15 days and diagnosed of AMI, were randomised within 24 hours of symptoms onset to receive triflusal 600 mg or ASA 300 mg once daily for 35 days. The primary endpoint was death, non-fatal myocardial reinfarction or non-fatal cerebrovascular event; secondary endpoints were the incidence of these individual outcomes and urgent revascularization.

Results: Baseline characteristics including age (61 ± 12 years), sex (82% males), prevalence of risk factors (smoking 55%, hypercholesterolemia 38%, diabetes 22%, hypertension 38%) or previous history of ischaemic heart disease (40%) or stroke (3%) were similar in both groups. No differences were observed in the treatment administered during the index event, including fibrinolytic drugs in 71% of patients and full-dose heparin in 67%. No difference between treatments was accepted with 80% power after recruiting 2124 eligible patients (triflusal, n = 1056; ASA, n = 1068) (adjusted odds ratio 0.882 [95% CI 0.634–1.227]). Non-fatal cerebrovascular events were significantly less frequent with triflusal (0.364 [0.146–0.908]; p = 0.030). There was no significant difference between treatments in mortality (0.816 [0.564–1.179]), incidence of non-fatal reinfarction (1.577 [0.873–2.848]) nor revascularisation (0.864 [0.644–1.161]). Generally, both drugs were well tolerated, although a trend towards fewer bleeding episodes and significantly fewer central nervous system bleeding episodes were observed in triflusal-treated patients (0.27% vs 0.97%; p = 0.033)

Conclusion: Triflusal and ASA have similar efficacy in preventing further cardiovascular events after AMI, but triflusal showed a more favorable safety profile. Triflusal significantly reduced the incidence of non-fatal cerebrovascular events compared with ASA.

3285 Antagonism of captopril by aspirin in severe heart failure: haemodynamic and neurohormonal demonstration

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ACE inhibitors are established treatment for congestive heart failure (CHF); however, simultaneous aspirin use could invalidate their beneficial effect due to pharmacologic antagonism. To objectively test this possibility we analysed hemodynamic and neurohormonal effects in 30 severe CHF patients (pts).

Methods: Pts were hospitalized for 5 days to receive fixed regimens of furosemide, nitroprusside and digitalis in the first 3 days. They were then randomised into 3 treatment groups: 1-captopril 150 mg/day orally; 2- aspirin 100 mg/day and, 3- captopril plus aspirin. Hemodynamic measurements with Swan-Ganz catheters were performed at baseline and 1 h after captopril administration twice a day/2 days. Noradrenaline (NA), by liquid chromatography analysis, was measured daily. Data were analysed by a repeated variance analysis. All data were expressed as mean ± SEM.

Results: Condensed hemodynamic results are shown on the table.

	Captopril (n = 10)		Aspirin (n = 10)		Cap-Asp (n = 10)	
	before	1 h	before	1 h	before	1 h
CI L/min/m^2	2.0 ± 0.06	2.5* ± 0.03	2.0 ± 0.02	1.9 ± 0.01	1.8 ± 0.02	2.0 ± 0.1
SVR dynes·s·cm^{-5}	2019 ± 87	1595* ± 32	2138 ± 40	2234 ± 40	2404 ± 84	2286 ± 138
PCWP mmHg	17 ± 1	14* ± 0.6	21 ± 0.2	21 ± 0.3	20 ± 1	19 ± 0.9

*$p < 0.001$

NA decreased significantly ($p < 0.001$) in captopril treatment pts, but remained unchanged in the other groups.

In conclusion: Results suport the notion that concomitant administration of aspirin and captopril in CHF, significantly abates both hemodynamic and metabolic effects of captopril.

3286 The use of protamine when administering abciximab after coronary stenting

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Background: Recent studies have demonstrated that Abciximab reduces ischemic complications after coronary stenting. However, hemorrhagic complications are associated with elevated activated clotting times (ACT) after infusions of IV heparin and abciximab. Reluctance exits to partially reverse the effect of IV heparin with IV protamine, due to the possibility of producing thrombotic complications.

Methods & Results: 20 consecutive pts receiving abciximab during coronary stenting, and receiving IV protamine, were evaluated. The mean age was 64 y-o (55–80) and 55% were male. 45% of pts were admitted with unstable angina, 35% with MI, and 20% with stable angina. 40% of pts had an intracoronary thrombus and 55% of pts had post-balloon coronary dissection. The mean ACT's prior to, after abciximab infusion, and after protamine were 229 ± 56 s, 326 ± 64 s and 223 ± 41 s, respectively. The mean dose of protamine was 12 ± 3 mg. There were no thrombotic complications during the procedure. There were 3 hemorrhagic complications, including one CVA and 2 large inguinal hematomas. These pts had higher ACTs than the mean.

ACT's Post Abciximab & Protamine.

Conclusion: The use of IV protamine in pts undergoing coronary stenting with abciximab can effectively reduce the ACT. There were no thrombotic complications associated with this treatment strategy. IV protamine used to regulate the ACT, may reduce hemorrhagic complications in this patient population.

ASSESSMENT OF MYOCARDIAL DYSFUNCTION: NEW NON-INVASIVE MODALITIES

3295 Clinical and experimental study on micron-order myocardial layer function by novel Doppler device

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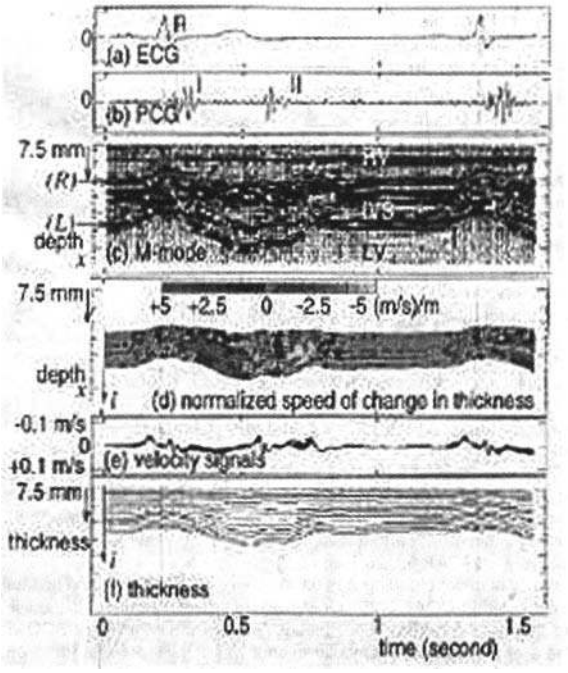
It was reported that the micron-order vibration (>0.5 μm/sec) was to be measured precisely by novel Doppler analysis (IEEE, 1997).

We aimed to clarify whether a quantitative evaluation of the myocardial layer function (MLF), i.e. thickening of a myocardial layer of 0.75 mm thickness across the wall could be of use to determine the early damage induced by doxorubicin (Dox) injection.

Method: (1) Ten age matched normal subjects (20 ± 5 y.o.) and 40 patients with acute lymphoblastic leukemia and malignant lymphoma (25 ± 7 y.o.; male, 25; female, 15) under Dox treatment were examined for left ventricular function by routine echo/Doppler method and MLF by the developed method (Rf; 9 kHz sampling fr: 1 Mhz, Doppler fr: 3.5 MHz). (2) The quantitative relation between histological damage and MLF was examined in 5 control and 12 Dox injected rabbits (2-weeks injection group = 2, 5-weeks = 3, 8-weeks = 5, 10-weeks = 2).

Result: In normal subjects, MLF across the septal wall showed homgenous distribution of thickening during the cardiac cycle. However, MLF in patients was characterized by 1) the decrease in the peak thickening and thinning rate, 2) the appearance of a nonfunctioning layer across the wall, 3) MLF showed strong correlation to the histological damage induced by Dox injection when examined at the intraventricular septum of the rabbit.



Color code of normal subject myocardium. The changing view of the thickening or thinning rate of each myocardial layer during the cardiac cycle. From top to bottom: (a) ECG; (b) heart sound on the chest wall; (c) M-mode image of the septum; (d) superposition of velocity signals from each sampling point at different depth (0.75 mm); and (f) the thickening of each layer, where the right ventricular surface of the septum was set as no movement for easy realization of the difference among layers.

Conclusion: By the novel ultrasonic Doppler device, we could evaluate quantitatively MLF in Dox treated patients. This noninvasive method may be useful for long term medical management of such patients, providing new insight concerning the MLF at the micron-order level.

3296 Prognostic value of transmitral flow patterns in patients with chronic congestive heart failure

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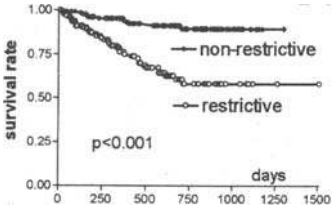
Background: Risk stratification of patients with end-stage heart failure is necessary for planning therapeutic strategies. The purpose of this study was to determine whether transmitral flow patterns are related to cardiac mortality.

Methods: A total of 328 patients (mean age 56, 276 males) with ischemic (n = 86) or dilated (n = 215) cardiomyopathy or valvular heart disease (n = 27) and left ventricular EF by radionuclide angiography <40% were prospectively studied. Peak early (E) and late (A) transmitral flow velocities and E-wave deceleration time (DT) were obtained using pulsed-wave Doppler echocardiography. Patients were assigned to groups with restrictive (E/A > 2 or DT < 140 ms) or non-restrictive (E/A < 1 or DT ≥ 140 ms) filling patterns. Patients with atrial fibrillation (n = 53) or inadequate Doppler tracings (n = 10) were excluded.

Results: During a mean follow-up period of 256 days (range 5–1509 days) 75 patients had died and 40 patients underwent heart transplantation. In the restrictive group (n = 128) survival rate was lower than that in the nonrestrictive group (n = 137), along with a lower LV-EF (19% ± 10 vs. 25% ± 12, p < 0.0001), higher NYHA scores (2.5 ± 0.7 vs. 2.1 ± 0.7, p < 0.0001) and lower peak VO_2max (13.2 ± 4 vs. 15.8 ± 6 ml/kg/min, p < 0.0001).



Conclusion: Mitral inflow patterns provide important information related to prognosis and functional status of patients with heart failure.

3297 Relation of transmitral flow velocity patterns to left ventricular end-diastolic pressure: new insights from combined haemodynamic and Doppler echocardiographic study

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The aim of the study was to investigate whether, deceleration time of A wave (Adt) identifies patients with elevated left ventricular end-diastolic pressure (LVEDP).

Material: 90 pts., 71 men (79%), mean age 54.53 ± 11.44 years with coronary artery disease: stable angina (25.5%), unstable angina (27%), and myocardial infarction (44.5%) were enrolled in this study. None had evidence of mitral stenosis, severe mitral regurgitation, atrial fibrillation or conduction disturbance such as second- or third-degree heart block.

Methods: Diastolic transmitral flow variables were recorded with pulsed-wave Doppler using 3.5 MHz transducer in apical four-chamber view with the sample volume placed 1 cm below the plane of the mitral annulus between the tips of the mitral leaflets and apical five-chamber view for isovolumetric relaxation time (IVRT). The measurement of LVEDP was done by left heart catheterization. Doppler traces were analyzed and the following variables were measured: peak E and A velocities (cm/s), E wave deceleration time (Edt, ms), A wave deceleration time (Adt, ms), IVRT (ms), E/A ratio, E/Edt, A/Adt and E/Adt ratio.

Results: LVEDP was 8 to 42 mmHg. Close negative correlation was found between LVEDP and Adt ($r = -0.77$) in total study pts. According to the Doppler transmitral flow velocity profile, as expressed by the E/A ratio, the study pts. were assigned to the following three groups: group 1 with E/A $\geq$ 2 representing "restrictive" filling pattern (8 pts., 9%); group 2 with E/A $\geq$ 1 and <2 which may signify a normal or "pseudonormal" filling pattern (34 pts., 38%) and group 3 with E/A < 1, impaired relaxation filling pattern (48 pts., 53%). There was a good correlation between LVEDP and Adt in all groups: group 1 ($r = -0.88$), group 2 ($r = -0.71$) and group 3 ($r = -0.78$). In all the study pts. Adt $\leq$ 70 ms predicted LVEDP 18 mmHg with a sensitivity of 98% and specificity of 94%. We find a good correlation between LVEDP and A/Adt ($r = 0.64$) in group 1; between LVEDP and E/Adt in group 1 ($r = 0.82$) and group 2 ($r = 0.68$).

Conclusions: A shortened Adt (70 ms) is useful marker of elevated LVEDP (18 mmHg). We found a good correlation between LVEDP and Adt in all three patterns of diastolic flow. Elevated LVEDP with shortened Adt are useful in differentiating a real normal from "pseudonormal" filling pattern. The E/Adt ratio has close correlation with LVEDP in "restrictive" and "pseudonormal" filling pattern.

3298 Mitral flow derived Doppler indices of left ventricular function in a general population: the Tromsø study

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Background: Left ventricular (LV) diastolic dysfunction has been proposed as the basis of heart failure with normal LV systolic function. Doppler indices of mitral inflow have been shown to correlate well with increased LV end-diastolic pressure in patients with cardiovascular disease and to change with age. We wanted to establish age specific criteria for normality of these indices in a large population based healthy reference sample.

Method: In our sample of 3287 subjects aged 25–85 years, 3186 had pulsed Doppler measurements of mitral inflow velocities and passive inflow deceleration time. The association of these indices to age and gender were established in a healthy reference sample of 1021 subjects from the total cohort.

Results: Age specific percentiles showed significant decline by age for peak passive mitral inflow velocity and the ratio of peak passive and active inflow velocities (E/A), whereas passive inflow deceleration time (DT) and peak atrial inflow velocity showed a significant increase by age. According to current criteria for diastolic dysfunction, the prevalence in the general population decreased by age, contrary to what would be expected. Restricting the analysis to subjects with signs or history of cardiovascular disease, did not alter this finding. Only 6% of the variance of DT was explained by cardiovascular disease or risk factors. For E/A, however, 37 and 48% of the variance were explained, for men and women, respectively.

Conclusion: Our data document a significant effect of age and gender on mitral Doppler indices of diastolic dysfunction. Age and gender specific criteria for normality is provided. Current guidelines for diagnosis of diastolic dysfunction do not seem to be applicable in a general population below the age of 50 years.

3299 Doppler tissue imaging expresses non-uniformity of left ventricular diastolic function during regional ischaemia

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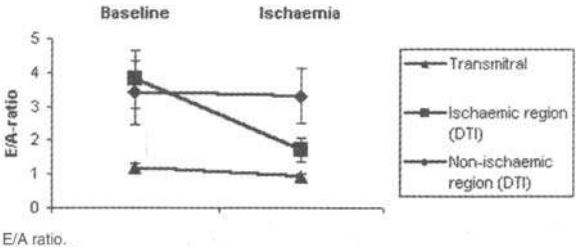
The diagnostic value of transmitral Doppler in diastolic dysfunction is limited by substantial overlap with normals. Possibly, regional filling by Doppler tissue imaging (DTI) could be a better marker of diastolic dysfunction. The aim of this study was to determine whether regional myocardial ischaemia causes non-uniformity of myocardial diastolic velocities and to compare myocardial and transmitral velocities.

Methods: In eleven open-chest anaesthetised dogs with inflatable occluders on the LAD, global LV filling was measured by transmitral pulsed Doppler and regional LV filling by DTI.

Results: Transmitral peak early (E) velocity decreased, atrial-induced (A) velocity increased, and the E/A-ratio decreased modestly ($p < 0.05$) after LAD occlusion. In the ischaemic septal region myocardial E-velocities decreased ($p < 0.05$), A-velocities were unchanged, and the E/A ratio decreased substantially ($p < 0.05$). However, along the non-ischaemic lateral wall regional E/A-ratio was unchanged.



E/A ratio.

Conclusion: Regional E/A-ratio measured with DTI could differentiate between ischaemic and non-ischaemic areas in the left ventricle. DTI may represent a new method for assessment of diastolic function, which could be more sensitive than global indices of diastolic function.

3300 Relationship between plasma natriuretic peptide concentration and left ventricular systolic and diastolic function in patients with old myocardial infarction: assessment with gated cardiac blood pool scintigraphy

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It has been reported that the levels of plasma atrial and brain natriuretic peptide concentration (ANP and BNP) increased in patients with various cardiac disorders. However, the relatioship between left ventricular systolic and diastolic function and the levels of plasma ANP and BNP is not fully understood. The purpose of this study is to clarify the relationship between plasma concentrations of ANP and BNP and parameters of left ventricular systolic and diastolic function assessed by gated cardiac blood pool scintigraphy.

Methods: Equilibrium gated blood pool scintigraphy at rest was performed in 45 patients with old myocardial infarction. Parameters of systolic (ejectoin fraction (EF; %), peak ejection rate (PER; end-diastolic count (EDC)/sec), time to peak ejection (TPE; msec)) and diastolic function (peak filling rate (PFR; EDC/sec), time to peak fillig (TPF; msec) and filling fraction in the first third of diastole (1/3 FF; %)) were obtained from time activity curve and its first derivative. A blood sample was taken from the brachial vein at the same time.

Results: Correlation coefficients (r) between both natriuretic peptide levels and left ventricular systolic and diastolic function were as follows:

	EF	PER	TPE	PFR	TPF	1/3 FF
ANP	-0.68^{***}	-0.59^{***}	-0.45^{**}	-0.55^{***}	-0.05	-0.41^{**}
BNP	-0.63^{***}	-0.51^{***}	-0.31^{*}	-0.51^{***}	-0.32^{*}	-0.56^{***}

$^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

For detecting systolic dysfunction (EF < 45%), the sensitivity and specificity for plasma ANP (cut off value > 25 pg/ml) were 87% and 56%; for plasma BNP (cut off value > 40 pg/ml) were 87% and 67%. For detecting diastolic dysfunction (PFR < 1.50 EDC/sec), the sensitivity and specificity for plasma BNP (cut off value > 25 pg/ml) were 76% and 57%; for plasma BNP (cut off value > 40 pg/ml) were 81% and 76%.

In conclusion, these data suggest that ANP and BNP were useful diagnostic marker to estimate both systolic and diastolic functions.

SELF-DEFENSE MECHANISMS OF THE JEOPARDIZED MYOCARDIUM

3310 "Electro-mechanical mismatch" in hibernating myocardium: normal local activation in areas with moderate myocardial dysfunction

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In 21 patients with regional left ventricular dysfunction and an indication for coronary bypass-surgery, multipolar epicardial mapping of local activation was performed during sinus rhythm. For simultaneous recording of the local electrograms, a sock electrode with 102 bipolar leads was used. Severity and extent of myocardial dysfunction were assessed from preoperative angiograms and projected on the grid of the intraoperative position of the sock electrode. This enabled regional comparison of electrical activation and mechanical function in a total of 1390 left ventricular areas (186 were hypokinetic, 130 akinetic and 35 dyskinetic).

For the characterization of local activation, amplitude [AMP], duration of activation [DUR] and the percentage of high-frequency components in the power spectrum [PHF, 50–250 Hz] were calculated for each signal using custom-made automated computer-algorithms.

	Normal	Hypokinetic	Akinetic	Dyskinetic
AMP [mV]	8.5 ± 7.2	8.5 ± 6.7	7.5 ± 5.8	*4.2 ± 4.5**
DUR [ms]	29.2 ± 19.1	29.3 ± 19.3	28.8 ± 17.5	*48.6 ± 28.2**
PHF [%]	10.8 ± 13.2	10.5 ± 15.0	8.1 ± 10.4	*4.1 ± 6.0***

(mean ± SD, *$p < 0.001$ and **$p < 0.01$ compared to all other groups)

Dyskinetic areas showed a distinct change in signal characteristics with reduction of local amplitudes, prolongation of signal duration and a shift of deviation in power spectrum density. Despite an impaired mechanical function, hypo- and akinetic areas showed normal or almost normal signal characteristics, indicating an electro-mechanical mismatch.

Conclusion: In patients with chronic ischaemic myocardium, an "electro-mechanical mismatch", defined as a mismatch between mechanical function and local electrogram characteristics, was observed in hypokinetic and akinetic areas. Thus, the identifiation of normal epicardial electrograms in regions of myocardial dysfunction by be an indicator for myocardial viability.

3311 High-energy phosphate metabolism in human preconditioning by magnetic resonance spectroscopy

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The ischemic preconditioning (IP) protects the myocardium by limiting infarct size in animal models. Its pathophysiology is uncertain. A paradigm of IP in humans involves the evaluation of patients with episodes of chest pain a day or two prior the infarction.

Methods: We studied 21 patients after a mean of 40 days period after anterior myocardial infarction (MI). All patients were submmited to a succesfull trombolytic treatment within six hours of the onset.The patients were divided in two groups: patients that presented with prior chest pain less than 48 hours before MI (IP group,n = 11, mean age 56) and 10 patients with no pain before MI (NIP, mean age 59). They underwent nuclear magnetic resonance imaging for measurement of left ventricle contractility. Image selected localized 31 P spectroscopy (MRS) of the antero-septal region was carried out on a 1.5 T imaging-spectroscopy Philips system using the ISIS technique. The acquisition time was 25 minutes. Cardiac PCr/ATP ratios were corrected for partial saturation and blood contamination.

The preconditioning group presented higher levels of PCr/ATP ratio than NIP group (1.64 ± 0.10 vs 1.38 ± 0.12, p = 0.008). The infarct area wall motion score trend better in IP group (1.4 ± 0.61 vs 1.84 ± 0.9, p = 0.3)

In conclusion: This preliminary study suggests that chest pain prior to infarction as a model of human ischemic preconditioning is associated with higher cardiac PCr/ATP ratios.

3312 Effect of nicorandil, an ATP-sensitive K-channel opener, on QT dispersion during coronary angioplasty

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Background. Activation of myocardial ATP-sensitive K channel (K_{ATP} channel) has been shown to mimic ischemic preconditioning. The aim of this study was to assess the effect of nicorandil, a K_{ATP} channel opener, on acute increase in QT dispersion (QTd) induced by repeated coronary occlusions at coronary angioplasty (PTCA) and to evaluate its cardioprotective effect against ischemia.

Methods. We studied 34 consecutive patients without previous myocardial infarction undergoing PTCA; 10 patients (NIC+) were taking nicorandil (5 mg orally tid) and 24 (NIC−) were not. PTCA consisted 4 of balloon inflations each lasting 2 min. Collateral filling of diseased coronary arteries was absent at diagnostic angiography in all cases. QTd were measured at baseline and immediately after each balloon deflations.

Results. QTd at baseline were not significantly different between 2 groups. After the first coronary occlusion. QTd increased significantly from the baseline value in NIC− group. The increase was not observed in NIC+ group. The following inflations did not significantly increase QTd in both groups.

	Baseline	1st	2nd	3rd	4th
NIC− QTd (msec)	28 ± 8	50 ± 8*	38 ± 11	28 ± 4	28 ± 4
NIC+ QTd (msec)	23 ± 6	37 ± 6**	37 ± 6	27 ± 12	27 ± 6

*$p < 0.005$ (vs. Baseline) and **$p < 0.05$ (vs. NIC−)

Conclusions. QTd was increased by ischemia during the first balloon inflation but not during subsequent ones; i.e., ischemic preconditiong. Nicorandil may prevent the increase of QTd at the first inflation by pharmacologically mimicking ischemic preconditiong.

3313 Activation of ATP-sensitive potassium channels is the common cardioprotective link between preconditioning and natural hibernation

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The tolerance of hibernating mammals to extended periods of cold hypoxia is related to a plasma factor which is chemically similar to agonists of δ-opioid receptors. The present study was designed to assess whether an activation of δ-opioid receptors could reproduce the cardioprotection conferred by ischemic preconditioning (IPC).

Methods: Isolated isovolumic buffer-perfused rat hearts were arrested with and stored in Celsior solution at 4°C for 5 hr before being reperfused for 2 hr. They were divided into four groups (n = 8, each group). Group 1 hearts were served as controls. In group 2, hearts were pharmacologically preconditioned with a 15-min infusion of the δ-opioid receptor agonist D-Ala^2-D-Leu^5-enkephalin (DADLE, 200 μmol/l) before arrest. In group 3, IPC was elicited by two 5-min global ischemia periods interspersed with 5 min of reperfusion before arrest. Group 4 hearts underwent a similar protocol to group 2, except that the infusion of DADLE was preceded by a 5-min infusion of the K_{ATP} blocker glibenclamide (50 μmol/l). End points included recovery of left ventricular (LV) systolic and diastolic function, including pressure-volume (P-V) curves assessed by linear regression analysis of the end-diastolic pressure (LVEDP) data, total release of creatine kinase (CK) over the first 45 min of reperfusion, endothelium-dependent coronary vasodilation to 5-hydroxytryptamine (10^{-7} mol/l) under constant perfusion pressure or to acetylcholine (10^{-6} mol/l) under constant flow and myocardial water content.

Results: Preischemic functional parameters were not different among the four groups. Main poststorage data (mean ± SEM) are summarised below:

Group	Slope of P-V cure (mm Hg/ml)	LVEDP (mm Hg)	CK release (IU/g dry weight)	Water content (%)
1	694 ± 27	37.8 ± 2.5	548 ± 79	81.23 ± 0.23
2	485 ± 19**	23.6 ± 1.6**	379 ± 62*	79.46 ± 0.37†
3	474 ± 20**	24.7 ± 1.6**	345 ± 54*	79.88 ± 0.22†
4	703 ± 27	39.9 ± 2.9	453 ± 43	80.90 ± 0.13

*$p < 0.05$ vs group 1; **$p < 0.001$ vs groups 1 and 4; †$p < 0.005$ vs groups 1 and 4

Neither recovery of contractile indices nor endothelium-dependent coronary vasodilatory responses to 5-hydroxytryptamine/acetylcholine were different among the four groups.

Conclusion: Activation of δ-opioid receptors, as occurs during natural hibernation, improves recovery of cold-stored hearts to a similar extent as IPC. These endogenous protective effects have a common pathway characterised by an opening of K_{ATP} channels.

3314 Hydroxylradicals increase calcium sensitivity of cardiac muscle

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Hydroxylradicals are involved in the etiology of postischemic reperfusion injury. Exposure of intact contracting cardiac muscle preparations to exogenous produced hydroxylradicals leads to an increase of diastolic tension. It is well known that oxidative stress causes a mitochondrial dysfunction with ATP-depletion as a consequence. It is also reported that hydroxylradicals directly attack the sarcoplasmic reticulum calcium-ATPase and reduce its activity. Both these effects synergistically lead to disorder of intracellular calcium handling with a subsequent increase of the free calcium concentration in the sarcoplasm. A third mechanism of oxidative damage which is currently under discussion is the direct attack of hydroxylradicals on the myofilaments. Changes in calcium sensitivity induced by oxidative stress have to date not been studied on the actin-myosin matrix directly.

Therefore we first exposed contracting muscle preparations (n = 9) of rabbit hearts to hydroxylradicals generated by H_2O_2 and Fe^{3+}-NTA (Fenton reaction). A brief hydroxylradical-exposure induces a rigor-like contracture; 15 min after application of hydroxylradicals we observed an increase in diastolic force from 5.40 ± 1.65 mN/mm^2 to 23.93 ± 5.70 mN/mm^2 ($p < 0.05$) and additionally after 30 min a loss in developed force (15.33 ± 2.74 mN/mm^2 to 8.24 ± 1.96 mN/mm^2; $p < 0.05$), while all twitch parameters in sham preparations (similar protocol except the exposition to free radicals; n = 8) were stable over the same time. Secondly, 45 min after hydroxylradical exposure muscle preparations were transferred to a solution containing 1% v/v Triton X-100 to access the myofilament matrix directly. 16–20 hours later we measured the force-pCa-relation. The $pCa_{50\%}$ under control conditions was 5.54 ± 0.10 vs. 5.79 ± 0.04 in the hydroxylradical-group ($p < 0.05$). Cooperativity and maximal developed force remained unchanged (3.33 ± 0.58 vs. 2.45 ± 0.38, p = 0.21; 55.05 ± 10.21 mN/mm^2 vs. 57.22 ± 9.21 mN/mm^2, p = 0.87).

We conclude that hydroxylradical exposure sensitises the myofilaments, which can contribute to the rise of diastolic tension. There are several substances with protective but unexplained effects on free radical exposed cardiac muscle. A possible mechanism of action of these compounds could be a desensitising effect on the myofilaments.

3315 Repetitive myocardial stunning in pigs is associated with an increase in the expression of inducible and constitutive nitric oxide synthases

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Nitric oxide (NO) has complex effects on myocardial function particularly following ischaemia-reperfusion. The goal of this study was to examine the result of repetitive myocardial stunning on myocardial NO release and expression of inducible (iNOS) and constitutive NO (eNOS) synthases.

Methods and Results: Propofol anaesthetised pigs underwent ten, 2-minute episodes of circumflex artery occlusion (n = 6) or acted as sham operated controls (n = 4). Measurements of segment shortening demonstrated a fall in function in the ischaemic territory to 52.5 ± 7.3% (mean ± SEM) of baseline shortening 30 minutes after the stunning stimulus, recovering to 92 ± 8.7% 5 ½ hours later. Function remained stable in sham controls. Local myocardial NO production fraction (local coronary venous [NO] – aortic [NO]/aortic [NO] × 100) increased in the stunned group vs. sham controls 6 hours after the final reperfusion (15.1 ± 5.7% vs. −6 ± 3.8%, p = 0.001). Western blotting and band optical density used to compare tissue from stunned territory (S), non-ischamic territory (NI) and sham control animals (C) demonstrated this was associated with an increase in the expression of both iNOS (S: 93 ± 13.4, NI: 37 ± 2.4 and C: 25 ± 4 [arbitrary units], $p < 0.01$ & p = 0.031) and eNOS (S: 104 ± 7.4, NI; 62.5 ± 7.4 and C; 75.7 ± 0.6, $p < 0.03$ & $p < 0.01$). Immunocytochemistry localised iNOS reactivity to vascular smooth muscle cells and cardiomyocytes in stunned tissue and eNOS reactivity to endothelial cells in all groups.

Conclusion: Recovery from repetitive myocardial stunning is associated with the increased expression of both iNOS and eNOS and would be compatible with a protective role for both these enzymes. This finding has possible relevance for both the late window of ischaemic preconditioning and myocardial hibernation.

MECHANISMS OF REMODELLING AFTER MYOCARDIAL INFARCTION

3316 Role of urokinase-type plasminogen activator in ventricular wall rupture, scar formation, and cardiac function after myocardial infarction

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Remodeling of the extracellular matrix may play a role in cardiac rupture, healing and function after myocardial infarction.

Methods: The role of proteolysis in these processes was studied after coronary artery ligation in mice lacking urokinase-type plasminogen activator (u-PA$^{-/-}$), tissue-type plasminogen activator (t-PA$^{-/-}$) and wild type (WT) mice. Healing of the infarct was studied at 2, 4, 7, 14 and 35 days after ligation by immunohistochemistry, electron microscopy and zymography. Cardiac function was analyzed by high fidelity pressure and cardiac output measurements, and by electrocardiographic recordings 2 weeks after ligation.

Results: About 1/3 of male wild type (10/27) and t-PA$^{-/-}$ (3/10) mice died of cardiac rupture within 4 days, associated in time with infiltration of macrophages expressing u-PA and matrix metalloproteinase-9 (gelatinase-B) in the ischemic zone. Rupture was not observed in u-PA$^{-/-}$ mice (0/18), nor in WT mice after adenoviral transfer of plasminogen activator inhibitor-1 (0/19). Deficiency of u-PA significantly reduced macrophage infiltration, removal of necrotic cardiomyocytes, neovascularization and collagen deposition in the infarct. Importantly, this impaired infarct healing in u-PA$^{-/-}$ mice lead to persistent ischemia 14 days after ligation. In addition, it depressed myocardial contractility, induced arrhythmogenicity, and increased mortality after adrenergic stress.

Conclusion: These data thus provide genetic evidence for an essential role of u-PA mediated proteolysis in cardiac wound healing and rupture following MI. Hence, exaggerated proteolysis mediated by leukocyte-generated u-PA may predispose to wall rupture. Transient inhibition of u-PA may prevent cardiac rupture after myocardial infarction, whereas prolonged inhibition of healing may impair cardiac functional recovery.

3317 Selective aldosterone receptor antagonism attenuates ventricular dilatation and reactive fibrosis but does not affect wound healing following myocardial infarction

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Introduction: Aldosterone receptor antagonism can prevent maladaptive reactive cardiac fibrosis during hyperaldosteronism in animals. However, the effect of aldosterone receptor antagonism on cardiac reparative fibrosis and wound healing is unknown and may have important clinical consequences. Purpose: To evaluate the effect of eplerenone, a selective aldosterone receptor antagonist, on myocardial wound healing and ventricular remodeling following infarction.

Methods: 78 rats survived left coronary artery ligation to produce myocardial infarction (MI) or sham MI. Following surgery sham MI rats received vehicle (VEH) and rats suffering MI received either eplerenone (EPL; 300 mg/kg/day, po) or VEH for 3, 7 or 28 days. Infarct thinning (width of the free wall:septal wall), infarct and noninfarct collagen volume fraction (%), and the diastolic pressure/volume relationship were determined.

Results: At day 3 (a time when there is a transition from edema to thinning and replacement of necrotic tissue), the thinning ratio of the MI EPL treated group (0.7 ± 0.1), but not the MI VEH treated group (0.9 ± 0.1) was significantly less than sham MI control (1.0 ± 0.1), suggesting that eplerenone may have altered the edematous transition. However, the thinning ratio of the two MI groups did not differ at days 7 or 28, indicating equivalent thinning of the healed infarction. The collagen volume fraction of the infarcted zone in animals receiving VEH and EPL at day 3 (5.2 ± 0.8 vs 4.6 ± 0.6), day 7 (48.1 ± 4.0 vs 48.3 ± 5.0), and day 28 (59.5 ± 3.1 vs 57.9 ± 4.4) was similar. In contrast, at day 28 the VEH treated animals (3.2 ± 0.4), but not the EPL treated animals (2.1 ± 0.4) had a significantly greater collagen volume fraction in the noninfarcted region than animals undergoing sham MI (1.7 ± 0.2). Moreover, the pressure/volume relationship revealed signficant left ventricular remodeling following MI in VEH treated rats but not EPL treated rats at day 28.

Conclusion: These data demonstrate that EPL does not adversely affect wound healing or infarct expansion following myocardial infarction, but rather that EPL attenuates maladaptive reactive fibrosis and left ventricular remodeling.

3318 The significance of free insulin-like growth factor-1 activation in the process of remodelling in patients with acute myocardial infarction

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The IGF-1 autocrine system was found to be activated in the viable ventricular myocytes shortly after experimental coronary occlusion in rats, while exogenous administration of IGF-1 induced a physiological form of cardiac hypertrophy, thus preserving cardiac function. The aim of our study is to elucidate the role of free IGF-1 (fIGF-1) in acute myocardial infarction (AMI) patients.

Methods: 27 patients with first attack of AMI, and no previous history of any other disease, were examined for plasma levels of fIGF-1, measured by ELISA, and compared to corresponding levels of 20 Normal controls (NC) with mean values: 7.81 ± 0.15 ng/ml. All pts were divided in 2 sex and age-matched groups Group A: pts with limited infarct size, EF > 45% and no subsequent LV dysfunction. Group B: pts with extensive AMI EF < 45% and residual heart failure. Plasma samples were collected at the time of hospital admission (0 hours) and 6 h, 12 h, 18 h, 24 h, 48 h, 3 days, 4 d, 5 d, 7 d, 15 d, 30 d thereafter.

Results are expressed as mean values ± SEM in ng/ml as follows:

Pts	0 h	6 h	12 h	18 h	24 h	48 h	3 d	4 d	5 d	7 d	15 d	30 d
A (13)	21.7 ± 2.8 ◇	22 ± 2.34 ◇	23.5 ± 2.8 ◇	24.8 ± 2.9 ◇	26.5 ± 3.8 ◇	24.3 ± 2.5 ◇	24.0 ± 2.6 ◇	24.3 ± 2.8 ◇	24.5 ± 2.9 ◇	23.5 ± 2.3 ◇	23.6 ± 2.4 ◇	24.4 ± 2.9 ◇
B (14)	8.04 ± 0.4 NS	8.7 ± 0.61 NS	8.56 ± 0.7 NS	8.66 ± 0.4 NS	9.41 ± 0.6 NS	9.15 ± 0.4 NS	9.11 ± 0.4 NS	8.7 ± 0.35 NS	8.58 ± 0.3 NS	8.55 ± 0.4 NS	8.56 ± 0.5 NS	8.48 ± 0.5 NS

p < 0.05 compared to corresponding values of: a) NC (◇) b) the relevant first plasma sample (*). NS = non statistical compared to NC (Wilcoxon test).

Conclusions: Plasma levels of fIGF-1 exhibited a progressive increase that became statistically significant 24 h after AMI in pts with limited infarct size and no LV dysfunction. All these samples were significantly raised compared to NC. This marked elevation of fIGF-1 may be associated with adaptive hypertrophy, thus leading to a "good quality" remodeling and preserving cardiac function. On the other side fIGF-1 remained inactivated in pts with large infarcts, probably because of the smaller amount of viable ventricular myocytes, thus leading to maladaptive hypertrophy and heart failure. fIGF-1 may prove to be a major factor in modifying the process of remodeling, following AMI, in the future.

3319 Left ventricular remodelling after myocardial infarction can be predicted by plasma brain natruretic peptide

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Background: Plasma brain natriuretic peptide (BNP) secreted from the infarct and the noninfarct segments after myocardial infarction (MI) reflects the left ventricular function as well as provides the prognostic information of patients. Left ventricular remodeling has been shown to be associated with the clinical worse outcome and predicts the poor prognosis. In this study, the relationship between these two prognostic factors was studied.

Methods: Plasma BNP level at aortic root (A) and anterior interventricular vein (AIV) were measured by the radioimmunoassay in 81 patients with first anterior MI, whose infarct-related artery were successfully reperfused within 24 hours from the onset and patent during the study period. Hemodynamic variables were measured by Swan-Ganz catheter. Left ventricular (LV) volume and global LV function were calculated with the area-length method, and regional LV function was assessed by the centerline method, using LV grams at 1 M and 6 M. Infarct size was calculated by Tl-201 SPECT at 1 M.

Results: Among the parameters obtained at 1 M, the increment of percent change of EDVI from 1 M to 6 M has significant correlations with PCWP ($r = 0.319$, $p < 0.05$), EDVI ($r = 0.269$, $p < 0.05$), ejection fraction ($r = 0.321$, $p < 0.05$), regional wall motion ($r = 0.256$, $p < 0.05$), and plasma BNP level ($r = 0.418$, $p = 0.0006$), but not the difference of plasma BNP level between A and AIV representing BNP level secreted from the infarct segment. Multiple regression analysis revealed that only plasma BNP level significantly correlated with the increment of percent change of EDVI from 1 M to 6 M among infarct size, time form the onset to reperfusion, LV functions at 1 M, hemodynamic variables at 1 M and medications including ACE inhibitor.

Conclusion: Plasma BNP level secreted form both the infarct and the noninfarct segment correlates the magnitude of LV remodeling after myocardial infraction, although LV remodeling has been influenced by many factors such as infarct size, infarct location, infarct arterial patency and medications, so on. This suggested that progressive LV remodeling is accompanied with the augmentation of BNP release from both the infarct and noninfarct segment of LV, and BNP level at 1 M is a biochemical marker for the prediction of progressive LV remodeling.

3320 Angina pectoris prior to myocardial infarction protects against subsequent left ventricular remodelling: the Healing and Early Afterload Reducing Therapy trial (HEART)

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To investigate the hypothesis that prior angina pectoris confers protection from remodeling following myocardial infarction, we analyzed echocardiograms from the Healing and Early Afterload Reducing Therapy Trial (HEART). 352 patients were randomized to receive one of three dosing regimens of ramipril. Echocardiograms were obtained within 24 hours of myocardial infarction, at 14 days and at 90 days. Left ventricular dilatation from day 0 to 90 was used as a measure of LV remodeling. LV volume change in patients with angina ($n = 111$) during the three month period prior to MI was -0.73 ± 25.5 ml over the 90 day period, compared with 6.8 ± 25.5 ml for patients ($n = 174$) without angina ($p = 0.016$). In contrast, there were no differences in change in ejection fraction based on prior angina. In addition, maximal CK was significantly lower in patients with prior angina (2093 vs. 2743, $p = 0.004$). In a multivariate model, prior angina remained predictive of less remodeling after adjusting for age, sex, baseline ejection fraction, killip class, history of diabetes, baseline end-diastolic volume, and drug treatment group ($p = 0.042$).

Conclusion: Ischemic symptoms prior to anterior myocardial infarction may protect against left ventricular remodeling, and may be associated with less enzymatic release. These protective effects may be secondary to recruitment of collaterals or ischemic preconditioning of the myocardium.

DIRECT PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY: IMPROVING BLOOD FLOW

3331 Is TIMI 2 flow after primary PTCA in acute myocardial infarction a successful procedure? Results from the Stent PAMI randomized study

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Results from the Gusto trial have shown that one-month mortality after acute MI treated by thrombolysis is related to TIMI flow at 90 min. with a clear difference between TIMI 2 and TIMI 3 flow. These results have changed the definition of successful thrombolysis.

The purpose of this study was to compare the outcome of pts with "successful" PTCA (TIMI 2 or 3 flow and residual stenosis < 50%) included in the Stent PAMI randomized trial according to the final flow (TIMI 2 or 3).

Of 1,458 pts in whom informed consent was obtained, 900 were randomized, 452 to stent and 448 to balloon. Procedural success was obtained in 98.5% of cases (Corelab analysis) with a 15.1% cross-over to stent in the balloon group.

Results are summarized below:

	TIMI 2	TIMI 3	p value
Balloon arm (%)	7.3	92.7	<0.001
Stent arm (%)	9.0	90.4	<0.001
Stent and Bail-out stent (%)	10.6	88.6	<0.001
Death up to 210 days (%)	9.1	2.9	<0.001
MACE up to 210 days (%)	23.4	16.6	<0.001

Death rate at 210 days was not statistically different in pts with TIMI 2 flow treated either by balloon or stent (respectively 8.3 vs 9.8%).

In conclusion, outcome of pts with with TIMI 2 flow after primary PTCA in acute MI is significantly worse than in pts with TIMI 3 flow, whatever the treatment applied. PTCA success must be redefined and all efforts must be made to obtain a TIMI 3 flow at the end of the procedure.

3332 Impact of vessel size and lesion length on outcomes after primary stenting versus primary angioplasty in acute myocardial infarction: results from Stent PAMI

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Long lesions and small vessels have an additive effect on target lesion revascularization (TLR) after elective intracoronary stenting. The comparative benefits of primary stenting versus primary angioplasty after acute myocardial infarction (AMI) acording to lesion length and vessel size are not known. PAMI Stent randomized 900 pts presenting within 12 hours of AMI to primary PTCA or stenting with the Cordis heparin coated stent. We reviewed the clinical outcomes of 868/900 pts randomized to PAMI Stent with available follow-up, according to varying lesion lengths and vessel sizes (<2.75 mm, N = 212; 2.76–3.25, N-332, >3.25 mm, N = 278). Independent angiographic core analysis with follow-up was available in 565 of 900 patients. Results by randomization arm are presented in the table.

% Restenosis

Vessel Size	LL ≤ 10 mm N = 339		LL 10–20 mm N = 304		LL > 20 mm N = 119	
	PTCA	Stent	PTCA	Stent	PTCA	Stent
≤2.75 mm	39.5	33.3	38.2	27.8	22.2	80.0†
2.76–3.25 mm	30.4	13.3†	31.9	13.3†	42.9	35.3
>3.25 mm	18.8	17.5	42.1	20.1†	16.7	40.0

†p < 0.05

Target vessel revascularization (TVR) was lower with stenting in patients with vessel sizes of 2.76–3.25 mm and lesion length < 10 mm (0% vs 10.1%, p = 0.02) as well as lengths of 10–20 mm (8.8% vs 18.6%, p = 0.08).

We conclude that after primary PTCA or stenting for acute myocardial infarction, restenosis rates increase with longer lesions in smaller vessels, with a greater variation occurring in the stent group. Primary stenting reduces restenosis and TVR in patients with intermediate (2.76–3.25 mm) vessel sizes, with no apparent additive benefit over PTCA in patients with smaller (<2.75 mm) or larger vessels (3.25 mm)

3333 Angiographic and clinical reasons for the higher in-hospital mortality in diabetic patients with acute myocardial infarction treated with primary angioplasty

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Diabetes mellitus (DM) is a strong risk factor for a worse outcome in patients (pts) with acute myocardial infarction (AMI). The objective of this study was to identify the reasons for the high in-hospital mortality in DM pts with AMI treated with primary angioplasty (PTCA).

Methods: 713 ptswith AMI were treated with PTCA within the first 12 hours after the onset of symptoms in our institution from 1.991 to 1.998. The in-hospital outcomes were compared between DM (n = 165; 23%) and non-DM (n = 548; 67%).

Results: The angiographic success rate was not statistically different between both groups, and coronary stenting was used more frequently in DM. However, DM pts had a higher in-hospital mortality (20.9% vs. 11.3%, p = 0.0023). After adjunsting by Killip class, mortality was not statistically different between DM and non-DM: 4.2% vs. 3.0% (NS) in Killip I, 21.9% vs. 20.8% in Killip II–III and 74.1% vs. 61.2% (NS) in Killip IV, in DB and non-DM pts, respectively. DM patients had an angiographic and clinical higher risk profile in comparison with non-DM patients:

	DM	NoDM	p
Re-AMI	4.9%	2.4%	NS
Death/Re-AMI	24.5%	13.3%	0.0010
Free wall rupture	2.4%	2.3%	NS
Angio. success	89.9%	93.2%	NS
Coronary stenting	58.8%	47.9%	0.0161
Proximal occlusion	55.6%	44.7%	0.0190
No. vessels	1.9 ± 0.8	1.6 ± 0.7	0.0003
LVEF	0.41 ± 0.14	0.46 ± 0.14	0.0416
Cardiogenic shock	18.4%	8.2%	0.0005
Age (years)	68 ± 10	62 ± 13	<0.0001
Female gender	31.1%	17.0%	0.0002
Hypertension	52.2%	42.0%	0.0221

Conclusion: Despite mechanical reperfusion with primary PTCA, a high angiographic success rate (90%) and a more frequent utilization of coronary stents, DM patients with AMI are at a high risk. However, this may be mainly explained by the worse clinical profile and more adverse angiographic findings in these patients.

3334 Is primary angioplasty of venous bypass grafts for acute myocardial infarction as effective as in native vessels?

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Objective: Success rates in primary angioplasty of native vessels are beyond 90%. A small proportion of acute myocardial infarction (AMI) is related to acute closure of venous bypass grafts (CABG). AMI after CABG appears to be a well delineated entity and patency rates of >85% have been reported. However data on functional parameters like TIMI flow and reflow are limited.

Methods: In a retrospective study 8 cases of primary angioplasty of venous bypass grafts were analyzed concerning initial treatment, angiographic outcome and clinical course.

Results: Out of 380 primary angioplasties in 1995–1998, 8 patients (2.1%) were diagnosed with AMI related to acute closure of a venous bypass graft. Stents were used in 1 patient, glycoprotein IIb/IIIa antagonists were used in 3 patients. Intracoronary fibrinolysis was applied in 7 patients.

Patient	Age	Sex	Residual stenosis	TIMI flow	No reflow	Death
1	46	f	0%	2	No	No
2	72	m	25%	2	Yes	No
3	64	m	0%	2	Yes	No
4	60	m	80%	3	No	No
5	54	f	30%	3	No	No
6	60	m	100%	0	–	No
7	55	m	60%	2	No	No
8	70	m	60%	0	–	yes

Conclusion: Incidence of AMI with a venous bypass graft as infarct-related artery is low (2.1%). Although patency of the IRA was achieved in 6 out of 8 cases (75%), TIMI III flow was achieved in only two cases. 50% of the patients with TMI II flow showed no reflow despite documented vessel patency.

3335 Primary angioplasty and stenting in acute myocardial infarction: predictors of acute and sub-acute stent thrombosis

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Background: At a time of widespread use of stents and ticlopidine for the treatment of acute myocardial infarction (AMI), predictive factors of acute and sub-acute stent thrombosis (ASAT) have not been precisely determined.

Methods: Since January 1995, over 735 pts have undergone primary angioplasty in our institution within 24 hrs of symptom onset. 647 pts (88%) received a stent. All were treated with aspirin and ticlopidine after stent implantation. ASAT occurred in 1.54% of pts (acute in 4 pts and sub-acute in 6 pts). Clinical and procedural variables were analysed in order to determine predictors of ASAT.

Results: Cardiogenic shock was the only clinical predictive factor associated with ASAT (present in 40.0% vs 11.4% in non ASAT pts, p = 0.02). Procedural variables identified multivessel stenting (30.0% vs 4.2% in non ASAT, p = 0.002), multiple stents (2.0 ± 0.5 vs 1.4 ± 0.7 stent/pt, p = 0.007) and residual stenosis (6.7 ± 11 vs 1.4 ± 7%, p = 0.01) as predictive factors significantly associated with ASAT. ASAT rate was found to be higher when non tubular stents were used (AVE or Cook stent) compared to tubular stents (NIR, Bestent, Crown, Palmaz Schatz, Multilink): 4.65 vs 1.16% (p = 0.01).

Conclusion: (1) Elective stenting with ticlopidine and aspirin in AMI is associated with an acceptable (1.54%) rate of ASAT. (2) Except for cardiogenic shock, predictive factors are mainly related to procedural variables. (3) Tubular stents may be preferred to coil or multicellular stents.

3336 Emergency room infusion of abciximab speeds up reperfusion in acute myocardial infarction eligible for primary PTCA

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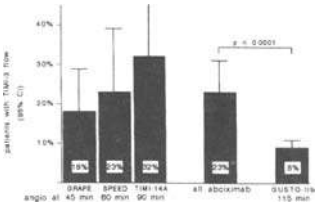
Background: Glycoprotein receptor antagonists have been shown beneficial in patients undergoing PTCA including those with acute myocardial infarction (AMI). Little is known about their potency of inducing reperfusion in AMI.

Methods: We analysed the 3 angiographic trials with abciximab *alone* given to patients in the emergency room: the GRAPE (Glycoprotein Receptor Antagonist Patency Evaluation, n = 60) study, the SPEED (Strategies of Patency Enhancement in the Emergency Department, n = 26) trial and the TIMI-14A (n = 31) study. TIMI 3 flow grade was core lab read in the 3 trials (all abciximab, n = 117) and compared to the core lab reading of the angioplasty arm (n = 511) of the largest primary PTCA trial, GUSTO-IIb Angioplasty Substudy.

Results:



Conclusion: Abciximab *alone* given in the emergency room is associated in a time dependent manner with TIMI-3 grade reperfusion in up to 32% of patients at 90 minutes, which is the usual door-to-balloon time in primary PTCA. Larger AMI trials with abciximab given early in-hospital or prehospital are warranted.

PROGNOSIS AND FOLLOWINGS AFTER INTERVENTION

3337 Prognostic value of thallium-201 single-photon emission computed tomographic myocardial perfusion imaging after intracoronary stenting

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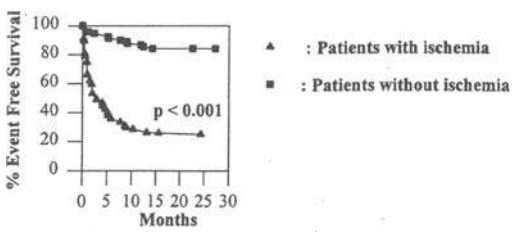
In patients with stable angina, normal thallium SPECT imaging indicates a low risk patient, and the extent of myocardial defect is an important prognostic predictive factor. However, its prognostic value has not been studied yet in a population of patients after coronary stenting. This study was designed to assess the value of thallium-201 SPECT imaging in patients after intracoronary stenting. and to examine the relation, if any, between the presence and extent of myocardial defect and future fatal or non fatal cardiovascular events (revascularization, myocardial infarction, unstable angina, death).

Methods. From September 1994 to September 1996, 201 patients received 204 intracoronary stents. Stress thallium imaging was performed 6 months after stenting on 155 asymptomatic patients and we followed-up patients during 16 ± 12 months.

Results. Fifty four patients suffered cardiac events during the follow-up: seventeen of the one hundred five patients after normal thallium SPECT imaging (16%), and thirty-seven of the fifty patients with ischemia scintigraphy (74%). The mean time to recurrence was respectively 21 ± 9 months for patients in group I and 8 ± 10 months in group II. The relative risk of cardiovascular events was 9.72 [4.6; 20.3]: $p < 0.001$.



Conclusions. In patients after coronary stenting, absence of ischemia on thallium SPECT imaging at six months indicates a low risk patient for cardiovascular events. These results have important implications in patient management and cost health delivery.

3338 Increased prognostic value of gated-SPECT studies with Tc-99m tetrofosmin, in patients with high, medial and low pre-scan likelihood of coronary artery disease

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Background: This research was undertaken to evaluate the correlation between the pretest probability (PSL) of myocardial disease with the single photon emission computed tomography (SPECT) gated studies with Technetium-99m (Tc-99m) labeled Tetrofosmin at our Institution.

Methods and Results: We selected 2,538 consecutive patients who underwent stress/rest gated-SPECT studies between October 1994, and May 1998, and were followed up for the presence of major cardiac events (M.C.E) (cardiac death, myocardial infarction or revascularization) over a mean follow up period of 25.3 months. The pretest probability of myocardial disease was also calculated for each patient using the Bayes Theorem. 648/2538 (25.6%) of the patients were classified as having low probability (≤20% for myocardial disease), 1346/2538 (53%) as a intermediate probability (21 to 80%), and 544/2538 (21.4) as high probability (more than 80%). The following table shows the correlation between the PSL, SPECT study result, and the development of M.C.E., during 25.3 months of follow up:

SPECT Study	Low Probability		Intermediate Probability		High Probability	
	M.C.E.(+)	M.C.E.(−)	M.C.E.(+)	M.C.E.(−)	M.C.E.(+)	M.C.E.(−)
Abnormal	44/217	173/217	339/652	313/652	130/348	218/348
(20%)	(80%)	(52%)	(48)	(37%)	(63%)	
Normal	24/431	407/431	45/694	649/694	5/196	191/196
(5.5%)	(94.5%)	(6.5%)	(93.5%)	(2.55%)	(97.45%)	

Among the 2,538 patients who underwent gated-SPECT, 648 had a low PSL for CAD, 1346 were classified as intermediate and 544 as high PSL. Of the 648 patients with low PSL 217 had an abnormal SPECT and 45/217 had a M.C.E., but only 24/431 with normal SPECT developed a M.C.E. On the other hand of the 544 patients with high PSL, 348 had an abnormal study, and in that particular group, 130/348 developed some M.C.E during de follow up. In the group with high PSL 196/544 patients had a normal SPECT, and only 5 developed some M.C.E at the end of the study. The interobserver agreement was 65% (kappa coefficient 0.3). The NPV in high probability patients was 97.9% and PPV 37.4%. In the low probability group the NPV was 94.7% and PPV 20.7%. In the intermediate probability group the PPV was 51.2% and the VPN 93.4%.

Conclusions: In patients evaluated for CAD, Gated-Spect studies with Tc-99m-tetrofosmin provide reliable prognostic value and can be used for risk stratification. The pretest probability alone is not a good prognostic indicator. The high incidence of mayor cardiac events in the low probability group was probably due to underestimated patient risk classification.

3339 Prognostic value of Tc-99m-sestamibi myocardial perfusion SPECT for the prediction of cardiac death or myocardial infarction

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99m-Technetium-Sestamibi myocardial perfusion single photon emission computed tomography (MIBI-SPECT) has become a routine testing technique for coronary artery disease. It has a high sensitivity and specificity. However there is little information about its prognostic value.

Methods: 1000 patients underwent MIBI-SPECT (Orbiter or MultiSpect 3, Siemens) and coronary angiography (DCI, Philips) in our institution for suspected or proven coronary artery disease between 1991 and 1994. Follow-up was obtainable in 800 subjects (223 female, 577 male). Follow up time was 44 months (maximum 71 months, minimum 24 months). Information was obtained by records and telephone interviews.

Results: According to the different results of MIBI-SPECT [discrete (discr.), severe (sev.), fixed (fix) or stress dependent = mismatch (mism.) perfusion defects] the following percentages of events were noted:

SPECT	n	All deaths	Cardiac death	AMI	PTCA	CABG
Normal	66	3.0	0	1.5	13.6	0
Discr. fix.	195	4.1	1.5	1.5	5.6	11.6
Discr. mism.	172	4.1	2.3	2.9	11.6	4.1
Sev. fix + mism.	150	7.3	5.3	3.3	33.3	13.3
Sev. fix + mism.	106	9.4	8.5	10.4	35.8	20.8
Sev. mism.	111	11.7	9.0	7.2	45.9	33.3

The difference between discrete and severe defects was highly significant for cardiac deaths, the combined rate of cardiac deaths and infarctions, PTCA and CABG ($p < 0.0001$). The difference between normal scintigraphic results and discrete defects was not significant ($p = 0.548$).

Conclusions: Patients with severe fixed or stress dependent perfusion defects in MIBI-SPECT had a worse prognosis than patients with discrete abnormalites. Patients without defects had an excellent outcome.

3340 Gated Tc-99m SPECT is superior to biochemical and inflammatory markers for predicting adverse cardiac events in patients presenting with acute chest pain

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Technetium-99m sestamibi gated SPECT (SPECT) is an established method for risk stratification in acute chest pain. However, it is not known whether the biochemical markers Troponin T (TnT) and Troponin I (TnI) and the inflammatory markers CRP, Interleukin-6 (IL6) and Tissue Necrosis Factor alpha (TNF) have independent or additive value as predictors of adverse cardiac events in patients admitted with non-ST-segment elevation acute coronary syndromes (ACS).

Method: 80 patients were studied within 6 hours of chest pain (mean 175 mins). 70% had an abnormal ECG, 20% had previous revascularisation, and 39% had previous MI. Venous samples were taken at admission and at 24 hours and batch assayed for CRP, IL6, TNF, TnT and TnI. Gated SPECT was performed, and perfusion (PER) and wall motion (WM) were scored as abnormal or normal. The other variables were scored as abnormal if they exceeded their upper reference range. The cohort was followed up for subsequent cardiac death, myocardial infarction and coronary revascularisation for a median of 227 days (154–298). Univariate analysis revealed that SPECT WM ($p = 0.01$), PER ($p = 0.03$) and previous MI ($p = 0.01$) were significant predictors of events. However combined WM and PER was the best predictor ($p = 0.0095$) in the univariate model, and the only significant predictor in the multivariant Cox model ($p = 0.01$, RR 3.8 (CI 1.3–11.1)). Thus, early gated SPECT is superior to the other markers measured for the early risk assessment of patients with acute chest pain.

3341 Specificity of exercise-dipyridamole Tc-99m-tetrofosmin myocardial tomography early after successful coronary stent implantation

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A high number (30–40%) of "false positive" ischemic defects early after coronary balloon angioplasty have been reported. However, the presence of reversible defects early after optimal coronary angioplasty (PTCA) with stent implantation has not been investigated. The purpose of our study was to evaluate the specificity of maximal exercise-dipyridamole 99mTc-tetrofosmin myocardial single-photon emission computed tomography (SPECT) early after coronary stent implantation. Inclusion criteria were: presence of myocardial ischemia before PTCA, one vessel coronary disease, absence of previous MI and successful PTCA (<30% of residual stenosis) obtained with stent implantation. After discontinuation of antianginal drugs, a maximal exercise 99Tc-tetrofosmin myocardial SPECT combined with intravenous administration of dipyridamole (0.56 mg/kg) if the level of exercise was insufficient, was performed within the week after PTCA. To date, 25 pts have been included (7 women, mean age of 57 years), and distribution of coronary disease was: LAD = 16 cases, LCX = 5 cases and RCA = 4 cases. Reference diameter of the vessels dilated was 3.11 ± 0.54 mm, with minimal lumen diameter and percent stenosis of 0.9 ± 0.36 mm and 68.2 ± 12.6% before PTCA, and 2.85 ± 0.46 mm and 9.6 ± 9.5% after PTCA. Exercise test was performed at 6.1 ± 0.8. days after PTCA and 3 pts received dipyridamole. Reversible myocardial defects were observed in 3 cases (12%): 1 LAD, 1 LCX and 1 RCA (specificity = 88%) and there were no differences in the extent of reversibility (rest uptake-exercise uptake > 10%) in polar map between patients with stent in LAD (5.46 ± 5.68%), LCX (5.36 ± 5.76%) and RCA (4.37 ± 7.78%) and a control group of 74 individuals (49 women, mean age of 55 years) with normal coronary angiography (9.4 ± 12.9%, 7 ± 9% and 11 ± 13%).

Thus, our study demonstrates a high specificity of maximal exercise-dipyridamole 99mTc-tetrofosmin myocardial SPECT early after successful coronary stent implantation.

3342 Determinants of positive follow-up Tl-201 perfusion imaging in asymptomatic patients without restenosis

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Discordance between positive Tl-201 stress tomography (SPECT) and absence of angiographic restenosis in asymptomatic patients, is a frequent clinical situation after PTCA. The aim of our study was to identify the determinants of positive SPECT in such situations.

Methods: We studied the results of exercise-redistribution SPECT performed in 123 patients, remaining asymptomatic, 6 ± 2 months after successful PTCA of 132 vessels. Coronary angiography performed, 1 to 7 days after SPECT revealed absence of restenosis in all patients (% diameter stenosis < 50%).

Results: factors significantly associated with positive (n = 31 vessels) compared to negative SPECT (n = 101 vessels) are reported in the table.

	SPECT+ (n = 31 vessels)	SPECT− (n = 101 vessels)
Pre PTCA ejection fraction	64 ± 14%*	70 ± 13%
Incomplete revascularization	51.6%†	20.8%
Infarct-related vessel PTCA	41.9%*	21.8%
FU % diameter stenosis	35 ± 11%*	29 ± 12%

*$p < 0.05$, †$p < 0.001$, positive compared to negative SPECT

On multivariate analysis only incomplete revascularization ($p = 0.007$) and infarct-related vessel PTCA ($p = 0.03$) were associated with positive SPECT.

Conclusions: Myocardial ischaemia due to incomplete revascularization and persisting myocardial sideration or hibernation after infarct-related vessel angioplasty could cause reversible perfusion defects interfering with the detection of restenosis by Tl-201 perfusion imaging in asymptomatic patients.

NEW MODALITIES IN STRESS ECHOCARDIOGRAPHY

3343 The quantitative and semi-quantitative evaluation of low-dose dipyridamole-dobutamine stress echocardiography

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The **aim** of our study was to compare the long axis M-mode (LAM-m) parameter changes with the accepted semi-quantitative wall motion scoring system for the evaluation of myocardial viability with low-dose Dypiridamole (DPD)-Dobutamine (DBA) stress echocardiography (DDSE).

Methods: The DDSE was performed in 105 patients (88 male, mean age 54.8 ± 9.2 years) on the 30th (±2.2) day of myocardial infarction (MI). Infusion of 0.28 ug/kg DPD over a 4 minute period, than 5 ug/kg/min DBA for 3 minutes and 10 ug/kg/min DBA for another 3 minutes were administered. The mitral annulus was sectioned at four different places by the M-mode cursor (four chamber view: infero-septal, antero-lateral; two chamber view: anterior, inferior). Each section represented three segments (apical, mid, basal). There were regional wall motion abnormality in 224 sections of the obtained 420. The section viability was defined as an improvement of at least I grade according to the 4 grade scoring system during the DDSE. The following LAM-m parameters were measured at rest: the total excursion of the mitral annulus *(d1)*, the mean velocity of the mitral annulus systolic movement *(v1)*; and also on the 10th minute of DDSE: *(d2, v2)*. The *d2/d1* and *v2/v1* quotients were calculated.

Results: There were 149 viable *(A group)* and 75 non-viable sections *(B group)* according to the semi-quantitative scoring system. We found significant differences between the two groups in the values of *d2, v2, d2/d* and *v2/v1*.

	d1 (cm)	d2 (cm)	v1 (cm/s)	v2 (cm/s)	d2/d1	v2/v1
A group	1.02 ± 0.29	1.37 ± 0.35	3.37 ± 1.12	4.82 ± 1.41	1.38 ± 0.27	1.50 ± 0.41
B group	1.12 ± 0.31	1.15 ± 0.34	3.72 ± 1.3	4.1 ± 1.6	1.04 ± 0.2	1.12 ± 0.24
p <	NS	0.0001	NS	0.001	0.00001	0.00001

The best parameter to distinguish viable from non-viable was d2/d1 (chisquare = 73.6, Wilks lambda = 0.72, sensitivity: 78.4%, specificity: 81.1%, positive predictive value: 89.2%, negative predictive value: 65%, accuracy: 79.3%).

Conclusion: Examination of LAM-m parameter changes during DDSE is a simple method. The evaluation of post-infarction viability can be quantified by this method with a high positive predictive value.

3344 Time course of myocardial systolic velocity changes during a dobutamine challenge in normal and infarcted myocardium: a Doppler myocardial imaging study

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Quantitative assessment of myocardial wall motion during stress echocardiography (SE) is still an unsolved issue. In experimental studies, systolic myocardial velocity measured with pulsed Doppler Myocardial Imaging (DMI) correlates closely to systolic function assessed with sonomicrometry. Therefore, DMI may improve the diagnostic accuracy of SE. In order to test this hypothesis, a standard 4 stages SE examination was performed in 16 patients: after a recent posterior myocardial infarction (MI) in 10 patients (58 ± 12 years) and for atypical chest pain (CP) diagnosis in 6 others (54 ± 10 years) considered as the control group (C). Myocardial systolic velocities (S) in basal (B) and mid (M) segments of the posterior wall (PW) were measured from an apical 2 chambers view using pulsed mode DMI at baseline, low dose, maximal dose of dobutamine, and recovery. Myocardial velocity gradient (MVG) was calculated as the difference between peak S velocities in basal and mid segments.

Results: All patients reached 85% of the maximal heart rate with no severe side effects. Controls had a normal ECG and no wall motion abnormalities during dobutamine perfusion. All patients of the MI group were found to have an abnormal wall motion of the PW in both basal and mid segments (severe hypokinesia to akinesia). At baseline, S velocity in B segment and MVG were significantly lower in the MI group. At low dose, S velocity in B segment and MVG increased significantly in controls by 41% and 60% respectively but not in the MI group. At maximal dose, S velocity in B segment increased in both groups (83% and 65% in C and MI group respectively), but MVG increased only in control group (table).

	Heart rate (b/min)		S basal (cm/sec)		S mid (cm/sec)		MVG (cm/sec)	
	C	MI	C	MI	C	MI	C	MI
Baseline	62	75*	8	5.8*	6	4.8	2	1*
	±11	±12	±1.4	±1.5	±1.2	±0.9	±0.9	1 ±1.2
Low dose	69	80	11.3#	7*	8.2	6.1	3.2#	0.9*
	±21	±23	±2.7	±1.9	±1.8	±1.4	±1.6	±1.7
Max dose	150#	149#	14.7#	9.6*#	7	7.1#	7.7#	2.3*
	±28	±16	±4.1	±3.6	±1.9	±2.1	±3.2	±2.6
Recovery	96#	96#	8.8	6.1	6.2	5.6	2.7	0.5*
	±12	±18	±1.5	±1.8	±1.2	±1.7	±1.7	±1.4

*$p < 0.05$ MI vs. C, #$p < 0.05$ vs. baseline

In conclusion, pulsed DMI may identify infarcted and normally contractile myocardium and offers a clinically useful approach of wall motion and myocardial systolic function quantification in stress echocardiography.

3345 Which off-line tissue Doppler parameters can be used to diagnose myocardial ischaemia during stress?

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Tissue Doppler echocardiography (TDE) is a very sensitive technique for quantifying changes in regional left ventricular (LV) function. Experimental studies during ischaemia have shown rapid and major alterations of both systolic and diastolic parameters, but the application of TDE to stress testing in patients has been limited by the time needed to sample data from every region 'on-line'. This difficulty has been overcome by the development of the Vingmed System Five which allows acquisition of digital TDE data from every region of the LV during a stress echocardiogram, at the same time that the grey-scale images are acquired. The digital data can then be analysed off-line after the stress test.

As part of the MYDISE study (Myocardial Doppler in Stress Echocardiography), we assessed the feasibility and reproducibility of measuring such data obtained during standard dobutamine stress echocardiography (DSE). Peak systolic velocity V (excluding isometric contraction), time-to-peak systolic velocity TTP, systolic velocity-time integral VTI, peak E and A diastolic velocities and E/A ratio, were measured in each of 16 segments (ASE model). 7 observers in 5 centres analysed the same 8 DSE studies in order to assess reproducibility.

At baseline, the mean coefficients of variability (CV) in 5 basal segments (4 from apical views, plus basal posterior from parasternal long-axis) for the 3 systolic parameters were 11, 13 and 13% for V, TTP, and VTI. For the diastolic parameters E, A, and E/A the mean coefficients were 17, 12 and 27%. As an example, detailed results for all indices from the basal inferior segment (apical 2-chamber view) are shown in the table.

TDE data

	V cm/s	TTP ms	VTI mm	E cm/s	A cm/s	E/A
Mean	7.2	125.6	1186.2	−6.7	−8.5	1.1
Pooled SD	0.6	16.0	84.1	0.9	0.9	0.3
CV (%)	8	13	7	13	11	27

TDE data for basal inferior segment (from A2C)

We conclude that in basal LV segments, systolic function can be accurately quantified off-line with good reproducibility, using V, TTP, and TVI. Diastolic parameters are less reliable, perhaps reflecting sub-optimal frame rates. Until signal averaging is available, myocardial ischaemia during stress echocardiography should be characterised from off-line quantification of changes in systolic indices.

3346 Automatic border detection in dobutamine stress echo: how do normal and ischaemic segments behave objectively and quantitatively?

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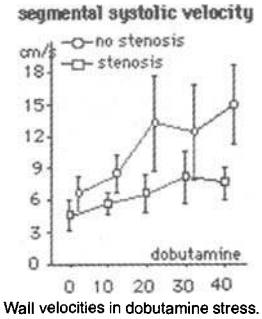
Analysis of dobutamin stress echo (DSE) is associated with significant interobserver variability. Objective, quantitative analysis of DSE may overcome these problems. Because few quantitative data are available about the pathophysiology of segmental wall motion DSE, we used automatic border detection to determine in nonischemic and ischemic segments the behaviour of segmental wall velocities at rest, during incremental dobutamine doses, and at peak dobutamine stress.

Methods: Using a previously validated ABD algorithm (Echo-CMS, MEDIS, Holland), segmental wall velocities were determined during DSE (0–40 μg/kg/min dobutamine) in 300 segment stages. Segments perfused by stenosed (>70% narrowing) coronary arteries and control segments in patients with and without coronary artery disease were compared.

Results: (Fig) In nonischemic segments, velocities increased early to reach a plateau of 14 ± 6 cm/s at 20–40 μg/kg/min dobutamine. In ischemic segments, velocity increases were also observed, but velocities at peak dobutamine were significantly lower (5.9 ± 3.7 cm/s) compared to normal segments ($p < 0.0001$). A biphasic response was often observed in ischemic segments at the last stage. The best cutoff value for discrimination of ischemic and nonischemic segments was 10.5 cm/s at peak dobutamine.



Wall velocities in dobutamine stress.

Conclusion: Quantitation of segmental wall velocities by automatic border detection in DSE is feasible and allows diagnosis of myocardial ischemia by objective, quantitative parameters. Normal values as well as a best cutoff for detection of ischemia are described. The frequently used ischemia criterion of worsening wall motion versus baseline appears not justified in quantitative DSE using segmental wall velocities, as a small velocity increase often occurred despite ischemia.

3347 Is strain rate better than myocardial Doppler velocity to quantify wall motion during exercise echocardiography?

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The strain rate or rate of deformation of a myocardial segment through the cardiac cycle can be derived from myocardial velocities obtained by tissue Doppler imaging; normal segments (sgts) are compressed during systole, so the strain rate is negative. We sought to determine if peak systolic strain rate (SR) can differentiate changes in contractile state during exercise echo (ExE) more accurately than myocardial Doppler velocity (MDV).

Methods. 107 pts (27F, age 60 ± 12, EF 64 ± 14) underwent ExE to evaluate known or suspected CAD; 2D echo and color myocardial Doppler were acquired at rest and post Ex. SR and peak systolic MDV were measured off line in basal and mid segments of the 3 apical views (Echopac 6.0). Sgts were classified as normal (n = 919), ischemic (n = 39) or scar (n = 114) according to results of 2D echo. ExE sgt score obtained at rest and stress was compared to MDV and SR using ANOVA. ROC curves were constructed for SR and MDV.

Results: MDV and SR were obtained in 1087/1284 sgts (85%). Scar sgts had lower SR and MDV than Normal at rest and stress ($^*p < 0.001$). Ischemic segments had lower SR and MDV at Ex and less ΔSR and ΔMDV (diff stress – rest) ($^*p < 0.001$). Area under ROC curve for SR (0.85) exceeded that for MDV (0.71). At optimal thresholds of MDV (6 cm/s) and SR (–1.42/sec), sensitivity of SR exceeded MDV (78% vs 68%), as did specificity (79% vs 66%).

	Normal	Ischemic	Scar
Rest MDV (cm/s)	4.5 ± 1.5	4.4 ± 1.3	3.8 ± 1.2*
Peak ex MDV (cm/sec)	8.4 ± 3.3	5.5 ± 2.9*	5.3 ± 3.2*
ΔMDV (cm/sec)	3.9 ± 2.7	1.1 ± 2.2*	1.7 ± 2.5
Rest SR (1/sec)	–1.1 ± 0.3	–1.0 ± 0.4	–0.6 ± 0.4*
Peak ex SR (1/sec)	–1.9 ± 0.9	–1.0 ± 0.8*	–0.8 ± 0.9*
ΔSR (1/sec)	–8 ± 0.8	–0 ± 0.7*	–0.2 ± 0.7

Conclusions: SR and MDV can differentiate scar and ischemic sgts during ExE but SR appears more accurate.

3348 Can ultrasound strain and strain rate imaging provide additional information on myocardial contractile reserve in patients with ischaemic cardiomyopathy?

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Background: Strain Rate (SR) and Strain (S) imaging, based on Colour Myocardial Doppler (CDMI) data, potentially allow regional myocardial deformation to be characterised in real time. Since myocardium is, in theory, incompressible the longitudinal strain of a segment will correspond inversely to any change in wall thickness. Thus alterations in inotropic state should modify segmental longitudinal S and SR values.

Aim of the study: A study was designed to characterise the regional response of chronically ischemic myocardium to low dose inotropic stimulation by comparing 2D imaging data with S and SR indices.

Methods: A 5.10 μg/kg/min Dobutamine (D) infusion protocol was performed in 20 pts (6F,aged 39–70 y) with dilated ischemic cardiomyopathy (LVEDD-5.99 ± 0.99 cm, LVESD 4.82 ± 0.88 cm, LVFS-18.2 ± 6.15%). Grey scale, DMI and SRI data sets (50–60 fps) were acquired at rest and during inotropic stimulation. Dysfunctional, but potentially viable, mid septal, mid lateral and mid RV wall segments were chosen for regional motion, velocity and strain analysis. Peak systolic velocity, velocity integrals, peak systolic Strain rate(SR) and systolic Strain(S) were calculated for both rest and 10 ug D echo studies. Based on visual assessment of inotropic response (one phasic response) the dysfunctional segments were divided into segments with (Gr.I, n = 28) and without inotropic improvement. (Gr. II, n = 16).

Results: see table.

Table

Segments	Improved rest	Improved dobutamine	Non-improved rest	Non-improved dobutamine
Peak Strain rate [Hz]	–2.05 ± 0.93**	–2.87 ± 1.01	–1.44 ± 0.86#	–2.28 ± 0.69
Systolic Strain	0.33 ± 0.15#	0.43 ± 0.18	0.21 ± 0.14	0.31 ± 0.09
Peak Velocity [cm/s]	4.11 ± 2.19*	5.39 ± 2.74	3.14 ± 1.33	5.01 ± 3.31
Velocity Integr	0.37 ± 0.39	0.45 ± 0.41	0.46 ± 0.21	0.63 ± 0.39

**p = 0.0007, * p = 0.03, # p = 0.02 rest vs dobutamine

Rest SR was lower in Gr.II segments compared to Gr.I (2.05 ± 0.93 vs 1.44 ± 0.86, p < 0.05)

Conclusions: At rest, systolic S and SR better characterised ischemic segments in both groups when compared to velocity data. Dobutamine infusion caused an increase in segmental velocities, S and SR in both Groups. The increase both in S and SR values was highly significant in Gr. I segments but was greater for SR. Thus SR imaging may offer a new approach to the quantitation of low dose Dobutamine studies for viability.

MYOCARDITIS: IMMUNOLOGY AND OTHER ASPECTS

P3367 No nested PCR evidence of enteroviral infection in hearts explanted from patients with dilated cardiomyopathy

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Although it has long been thought possible that enteroviruses can be involved in the pathogenesis of dilated cardiomyopathy (DCM), few cases of entervirus-infected hearts with DCM have been convincingly documented. In this study we used nested PCR to detect the presence of enteroviral RNA in the miocardia of hearts explanted from heart transplant (HT) donors and receivers so as to compare the prevalence of infection in DCM patiens

Methods: Myocardial muscle samples were collected from the atria of 70 donor hearts and from 68 hearts explanted from patiens with DCM (22 cases), coronary artery disease (42), amyloidosis (1), myocarditis (1) or valve disease (2). All samples were snap frozen for molecular analysis. RNA was extracted by Chomzynski and Sacchi method. To check the quality of the extratcted RNA, each sample was subjected to RT-PCR with primers specific for *abl* protooncogen; which is expresed from all human RNA samples. A high sensitivity nested RT-PCR with specificity for all enterovius was used to amplify the 5'noncoding region. Sequencing: PCR products were isolated from agarose gel bands, purified and sequenced in a automatic sequencing apparatus (*Pharmacia Biotech*).

Results: *abl* protooncogen was correctly amplified from all the RNA samples. All the controls were correctly amplified. All heart tissue samples from cardiac biospses were negative for enterovirus. Incidentaly, one enterovirus-specific PCR produc was obtained; but upon sequencing it was found to be identical to the positive control and corresponding to poliovirus type 3.

Conclusions: In our sample of hearts explanted from HT patients, nested RT-PCR showed no evidence of the presence of enteroviral RNA. This suggests that if enterovirus had a role in the genesis of DCM, this role does not require or lead to the persistence of the virus in myocardial tissue.

P3368 Elevated levels of tumor necrosis factor-a in the peripheral blood and coronary sinus of patients with myocarditis and their correlation with an increased gene expression in the myocardium

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Pro-inflammatory cytokines seem to play an important role both for the induction and persistence of human myocarditis (MC). The local concentration of cytokines in the myocardium is of major importance, however, their levels cannot be determined directly due to the small size of the human endomyocardial biopsies.

Methods: We analysed the gene expression of tumor necrosis factor-a (TNF-a), which is an indicator of an activated immune system and can induce apoptosis, in endomyocardial biopsies of patients with MC and compared these results with the protein levels of TNF-a in the peripheral blood and the coronary sinus. Gene expression was measured in the biopsies of 19 patients with immunhistologically proven MC and 12 patients with suspected MC, however, having normal biopsies using quantitative PCR with a plasmid as internal standard. For the serological studies we analysed the sera of 58 patients with MC and 36 patients without MC with a quantitative photometric assay for the levels of TNF-a in the peripheral blood and the coronary sinus.

Results: Patients with immunhistologically proven MC had significantly elevated levels of TNF-a in the peripheral blood (102 ± 29.5 pmol/l) and the coronary sinus (87.6 ± 25.4 pmol/l) compared to patients without MC (7.7 ± 1.5 pmol/l, p < 0.05). The gene expression of TNF-a was significantly elevated in the myocardium of patients with MC (1.18 ± 0.56 attomol/μg RNA) compared to the normal controls (0.5 ± 0.1 attomol/μg RNA, p < 0.01).

Conclusion: Patients with immunhistologically proven MC have significantly elevated protein levels of TNF-a in the peripheral blood and coronary sinus. The elevlated gene expression of the TNF-a in the myocardium suggests a pathogenetic significance of pro-inflammatory cytokines in human MC and may offer a specific approach for an immunmodulatory therapy.

P3369 T-cell-dependent immune response protects human heart tissue from a virus-mediated alteration in the ADP/ATP carrier isoform transcription

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We recently reported that the myocardial adenine nucleotide translocator isoform transcription pattern (ANTitp) is altered in patients with myocarditis. Myocarditis is known to be induced by enteroviral infection. The aim of the present study was to evaluate the relevance of the enteroviral infection and the intramyocardial T-cell immune response for the alteration in the ANTitp.

Methods: The ANTitp was analyzed in endomyocardial biopsies from 52 patients with clinically suspected myocarditis (csMC). Explanted heart tissue from 22 patients with ischemic cardiomyopathy, already shown to have a normal ANTitp, served as controls. Enteroviral RNA was detected in the biopsies using the PCR technique. T-lymphocyte subtypes ($CD3^+$, $CD45R0^+$, $CD4^+$ and $CD8^+$) were quantified using immunohistochemistry.

Results: The ANTitp was altered in 21 patients with csMC. Enteroviral genome was found in the heart specimens of 15 of these 21 patients (71.%). Only 6 of 25 virus-negative patients (24%) were affected by the shift in the ANTitp ($p < 0.021$). The infiltration with $CD3^+$, $CD45R0^+$ and $CD8^+$ was substantially lower in myocardial specimens showing an altered ANTitp than in biopsies with a normal ANTitp ($CD3^+$: 6.1 ± 1.0 vs. 11.9 ± 2.4 cells/mm^2, $p < 0.011$; $CD45R0^+$: 2.3 ± 3.2 vs. 7.9 ± 3.2 cells/mm^2, $p < 0.024$ and $CD8^+$: 3.3 ± 0.6 vs. 8.5 ± 2.6 cells/mm^2, $p < 0.026$); the infiltration with $CD4^+$ cells was only tendentially lower (2.5 ± 0.4 vs. 5.7 ± 2.6 cells/mm^2, $p < 0.45$). Combining the data, it was found that virus-positive biopsies with an altered ANTitp were significantly less infiltrated with lymphocytes (5.9 ± 1.3 $CD3^+$/mm^2) than virus-positive biopsies with a normal isoform transcription (13.7 ± 5.25 $CD3^+$/mm^2, $p < 0.05$).

Conclusion: Changes in the ANTitp is linked to the presence of enteroviral genome in the myocardium. The shift is however not caused by the virus-induced T-cell response but appears moreover to be prevented by an active T-cell dependent immune process.

P3370 Selective induction of CXC- and CC-chemokines in experimental autoimmune myocarditis

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Chemokines are cytokines with chemoattractant properties for leukocytes. They may play a critical role in directing leukocytes to the myocardium in myocarditis and provide a target for therapeutic intervention. Experimental autoimmune myocarditis (EAM) was induced in 12 week old BALB/c mice by immunization with a synthetic peptide corresponding to amino residues 614–643 of heart myosin heavy chain alpha, control animals received CFA only (N = 5 each). On days 14 and 21 after immunization left-ventricular expression of several cytokine and chemokine genes was measured by quantitative reverse transcription-PCR assay using the TaqMan fluorogenic detection system. Values were corrected for RNA content using GAPDH expression and are expressed as ratio between mRNA levels in immunized versus control mice. Cellular infiltrates were scored on histology slides and cardiac necrosis was assessed by ELISA of troponin-T in serum. Spearman rank order correlations between Infiltrate scores and troponin-T values were highly significant ($p < 0.005$). In EAM mice transcript levels for the CC-chemokines MIP-1a and MCP-1 were modestly elevated on day 14 (5.7x and 2.3x, respectively) and markedly elevated on day 21 (159x and 52x, respectively). The CXC-chemokines IP-10 and MIG were induced in EAM mice on day 14 (11x and 15x, respectively) but they were not significantly elevated on day 21. TNFa and IL-10 were slightly induced on day 14 (2.3x and 2.4x, respectively) and they were strongly induced on day 21 (45x and 372x). The temporal expression pattern of chemokines in EAM with the appearance of CXC chemokines (which attract predominantly neutrophils) followed by CC-chemokines (with a preference for mononuclear leucoytes) might determine the histological picture. Experiments in chemokine-knock-out mice should further characterize the role of chemokines in EAM.

P3371 Quantitative assessment of the myocardial Na^+/Ca^{+2} exchanger transcription in inflamed heart tissue

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An upregulation of the sarcolemmal Na^+/Ca^{+2} exchanger (EXCH) expression is one of the characteristics of disturbed myocardial calcium homeostasis in end stage heart failure due to ischemic (ICM) or dilated cardiomyopathy (DCM). The aim of this study was to evaluate whether changes in the EXCH transcription occurs also in inflammatory heart disease (infHD), leading under special conditions to DCM.

Methods: We established a quantitative PCR method using an internal RNA standard for the determination of the EXCH mRNA copy number in small biopsy samples. Right ventricular biopsies of 13 patients with infHD and 16 patients with end stage heart failure due to ICM or DCM were analyzed. Myocardium from 4 individuals without heart disease served as controls.

Results: The EXCH mRNA level of the controls amounted to 2.2 ± 1.3 atmol per ng total RNA. The amount of EXCH mRNA from patients with infHD was similar to the level of the controls making up 2.3 ± 1.6 atmol/ng total RNA. However, patients with end stage heart failure showed a significant increase in the EXCH mRNA level to 9.5 ± 2.0 atmol/ng total RNA ($p < 0.003$). No correlation between the EXCH transcription and the grade of inflammation was found.

Conclusion: An alteration in the myocardial EXCH transcription is not related to an inflammatory process in the heart tissue. The switch in the EXCH transcription appears to be a phenomenon of end stage heart failure.

P3372 Prognostic significance of left-ventricular aneurysms with normal global function caused by myocarditis

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Left ventricular aneurysm may result from idiopathic or viral myocarditis. The prognostic significance of this entity, when associated with a normal global cardiac function, is unknown, as a long-term follow-up on a consistent number of patients is actually not available.

Methods: Among 352 patients (pts) with a histologic diagnosis of myocarditis, from January 1989 to November 1998, 11 pts (3.1%) had single or multiple localized left ventricular (LV) aneurysms (size 10.6 ± 3.1 in length and 7.4 ± 4.2 in width) with normal global LV function. Presenting symptoms were: ventricular tachyarrhythmias in 8 pts (sustained ventricular tachycardia (VT) in 4, non sustained VT in 4) and unexplained chest pain in 3 pts. All pts underwent laboratory tests (including serologic tests for cardiotropic viruses and immunologic studies), non invasive (ECG, Holter monitoring, exercise stress testing, 2D-echocardiography) and invasive cardiac exams (cardiac catheterization, biplane left and right ventriculography, coronary angiography, biventricular endomyocardial biopsy, electrophysiologic study in patients with sustained VT). Serology suggested a viral infection in 3 pts, an immunologic disorder in 2 pts while it was negative in 6 of them. In all patients LV endomyocardial biopsy showed a lymphocytic myocarditis (in 1 pt with vasculitis and in 5 with fibrosis) with focal myocytolysis more evident in the fragments from the area closest to the aneurysm, while was non diagnostic in RV specimens in 8 of 11 pts. Treatment included antiarrhythmics (propafenone, sotalol, amiodarone and/or metoprolol) in 8 pts with VT, beta-blockers in 1 pt with chest pain, immunosuppression (prednisone and azathioprine for 5 months) in 4 pts (2 with chest pain and 2 with VT) with active myocarditis.

Results: Long-term follow-up (mean 56.3, range 12–120 months) including clinical examination, Holter monitoring, 2D-echocardiography, cardiac NMR, LV angiography and LV endomyocardial biopsy, showed normal LV volumes and function in all pts, LV aneurysm occlusion in 2 pts with histologic evolution to a healed myocarditis. All pts were asymptomatic, no VT recurrence or major clinical events were registered and none required implantable electrical devices or a surgical intervention.

Conclusions: LV aneurysms with normal global function caused by myocarditis are an uncommon benign entity where major therapeutic regimens are usually unnecessary.

P3373 Active versus borderline myocarditis: can a differential diagnosis predict the clinical outcome?

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Myocarditis is an inflammatory disease of the myocardium characterized by polymorphic clinical presentation, evolution to dilated cardiomyopathy and high mortality. The histological diagnosis based on the Dallas criteria allows a classification between active (AM) and borderline myocarditis (BM). We reviewed,among the 419 endomyocardial biopsy (EMB) performed at our institution from 1991, 48 (11%) EMB that were diagnostic for myocarditis according to histologic criteria. On bioptic samples immunohistochemistry and polymerase chain reaction (PCR) for a panel of viruses were performed. Clinico-pathological correlations were also carried out. The mean age of the patients was 34 ± 19 years (range 1–77); the histologic diagnosis was AM in 33 cases (69%), lymphocytic in 27 (82%); BM in 15 cases (31%).Clinico-pathologic correlations between AM and BM revealed no differences in terms of number of fragments analyzed, amount of fibrosis, NYHA class at the time of symptoms onset and at follow-up, LVEF and mortality. We found a statistically significant difference time intercurring between onset of symptoms and EMB execution (AM: 113 ± 232 days vs BM: 802 ± 175 days $p = 0.03$); LVEDV (AM: 85 ± 39 vs BM: 131 ± 57 $p = 0.002$) and degree of inflammatory infiltrates (score 0–4) (AM: 2 ± 1.1 vs BM: 1 ± 0 $p = 0.001$)were also different. PCR analysis detected a positivity for viruses in 40% of AM cases and 25% form BM cases. Enteroviruses were detected in 43% of PCR positive cases. BM seems to encompass ongoing forms with a less aggressive inflammatory infiltrate composed mainly by macrophages. The absence of myocytes necrosis does not predict a more favourable prognosis in terms of death/CHF. Our data suggest that a new classification of myocarditis is required. Besides histologic, immunohistochemical and molecular findings, clinical criteria should also be used for diagnosis.

P3374 Chronic chagasic cardiomyopathy, but not dilated cardiomyopathy, presents overexpression of adhesion molecules and induction of class I HLA on the cardiomyocytes

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Heart failure and cardiac enlargement occur in both chronic chagasic cardiomyopathy (CCM) and dilated cardiomyopathy (DCM). Although significant chronic lymphocytic myocarditis is usually present in CCM, but not in DCM, autoimmunity is considered to be involved in both cardiomyopathies. Since the expression of adhesion molecules modulates the inflammatory reaction, and class I HLA is usually enhanced in autoimmune reactions, we performed immunohistochemistry for differential analysis of ICAM-1, VCAM-1, LFA-1, and class I HLA in myocardial biopsies from patients with CCM and DCM.

Methods: Frozen sections of 12 ventricular biopsies from patients with CCM, 9 ventricular biopsies from patients with DCM, and 8 right atrial appendage biopsies from patients submitted to graft coronary surgery (control group) were incubated with the following monoclonal antibodies: anti-CD8+ T cells, anti-ICAM-1, anti-VCAM-1, anti-LFA-1, and anti-class I HLA. The mean number of CD8+ T cells per high power field was used to evaluate the intensity of the inflammatory infiltrate in each case. The evaluation of adhesion molecules and class I HLA immunoreactivity was conducted in a semi-quantitative fashion. The scores (0 to 3) were attributed independently for the endothelial/interstitial (E/I) cells and the cardiomyocytes.

Results: Significant lymphocytic inflammatory infiltrate was present in CCM group, but not in DCM and control groups. ICAM-1 and class I HLA were detected on E/I cells in all cases. VCAM-1 was distinct only at the inflammatory sites of CCM group, located on the endothelial cells. CCM group presented higher scores for both ICAM-1 on E/I cells and VCAM-1 than DCM and control groups. ICAM-1 was detected on the cardiomyocytes in 2/12 cases of CCM group, but not in DCM and control groups. Class I HLA was detected on the cardiomyocytes in all cases of CCM group, in 2/9 cases of DCM group, but not in the control group. CCM group presented higher score for class I HLA on the cardiomyocytes than DCM and control groups. LFA-1 was present only on lymphocytes.

In conclusion, CCM presents overexpression of both ICAM-1 on E/I cells and VCAM-1. Additionally, CCM presents induction of class I HLA on the cardiomyocytes. These findings are probably related to the high levels of cytokines at the inflammatory sites of CCM. The induction of class I HLA on the cardiomyocytes should not be considered an irrefutable evidence for autoimmunity in CCM. There is no significant myocardial inflammation in DCM, that presents expression of ICAM-1, VCAM-1 and class I HLA similar to the normal myocardium, differently from CCM.

P3375 E-selelctin-dependent adhesion of leukocytes is induced by CD40-CD40 ligand interaction on human vascular endothelial cells

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CD40 is a receptor on B-lymphocytes, monocytes with high homology to the TNF receptors and was found recently to be expressed also on endothelial cells. Ligands for CD40 (CD40L) are expressed on activated CD4+ lymphocytes and activated platelets. In the current study we investigated the effects of CD40 stimulation on endothelial cells on expression of adhesion molecules, secretion of chemokines and adhesion of leukocytes.

Expression of the adhesion molecules E-selectin, VCAM-1 and ICAM-1 on endothelial cells, derived from umbilical cords (EC), was assessed by flow cytometry. Secretion of the chemokines IL-8 and MCP-1 by ELISA. Adhesion of HL60 cells, with high expression of sialyl $Lewis^x$, ligands for E-selectin, was measured with an adhesion assay under flow conditions (wall shear stress 0.6–2.6 dyne/cm^2). Stimulation of EC with CD40L induced an increase in expression of E-selectin, VCAM-1 and ICAM-1 which reached about 50–70% of TNFα-induced effects. Adhesion of HL60 cells increased from 4 ± 2 (control) to 41 ± 10 cells per high power field ($n = 5$, $p < 0.01$). The CD40L induced adhesion reached 51% of the TNFα induced effects. The E-selectin dependence was demonstrated by adhesion blockade with anti E-selectin antibodies (BBA2). CD40L and TNFα induced comparable MCP-1 and IL8 secretion in EC. All CD40L induced effects could be blocked by anti CD40L antibodies (anti-TRAP).

In conclusion, CD40-CD40L interactions induce the expression of adhesion molecules, secretion of chemokines and induce E-selectin-dependent adhesion to endothelial cells. CD40 may augment and prolong inflammatory responses locally in addition to its effects in the immune system.

P3376 Is troponin I of prognostic value in the detection of anthracyclin cardiac toxicity?

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Aim of the study: Antracyclin drugs have allowed tremendous progress in the medical treatment of certain solid tumors. One of the most limiting side effects is undoubtedly cumulative cardiac toxicity.

The aim of our study was to assess in a prospective study the value of troponin I in the detection of early anthracyclin cardiac toxicity and compare it to the standard widely used criteria for the definition of cardiac toxicity ie; Echocardiographic and isotopic Systolic LVF parameters.

Method: From January 95 to April 97 we prospectively included 32 patients who have to be treated with an anthracycline drug. All patients were checked before the begining of the anti-cancer treatment, in particular, with echocardiography and isotopic left ventricular examination. In addition, blood samples were collected in order to assay troponin I before treatment (Sanofi-ERIA pasteur). After commencement of the anti-cancer treatment, the same examinations and sampling were performed after the 2nd the 6th and the final course. In addition, samples for troponin I assay were collected before and after each course

Results: 32 patients were included and followed for a sufficient period to allow comparisons.

Using our criteria (A drop of at least 10% in LVEF between 2 investigations occurring during the cancer treatment both at echocardiography and isotopic examination), 7 patients (toxic group) over 32 reached the definition of a cardiac toxicity assessed with echocardiography and isotopic examinations:

Troponin value: With cut-off positivity at >0.1 ng/ml, we found 18 positive assays over 167. When comparing the 2 patiens groups, positive troponin assays were not more frequent in the toxic group. In the non toxic group 88 assays were negative vs 11 positive; in the toxic group 61 assays were negative vs 7 positive: ($X2 = 0.028$; $p = 0.867$).

Conclusion: Troponine I, at least when measured with a common non ultra-sensitive method, cannot predict the occurrence of cardiac toxicity in patients treated with anthracyclin.

NOVEL MOLECULAR AND CLINICAL ASPECTS OF HYPERTROPHIC CARDIOMYOPAHTY

P3377 Disarray as a marker of risk in patients with hypertrophic cardiomyopathy

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Hypertrophic cardiomyopathy (HCM) is characterised by hypertrophy with myocyte disarray. Many patients die prematurely and yet the histological determinants of these deaths are not well defined. We studied the clinical profiles of patients with HCM and related these details to the degree of myocyte disarray.

Methods: The symptoms, echo data, risk profile and an ischaemia score (according to presence of typical chest pain, ST depression on exercise and reversible defects on thallium scanning) were noted in 68 HCM patients who had suffered sudden cardiac death (SCD), cardiac failure leading to death or transplantation, or death due to other causes. Each heart was quantitatively assessed for% disarray at the base, mid-level and apex of the LV, Intraventricular septum and RV (total of 18 sections).

Results: Patients with premorbid symptoms of chest pain exhibited significantly more disarray than those without (% disarray 29.8% vs. 17.3%, p = 0.006), as did patients with abnormal vascular response to exercise compared to those with an appropriate rise (30% vs. 18%, p = 0.03), and patients diagnosed or presenting with symptoms before the age of 18 years compared to those presenting in adulthood (26% vs. 18%, p = 0. 03 and 28% vs. 17%, p = 0.02 respectively). A weak, but positive correlation was seen between disarray and a family history of sudden premature cardiac death (r = 0.4, p = 0.006), and disarray and ischaemia score (r = 0.4, p = 0.04).

No association was seen between disarray and syncope, or disarray and episodes of non sustained VT.

Conclusion: Myocyte disarray was greater in patients with chest pain and a high ischaemia score. The known risk factors of a family history of sudden premature death, an abnormal vascular response to exercise, and onset of symptoms or diagnosis during childhood were all associated with significantly more disarray.

The relation between risk and disarray did not appear to relate to arrhythmic markers (i.e. NSVT) and suggests that marked disarray may predispose to sudden death by mechanisms other than arrhythmogenesis.

P3378 Hypertrophic cardiomyopathy: inverse relation of subclinical skeletal myopathy with sudden death in the family

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Background: Hypertrophic cardiomyopathy (HCM) is a heterogeneous disorder caused by mutations in proteins of the cardiac sarcomere. Some mutations (b-myosin heavy chain) may be associated with skeletal muscle (SM) fibre dysfunction.

Methods: This study determined the prevalence of subclinical skeletal myopathy in 46 unrelated consecutive patients (pts) with HCM (26 male, 49 ± 18 years) using conventional and quantitative electromyography (EMG) of deltoid, quadriceps, tibialis anterior and soleus muscles. No pt had clinically detectable muscle weakness.

Results: Myopathic EMG findings were demonstrated in 12 (26%) pts, 25 pts had normal studies and 9 pts had indeterminate recordings. The relation of abnormalities to clinical parameters were:see table.

	Myopathic EMG	Normal EMG	p	Indeterminate EMG
Age (years)	53.6 ± 20.3	47.0 ± 16.3	NS	54.3 ± 19.5
Interventricular septum (cm)	1.85 ± 0.3	1.92 ± 0.4	NS	1.9 ± 0.4
Posterior wall (cm)	1.22 ± 0.2	1.22 ± 0.3	NS	1.22 ± 0.2
NYHA (I-II-III) (n)	3-6-3 /12	7-15-3 /25	NS	2-5-2 /9
LVOT obstruction (n)	8/12 (67%)	11/25 (44%)	NS	4/9 (44%)
Syncope (n)	3/12 (25%)	4/25 (16%)	NS	0/9
Nonsustained VT (n)	0/12	3/25 (12%)	NS	0/9
Sudden death in the family (n)	0/12	9/25 (36%)	<0.05	1/9 (11%)

Conclusion: A substantial minority of pts with HCM show evidence of subclinical skeletal myopathy. The higher prevalence of a family history of sudden death in pts with normal EMG may reflect a higher prevalence of high risk mutations that are not expressed in SM (e.g. troponin T).

P3379 Haemodynamic determinants of syncope in hypertrophic cardiomyopathy

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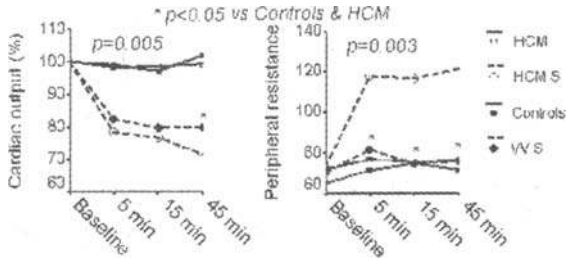
Background: Syncope (S) occurs in about 1/4 of patients with hypertrophic cardiomyopathy (HCM); its hemodynamic mechanisms, however, are not well established. Ambulatory radionuclide monitoring device (VEST) allows a reliable, noninvasive evaluation of left ventricular (LV) function during exercise or volume changes. Tilting test is an useful tool for identifying patients with vasovagal S (VV S).

Methods: To assess the hemodynamic determinants of syncope, we studied 25 HCM patients without history of S (age 39 ± 14 years, 21 men), 7 HCM patients with S (38 ± 9 years, 5 men [HCM S]), 9 controls (age 36 ± 14 years, 6 men), and 6 patients with VV S (age 34 ± 7 years, 4 men); all underwent head-up tilt at 70° for 45 minutes during VEST. VEST data were averaged for 60-second intervals, and analyzed at baseline and after 5, 15, and 45 minutes of tilting. LV end-diastolic and stroke volumes (SV), and cardiac output (CO) were expressed as% of the baseline values.

Results: All VV S patients and 3 patients with HCM S experienced a positive response to tilt test. VV S patients and HCM S patients showed a similar, significant decrease in SV and CO compared to HCM and control group (Figure, left); a marked increase in peripheral resistance was observed only in HCM S (Figure, right).



Conclusions: Both patients with HCM S and with VV S have a fall in CO and SV with tilting. In the former group, however, the primary mechanism appears to be a decrease in filling of a stiff left ventricle secondary to acute volume unloading, associated with reflex peripheral resistance increase; patients with VV S, in contrast, do not exhibit compensatory vasoconstriction to CO fall.

P3380 Improvement in exercise haemodynamics after transcoronary ablation of septum hypertrophy for hypertrophic obstructive cardiomyopathy

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Transcoronary Ablation of Septum Hypertrophy (TASH) is a catheter interventional treatment for hypertrophic obstructive cardiomyopathy (HOCM). Major results – reported in the literature – are a reduction of septal thickness and outflow obstruction and an improvement of NYHA functional class and exercise capacity.

To evaluate objectively the hemodynamic effects of TASH serial left heart and exercise right heart catheterization were performed before as well as 2 weeks, 7 months and 21 months (n = 9) after intervention. The study population consists of 39 pts. with HOCM and severe symptoms (57 ± 14 years, 24 men). In all pts the long-term benefits of TASH on subjective improvement, NYHA functional class, intraventricular gradients, exercise capacity, pulmonary artery mean pressure at workload, cardiac index at workload and peak oxygen consumption were estimated.

43% of the pts. were marked improved, 49% were improved and 8% were unchanged. None of the pts. reported on a further deterioration of symptoms and no late deaths occurred. NYHA functional class improved from 3.0 ± 0.2 to 1.8 ± 0.5 (p < 0.001), exercise capacity increased from 74 ± 31 to 92 ± 36 watts (p < 0.001), peak oxygen consumption from 14.8 ± 4.9 to 16.8 ± 5.7 ml/kg/min (p = 0.015), cardiac index from 6.1 ± 1.9 to 6.5 ± 2.4 l/kg/min (n.s.) and pulmonary artery mean pressure from 44 ± 8 to 36 ± 10 mmHg at identical workloads (p < 0.001). The improvement in NYHA functional class and exercise capacity were significantly correlated to a decrease in pulmonary artery mean pressure at workload and to an increase in peak oxygen consumption.

Conclusion: During long-term follow-up TASH induced reductions of symptoms were accompanied by significant improvements in exercise hemodynamics.

P3381 New mutations in MyBP-C gene associated with hypertrophic obstructive cardiomyopathy (HOCM)

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Hypertrophic cardiomyopathy (HCM) is a primary and heterogenous cardiac disease, and is caused by defects in genes encoding for sarcomeric proteins. A number of disease causing mutations in cardiac myosin binding protein C (MyBP-C) have been identified in patients with a relatively benign clinical course and late disease manifestation.

To search for new mutations in the MyBP-C gene and to analyze genotype/phenotype correlations we screened 71 patients with HCM for mutations in the MyBPC-gene.

Diagnosis of HCM was based on echocardiography (LV hypertrophy, septal hypertrophy $\geq$ 13 mm), RV and LV angiography and hemodynamics and/or preceeding myectomy. DNA was PCR amplified with intronic primers and SSCP-analysis was performed at 4°C and RT. Aberrant PCR-products were directly sequenced on a DNA sequenzer (ABI377).

We identified 5 mutations. Two of them have already been described (insAA1042 and insG791) and three mutations were newly identified. The first new mutation is a 1-bp del in codon 1047 (delG1047) in a 39 y old turkish mother, her father (66 y) and her son (17 y). This mutation leads to a MyBPC-product lacking titin and myosin binding sites and thus affects protein structure and function. The second mutation is a Val-896-Met substitution and was identified in a 28 y old woman from greece. The third mutation identified was a Gln-1233-Ter substitution in exon 34 leading to a protein which lacks parts of the functionally important myosin-binding site. All patients with MyBP-C mutations presented with the typical features of HOCM (one after myectomy, all with septal thickness >15 mm, and ventricular arrhythmia).

We identified a wide spectrum of MyBP-C mutations (two deletions, one insertion, 2 aminoacid exchanges) that affect protein structure and function. In contrast to previously decribed patients with MyBP-C mutations, one family presented with typical HOCM and an early disease manifestation.

P3382 Chronotropic incompetence is an important determinant of functional limitation in hypertrophic cardiomyopathy

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Patients (pts) with hypertrophic cardiomyopathy (HCM) have reduced peak oxygen consumption (pVO_2). Failure to augment stroke volume is contributory but there are few data on the effect of heart rate response. This study assessed the effect of chronotropic incompetence (CI) on pVO_2.

Methods: One hundred and thirty four HCM patients (29% with a left ventricular outflow gradient > 30 mmHg) with a mean left ventricular wall thickness (LVWT) of 19 ± 5 mm; 9–47 mm underwent upright cardiopulmonary exercise off all medication (except amiodarone) prior to the test using a bicycle ramp protocol. Heart rate (HR) and pVO_2 were measured at 10 second intervals. CI was defined as a peak HR of less than 80% predicted for age and pVO_2 was expressed as a percentage of the maximal predicted VO_2.

Results: Forty nine (36%) pts had CI. Eleven were taking amiodarone. There was no significant difference in peak HR between pts taking amiodarone and those not taking the drug. CI was associated with a lower % pVO_2 than a normal HR response (46.7 ± 14.3 v 68.3 ± 16.8; $p < 0.001$). The V02 versus HR relationship in pts with CI demonstrated two distinct patterns of HR response: Type 1. a steep increase in HR which stopped abruptly on cessation of exercise, and Type 2. a progressive increase in HR which plateaued at least 60 seconds before peak exercise. Pts with a type 2 response were thought to have unequivocal CI whereas pts with a type 1 response may have stopped due to the onset of limiting symptoms rather than failure to increase HR. 29 (21.5%) patients had a type 2 response. In univariate anlaysis there was no correlation between LVWT and pVO_2 but there was a correlation between left ventricular outflow gradient and pVO 2 ($r = 0.5$; $p < 0.0001$) and between CI and pVO_2 ($p < 0.0001$). In multivariate analysis including left ventricular wall thickness, outflow gradient and CI in the model only CI was an independent determinant of pVO_2 ($p < 0.0001$).

Conclusion: Over 20% of HCM patients have CI which appears to be an important cause of exercise intolerance.

P3383 Familial hypertrophic cardiomyopathy. A phenotype–genotype analysis: prognosis depends rather on mutation than on gene

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Familial hypertrophic cardiomyopathy (FHC) is a heterogeneous genetic disease with autosomal dominant inheritance. The highly variable clinical course has been suggested to be related to affected gene, *MYBPC3* mutations seeming to be more benign than β-MHC mutations.

Methods: seven informative families were recruited from French western region. Informed consent, clinical, 12 lead-ECG, echocardiographic data and blood samples were collected for phenotype (P) and genotype (G) analysis. Major cardiac events such as heart failure (HF), heart transplantation (HTx) and cardiac death (CD) were analysed. Microsatellite haplotyping, single-strand conformation polymorphism analysis, and DNA sequencing were used to assess genotype.

Results: 193 patients (pts) were genotyped; among the 60 carriers of mutation (G+), 36 were phenotypically affected (G+/P+). We identified 4 missense mutations in the *β-MHC* gene (Asn232Ser, Arg453Cys, Asn479Ser and Gly768Arg) and a splice donor site mutation of *MYBPC3* gene exon 6 (SDS mut). On 2 occasions, 2 families, suggesting a founder effect, carried the same mutation (Asn232Ser and Asn479Ser). Three of these mutations have been previously described (Asn232Ser and SDS mut as benign; Arg453Cys as severe). Numbers of subjects (G+, G+/P+) carrying each mutation and major cardiac events are listed in table below. *β-MHC* mutations were associated with variable clinical course and the *MYBPC3* mutation with a high penetrance and a poor prognosis.

Gene	Mutation	pts G+/pts G+P+	HF/HTx (age)	CD (age)
β-MHC	Asn232Ser	10/7	0/0	2 (18 y, 38 y)
β-MHC	Arg453Cys	3/2	0/1 (27 y)	0
β-MHC	Asn479Ser	34/16	1/0	1 (33 y)
β-MHC	Gly768Arg	7/6	1/0	1 (47 y)
MYBPC3	SDS mut	6/4	1/1 (41 y)	1 (18 y)

Conclusion: clinical course of FHC seems to be related rather on mutation within the gene than gene itself when *β-MHC* and *MYBPC3* mutations are compared.

P3384 Age-related changes of exercise capacity in patients with hypertrophic obstructive cardiomyopathy

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Pts. with HOCM often report on decrease in vitality. Left ventricular outflow tract (LVOT) obstruction and diastolic dysfunction may be the main causes. Objective parameters of exercise capacity can be determined by spiroergometry (SE).

77 consecutive pts. (50 ± 16 years, 45 men), underwent SE using a bicycle ergometer ramp protocol (Δ 10 watts/min). We measured peak oxygen consumption (pVO_2), % of maximal predicted oxygen consumption (%VO_2), anaerobic threshold (AT), oxygen pulse (O_2 pulse), maximal work load, and by echo left atrial diameter (LA), LVOT-gradient (LVOTG) at rest and at Valsalva.

Only 35% of pts. with HOCM reached normal %VO_2 values (≥80%). Pts. ≥60 years achieved a higher %VO_2 than youngers (117 ± 71 vs. 69 ± 17; $p < 0.01$) normal %VO_2-values (71% vs. 21%). Details are listed in the table.

Table. Results of SE and echo Doppler study

(n)	<40 years (23)	40–59 years (33)	≥60 years (21)
Peak VO_2 [ml/kg/min]	$27.1 \pm 7.2^{(1)(2)}$	$20.1 \pm 5.2^{(1)(3)}$	$18.2 \pm 5.5^{(2)(3)}$
%VO_2 [%]	$69 \pm 17^{(4)}$	$68 \pm 17^{(5)}$	$117 \pm 71^{(4)(5)}$
AT [ml/kg/min]	$17.1 \pm 3.6^{(6)}$	$15.1 \pm 4.2^{(7)}$	$13.3 \pm 3.5^{(6)(7)}$
LVOTG at rest [mmHg]	48 ± 21	46 ± 28	60 ± 38
At Valsalva [mmHg]	102 ± 52	110 ± 47	110 ± 54
NYHA	$2.5 \pm 0.5^{(8)}$	$3.0 \pm 0.4^{(8)}$	2.9 ± 0.4

(P-value <: $^{(1)}$0.01, $^{(2)}$0.001, $^{(3)}$0.05, $^{(4)(5)}$ 0.01, $^{(6)(7)(8)}$ 0.05).

There is no correlation between LVOTG and pVO_2, %VO_2, AT, and O_2 pulse. In a multivariate regression analysis only LVOTG at rest influences %VO_2 (OR 0.6, $p < 0.01$).

Conclusions: The majority of younger pts. with HOCM have reduced exercise capacity, whereas pts. ≥60 years of age reached more often normal values of %VO_2. Furthermore, only a small influence of LVOT gradient on exercise capacity is detectable.

P3385 Long-term morphological evolution of familial hypertophic cardiomyopathy caused by Arg92Trp mutation in the cardiac troponin T gene

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Familial hypertrophic cardiomyopathy (FHCM) can be caused by a mutation in the cardiac troponin T (cTnT) gene. Previous report suggested that mutations in the cTnT gene were notable because they were associated with a particulary poor prognosis but only mild hypertrophy. However, long-term morphological evolution of FHCM caused by cTnT gene mutations are unknown. We studied two families with the Arg92Trp mutation in the cTnT gene.

Methods: 140 probands with FHCM were screened for mutations in the cTnT gene. The Arg92Trp missense mutation was found in two probands. The two families were analyzed genetically and clinically.

Results: Ten (4 males, 6 females, mean age 49 ± 15 yrs) were affected with the Arg92Trp mutation. Distributions of morphology on ultrasound cardiogram (UCG) were dilated cardiomyopathy-like features (D-HCM) (left ventricular end-diastolic dimension: LVDd > 55 mm, fractional shortening: FS < 25%) in three, asymmetric septal hypertrophy (ASH) with normal LVDd (LVDd ≤ 55 mm) in five, ECG abnormality without UCG abnormality in one male (32 yrs), and non penetrance in one female (27 yrs). Disease related sudden death was seen in three individuals in their family history (1 yrs female, 14 yrs female, and 53 yrs male). The three D-HCM patients were followed up for 6 to 19 years, respectively. LVDd/left ventricular end-systolic dimension (LVDs) of the 65 yrs D-HCM female was 45/32 (mm) in 46 yrs, and dilated to 65/59 in 60 yrs, 67/59 in 65 yrs. Left ventricular hypertrophy with ASH decreased in the course (interventricular septal wall thickeness/posterior wall thickness: 29/13 to 7/10). LVDd/LVDs of the 56 yrs D-HCM male was 60/52 in 50 yrs, and 66/59 in 56 yrs. LVDd/LVDs of another 54 yrs D-HCM male was 52/40 in 45 yrs, and 68/55 in 54 yrs. Considering gender, the five ASH patients were younger than D-HCM patients (a 26 yrs male and four female from 49 to 64 yrs).

Conclusion: There is a tendency to develop into D-HCM in their fifties in male and in their sixties in female in FHCM patients with Arg92Trp mutation in the cTnT gene.

P3386 Ischaemia during daily life in hypertrophic cardiomyopathy

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Background: Myocardial ischemia is common in hypertrophic cardiomyopathy (HCM) and it appears to be linked to symptoms and sudden death. The impact of spontaneous ischemia in non selected patients with HCM has never been investigated. To address this issue we evaluated the presence and duration of ischemia during daily life using ECG monitoring (EM).

Methods: We recorded 24 hour EM of 70 patients with HCM. Total ischemic burden (TIB) was calculated as the sum of the duration in minutes of each ischemic episode (ST segment shift from the baseline >1 mm and lasting >1 min). By echocardiogram, we measured the extent of left ventricular (LV) hypertrophy (EH) by adding maximal thickness in 4 left ventricular segments, and left atrial fractional shortening (LAFS), an index of passive diastolic function. By upright exercise test with the analysis of expired gases, we measured maximal oxygen consumption (VO_2 max ml/kg/min).

Results: Calculation of TIB was possible in 57 patients (84%) who had good quality recordings; 17 of them had significant ischemia (TIB>30 min) during EM. The 2 groups did not differ for age and basal ejection fraction. Compared to patients without ischemia, patients with ischemia had a worse diastolic function (LAFS 19 ± 6 vs 24 ± 7%, p = 0.016) a lower exercise tolerance (VO_2 max 21 ± 4 vs 26 ± 7 ml/kg/min, p = 0.009), an higher NYHA functional class (1.68 ± 04 vs 1.34 ± 0.5, p = 0.02), a greater extent of LV hypertrophy (EH 59 ± 13 vs 70 ± 19 mm, p = 0.04) and a higher LV outflow tract obstruction (8 ± 22 vs 29 ± 40 mmHg, p = 0.012). Ischemia was a determinant of NYHA functional class and VO_2 max also in the subset of 40 nonobstructive patients.

Conclusion: Myocardial ischemia can be assessed by a non invasive method. Prolonged ischemia during daily life is associated with a lower exercise tolerance and worse diastolic function. LV outflow tract obstruction and high extent of hypertrophy are determinants of ischemia.

P3387 Long-term follow-up of hypertrophic cardiomyopathy

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Objectives: Aim of this retrospective study was the clinical evaluation of our patients with hypertrophic cardiomyopathy (HCM) receiving medical and/ or surgical treatment, and the calculation of cumulative survival rates.

Patients and Methods: 85 patients – 56 males and 29 females – with HCM have been followed up for 1–26 years (mean 10 years). Mean age at the initial diagnosis was 46 (7–77) years. 79 patients received medical treatment, predominantly verapamil. Six patients – three males and three females – with typical (subaortic) hypertrophic obstructive cardiomyopathy underwent transaortic septal myectomy/ myotomy and were treated with verapamil subsequently. Patients' examination included history, physical examination, ECG and echocardiography. Cumulative survival rates were calculated by life table analysis.

Results: Of those patients treated medically, clinical improvement occurred in 37%, no changes were found in 29%, 15% deteriorated, and 15 patients (19%) – twelve males and three females – died up to 26 years (mean 8 years) after the initial diagnosis. Clinical improvement was obtained in all patients that were treated surgically, lasting up to 15 years postoperatively in five patients. One patient showed clinical deterioration eleven years after initial myectomy; remyectomy was performed, but did not ameliorate symptoms. 10- and 20-year survival rates of medically treated patients were 88% and 63%, respectively (annual mortality rate 1.8%). Survival rate of surgically treated patients with subsequent verapamil-therapy was 100% over a mean follow-up period of 10 (5–18) years.

Conclusions: Medical treatment yielded clinical improvement in about one third of patients. Long-lasting clinical improvement occurred in all patients following myectomy/ myotomy, but recurrence of symptoms could not be avoided completely. Long-term outcome appears to be best in patients treated surgically with subsequent verapamil-therapy. However, DDD pacing as well as percutaneous transluminal septal myocardial ablation were not yet available for our patients.

P3388 Utility of metabolic exercise testing in the differentiation of physiological hypertrophy of athlete's heart from hypertrophic cardiomyopathy

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The echocardiographic and electrocardiographic distinction between physiological left ventricular hypertrophy (LVH) in highly trained athletes and mild (13–16 mm) LVH in HCM is difficult. We evaluated the role of cardiopulmonary exercise in differentiating the athlete's heart from HCM with mild hypertrophy.

Methods: 8 recreational male athletes with genetically proven HCM (6 = troponin T and 2 = b myosin heavy chain mutations) and mild LVH (<16 mm) were compared with 8 elite male athletes matched for age and body surface area with LVH of similar magnitude, 8 elite athletes without LVH and 12 healthy recreational sportsmen without LVH. All subjects exercised to the point of exhaustion using a maximal ramp cycle ergometer exercise test with simultaneous gas exchange analysis. Peak oxygen consumption(pVO_2), anaerobic threshold (AT) and oxygen pulse (O_2 pulse) were measured.

Results:

Parameter	HCM	Athletes with LVH	Athletes without LVH	Recreational Sportsmen
Age (years)	24.7 ± 6.3	23.9 ± 3.9	24.8 ± 4.3	25.4 ± 5.4
LVWT (mm)	13.7 ± 1.4	12.8 ± 1.0	10.7 ± 0.7	9.9 ± 1.0
PVO_2 (ml/kg)	34.2 ± 8.9	67.2 ± 4.9	66.7 ± 5.1	45.6 ± 3.2
AT (%pred VO_2 max)	41.4 ± 7.0	55.4 ± 12.6	62.1 ± 6.5	46.8 ± 2.8
O_2 pulse (ml/beat)	14.3 ± 2.6	29.1 ± 12.6	27.4 ± 6.2	16.8.0 ± 2.1

Highly trained athletes with and without LVH had significantly greater pVO_2, AT and O_2 pulse when compared to active HCM patients with mild LVH and normal healthy recreational sportsmen ($p < 0.001$). Athletic HCM patients had significantly lower metabolic parameters compared with healthy recreational sportsmen ($p < 0.001$).

Conclusion: Cardiopulmonary exercise testing is a useful non invasive method of differentiating physiological LVH in highly trained athletes heart from HCM with mild hypertrophy.

P3389 Dispersion of repolarisation in hypertrophic cardiomyopathy and hypertensive cardiac hypertrophy

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Background: QT disspersion in the 12-lead ECG reflect the disspersion of cardiac repolarisation (DCR). In order to check the hypothesis that DCR in HCM is mainly due to structural abnormalities but not cardiac hypertrophy the extend of DCR in patients with hypertrophic cardiomyopathy (HCM) and hypertensive left ventricular hypertrophy (LVH) was compared.

Methods: The study group consisted of 15 patients with HCM, 25 with LVH and a control group of 15 patients without cardiac disease. DCR was assessed in each patient by measuring the duration of QT interval in the standard 12-lead ECG. The following parameters were calculated: 1) QT disspersion (QTd) as the difference between the longest and the shortest QT, 2) QTc disspersion (QTcd) as the difference between the longest and the shortest QTc. Left ventricular mass corrected for body surface area (LVmass/BSA) was estimated during echocardiography. QT and QTc disspersion index, defined as QTd/(LVmass/BSA) and QTdc/(LVmass/BSA), was also calculated.

Results: All the calculated DCR parameters were significantly longer in the HCM group, compared to the LVH or the control group. QT and QTc disspersion index was significantly bigger in the HCM group, while there was no difference between the LVH and the control group.

	HCM	LVH	Control	p value between HCM & LVH
QTd [s]	51 ± 29	23 ± 14	14 ± 8	< 0.001
QTcd	56 ± 29	28 ± 16	17 ± 9	< 0.001
LVmass/BSA [g/m^2]	221 ± 55	182 ± 42	120 ± 27	< 0.05
QTd/(LVmass/BSA) [s/(g/m^2)]	0.24 ± 0.13	0.12 ± 0.8	0.11 ± 0.3	<0.01
QTcd/(LVmass/BSA) ['/(g/m^2)]	0.27 ± 0.14	0.15 ± 0.1	0.14 ± 0.4	< 0.01

Conclusions: 1) Disspersion of repolarisation is significantly prolonged in HCM compared to LVH or control, 2) The prolongation of DCR in HCM is not a result of cardiac hypertrophy but is mainly due to structural abnormalities.

P3390 Novel mutations in the cardiac myosin binding protein C gene in patients with hypertrohic cardiomyopathy

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Hypertrophic Cardiomyopathy (HCM) is characterized by left and/or right ventricular hypertrophy leading to arrhythmias and sudden cardiac death. HCM is the most frequent genetic disorder of the myocardium. The disease is inherited as an autosomal-dominant trait. Seven different disease genes are known. All these genes encode for proteins of the myofibrillar apparatus. This shows that familial HCM is a disaese of the sarcomere. Mutations in the cardiac myosin binding protein C (MYBPC3) are responsible for about 15% of cases.

Methods: 145 unrelated patients with HCM were evaluated using physical examination, ECG and echocardiography. DNA was extracted from blood. Screening of the 34 coding exons of the MYBPC3 was done using PCR, single strand conformation polymorphism analysis (SSCP), and automated sequencing.

Results: We detected 9 novel mutations in the MYBPC3. 5 missense mutations leading to an aminoacid exchange were found. One mutation leading to a stop codon is predicted to produce a truncated protein. Hot spots were detected in the exon 6 and exons 24–27. Furthermore we identified 3 deletions and one insertion in the exons 29–33 leading to a frameshift. The clinical phenotype of these genotyped patients showed no significant differences to the phenotype described for other HCM disease genes.

Conclusion: The described mutations in the MYBPC3 confirm the wide allelic heterogeneity of HCM.

PERICARDIUM IN HEART DISEASE: AN UPDATE

P3391 Diagnostic value of pericardial biopsy: improvement with aggressive sampling enabled by pericardioscopy

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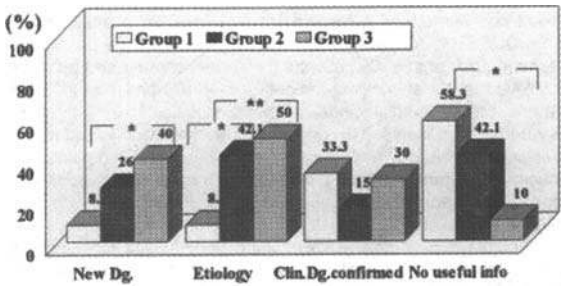
Diagnostic value of pericardial biopsy (PB) is still a matter of debate. To elucidate this issue, we compared PB results using fluoroscopy (Group 1: 12 pts, 66.7% males, mean age 46.7 ± 12.2 yrs, 3–6 samples/pt, mean 5.2) and aimed PB performed using flexible percutaneous pericardioscopy (PCS) with standard and aggressive sampling (Group 2: 19 pts, 52.6% males, mean age 52.3 ± 11.2 yrs, 4–6 samples/pt, mean 5.9 (range 3–6))(Group 3: 10 pts, 60% males, mean age 42.3 ± 14.6 yrs, 18–20 samples/pt, mean 19.2). All pts initially underwent pericardiocentesis due to a pericardial effusion (PE) >2 cm or imminent tamponade. In Group 1 left lateral PB was performed, using 9F sheath and Olympus FB-43ST forceps. In Group 2 and 3 aimed PB with FB-43ST forceps were enabled by PCS with Olympus HYF-1T 16F endoscope. Sampling efficiency was better in Groups 2 and 3 in comparison to Group 1, 86.2% and 87.3% vs. 43.7% respectively ($p < 0.01$). Sensitivity of the histology findings was 41.7% in Group 1, 57.9% in Group 2, and 90% in Group 3, while specificity was 100% in all groups. No major complications occurred in either group, while in Groups 2 and 3 short run VT (1/19), pain during dilatation (11/19 and 7/10 pts), and transient fever (8/19 and 4/10 pts) were noted. Patohistology revealed (Group 1 vs. 2 vs. 3)(%): Planocellular Ca 8.4/10.5/10; Adeno Ca 0/15.7/0; Mesothelioma 0/0/10; Plasmocytoma 0/5.3/0; M. Hodgkin 0/5.3/10, Tuberculosis 0/5.3/20. Nonspecific inflammation 33.3/15.7/40. Diagnostic values of the procedures are depicted in the figure.



Conclusion: PCS with Olympus HYF-1T enables excellent visualization, superior extensive pericardial sampling, offering better diagnostic value especially regarding establishing the new diagnosis and etiology of the pericardial disease.

P3392 Effect of pericardial pressure on human coronary circulation

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Despite the fact that pericardial pressure (PP) has been clinically diagnosed since the 19th century and numerous reflexes and systemic cardiovascular effects have been well described, only a very few studies have dealt with the effects on coronary blood flow and these used experimental animal models. The aim of this study was to assess the effects of PP on human coronary circulation.

Methods: We studied 4 patients (3 men), mean age 53 ± 8 years, programmed for percutaneous balloon pericardiotomy because of rapid pericardial fluid accumulation due to extracardiac malignancy. A 0.014" 15 MHz guide wire was used to record coronary blood flow velocities in the left anterior descending coronary artery at increasing PP achieved by infusion of warmed normal saline at a rate of 30 ml/min. All patients received 200 μg intracoronary nitroglycerin before the procedure. Time-averaged peak velocity (APV) was measured before (R) and after (H) administration of 18 μg intracoronary adenosine, to achieve maximal hyperemia. Coronary flow reserve (CFR) was calculated as the ratio of APV-H to APV-R. Measurements were made at the beginning and at the end of the study. The study was terminated at the onset of any symptom.

Results: After infusion of 166 ± 36 ml of normal saline, the pericardial pressure was 16 ± 3 mm Hg. The coronary blood flow velocity data are given in the table below.

Table

PP (mm Hg)	APV-R (cm/s)	APV-H (cm/s)	CFR
2 ± 1	25.7 ± 6.1	53.2 ± 11.4	2.1 ± 0.2
16 ± 3	14.5 ± 2.6*	31.2 ± 5.4*	2.2 ± 0.4

p < 0.05 vs. low PP

Conclusion: With increasing pericardial pressure there is a decline in coronary blood flow and an unaffected coronary flow reserve. The maximal hyperaemic flow is far less under increased pericardial pressure than at normal pressure, which implies an augmented susceptibility to myocardial ischaemia.

P3393 New concept in pericardiocentesis: preliminary experimental and clinical experience with protected needle and vacuum device

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Percutaneous approach to normal pericardium was until recently unrealistic. Objective of present study was to evaluate feasibility and safety of a new instrument for percutaneous access to the pericardium with small or no effusion (PerDUCER®, Comedicus Inc., USA), both in experimental and clinical setting.

Key feature of the device is a distal view tube with a side hole cavity, where pericardium is captured by vacuum and tangentially punctured by introducer needle. The device was studied in four animal experiments (two F1 white pigs in general anesthesia, mean weight 28.6 kg) as well as in five patients with pericardial disease in local anesthesia (two males, mean age 50.4 years, pericardial effusion 0.8–2.2 cm, mean 1.6 cm). The procedure was performed under fluoroscopic control and includes two distinct techniques: 1) access to the mediastinal space and, 2) pericardial capture, puncture, and insertion of the 0.018" guidewire. Access to the mediastinal space includes the introduction of the blunt cannula, 0.038" guidewire, dilator-introducer sheath set and insertion of PerDUCER®. Access to the mediastinal space was possible in 4/4 animal experiments, and in 4/5 patients. Pericardial capture and puncture were also achieved in 4/4 animal experiments and in 4/5 patients. Insertion of the guidewire and pericardial catheter was accomplished in 3/4 animal experiments and in 0/5 patients. The procedure was very well tolerated. No major complications developed, while minor complications included pain at the dilator-introducer sheath entry site (5/5) and the mild transient fever (2/5).

Conclusion: Both in animal and clinical setting the PerDUCER® was successful regarding access to the mediastinal space, pericardial capture and puncture. Insertion of the pericardial guidewire and catheter was achieved only in animal experiments. Further studies and presumably minor modifications are needed to improve efficacy in patients with small or no pericardial effusion.

P3394 Transient left ventricular remodelling as a measure of left ventricular compression in patients with cardiac tamponade

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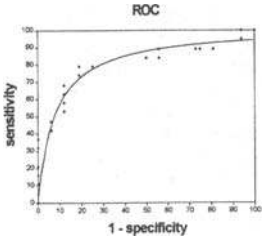
Transient left ventricular remodeling characterized by increased wall thickness, decreased cavity size and normal left ventricular mass has been observed clinically and experimentally in cardiac tamponade but its exact diagnostic value is not known. The purpose of this study was to establish the quantitative relationship between the degree of LV remodeling and cardiac tamponade. The study population consisted of 70 consecutive patients (age: 50 ± 16, range: 17–84; F:M; 29:41) with large or moderate pericardial effusion. Symptomatic patients who underwent pericardiocentesis were considered to have cardiac tamponade (n = 33). The receiver operating curve (ROC) of left ventricular relative wall thickness [(LVRT%) = (PW thickness) * 100/(LVEDD/2)] as a marker of cardiac tamponade showed the best accuracy using LVRT ≥ 50%. The diagnostic value of LVRT ≥ 50% was compared to other known echocardiographic signs of cardiac tamponade.



	RA↓	RV↓	IVC↓	Res Var↑	LVRT ≥ 50%
Sensitivity	73%	73%	83%	90%	76%
Specificity	76%	78%	45%	35%	84%
Accuracy	74%	76%	63%	61%	80%

RA↓; right atrial collapse, RV↓ right ventricular collapse, IVC↓ reduced variations of inferior vena cava, Res Var↑ increased respiratory variations of left ventricular flow

Conclusion: Transient left ventricular remodeling emerged as a powerful predictor of cardiac tamponade. The highest accuracy was achieved with a threshold value of ≥50% of LVRT.

P3395 Pericardioscopy after percutanous balloon pericardiotomy: facilitated endoscope placement and verification of the pericardial window

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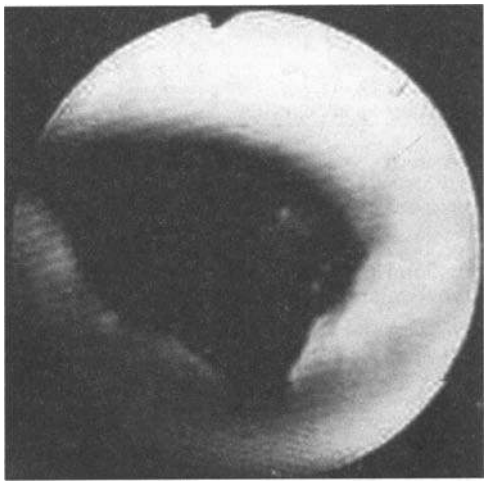
Placement of a large sheath-dilator set for percutaneous pericardioscopy (PCS) is often tedious and painful despite proper analgesia and local anesthesia. Since the introduction of percutaneous balloon pericardiotomy (PBP), controversial issue of its mechanism of action emerged. In order to elucidate this issue we selected 6/22 pts in whom PBP was performed (66.7% males, mean age 58.6 years) for PCS with Olympus HYF-1T, 16F flexible endoscope. Gradual dilatation of entry site from the 9F size needed for PBP to 16.5F for PCS was performed over a J 0.038" guidewire. Procedure was successful in 5/6 pts, while in one pt it was aborted before the advancement of the endoscope. Dilatation of the entry site was facilitated after PBP with no significant pain in 5/5 pts in comparison to other 24/29 PCS procedures performed without previous PBP (painful procedure in 75% of pts)($p < 0.01$). PCS in all five cases confirmed the triangularly shaped appearance of the pericardial window due to the type of the balloon catheter applied for PBP (Schneider Trefoil-Meier) (figure). There were no complications in five pts included in the study. However, in the sixth pt the procedure had to be canceled due to the cardiac perforation by a 9F dilator. That was the consequence of the sheath dislocation after PBP and further pericardial dilatation over a thin PBP guidewire. Cardiac perforation was successfully treated by surgery.



In conclusion, PCS was facilitated by previous PBP due to the pericardial dilatation with a large size balloon catheter. PCS can successfully visualize the pericardial window created by PBP. To avoid complications, it is essential to keep the PBP sheath in place and to exchange the guidewire used for balloon catheter with a thicker J wire for PCS introducer set.

EMERGING CONCEPTS IN DILATED CARDIOMYOPATHY

P3396 Contractile reserve identified by dobutamine stress echocardiography predicts maximal exercise tolerance in patients with dilated cardiomyopathy

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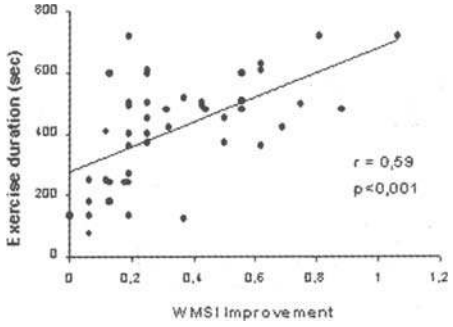
In order to investigate the relationship between contractile reserve, identified by dobutamine stress echocardiography (DSE), and maximal exercise tolerance (MET), we have evaluated 48 pts with dilated cardiomyopathy (DCM) who underwent DSE and maximal bicycle ergometry. DSE was performed using 5, 10, 20, 30 and 40 mcg/kg/min infusions, in progressive stages lasting 5 minutes each. Contractile reserve was assessed using improvement between resting and peak DSE left ventricular (LV) wall motion score index (WMSi). WMSi was calculated according to the 16-segment model. Bicycle ergometry was performed in 25 W increments, lasting 2 minute each, until 150 W or until MET was reached. LV end-systolic (ESVi) and end-diastolic (EDVi) volume indexes, as well as EF, in rest and peak DSE, were calculated using Simpson's biplane formula.

Results: Mean exercise duration was 410 ± 167 sec, whereas mean improvement in WMSi was 0.34 ± 0.24 ($p < 0.001$, vs. baseline). Cardiac index improved from 2.25 ± 0.85 to 3.51 ± 1.35 L/min/m^2 ($p < 0.001$). Similarly, ESVi and EDVi decreased in peak DSE compared to baseline (90.3 ± 30.8 vs. 82.2 ± 32.4 ml/m^2, $p < 0.001$, and 110.1 ± 30.4 vs. 108 ± 30.6 ml/m^2, $p < 0.05$, respectively), whereas EF increased (19.2 ± 8.4 vs. 25.8 ± 12%, $p < 0.001$). Univariate analysis, that included DSE induced changes in EF, ESVi, EDVi, WMSi, and CI, revealed that exercise duration correlated with change in WMSi ($r = 0.59$, $p < 0.001$) (figure) and change in EF ($r = 0.49$, $p < 0.001$). However, multiple linear regression showed that the only predictor of maximal exercise duration was change in WMSI ($p < 0.001$).



Conclusion: Our data indicate that contractile reserve assessed by DSE is a good predictor of MET in pts with DCM, suggesting that DSE may be a valid alternative for pts who can not exercise.

P3397 Depressed heart rate variability is associated with poor prognosis in non-ischaemic dilated cardiomyopathy

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Prognostic value of heart rate variability (HRV) in patients with non-ischaemic dilated cardiomyopathy (DCM) is not as well established as in post-infarction pts or pts with heart failure of various etiology.

Methods: HRV analysis was performed using 24 hr digital Holter recordings in 69 DCM pts (age 40 +– 12 yrs, 60 M, mean EF 31 +– 10%, 19 pts in NYHA III/IV) who were then followed for mean 20 (6–35) months. Also analysed were arrhythmia, 12 lead ecg, demographic, clinical and haemodynamic variables.

Results: during follow-up cardiac events occurred in 18 (26%) pts (10 deaths, 8 transplantations). Age, gender, arrhythmia, duration of symptoms, history of syncope were not significantly associated with prognosis both in multi- and univariate Cox proportional hazards analysis. Parameters significantly associated with prognosis are given in the table:

	Cox univariate		Cox multivariate	
Parameter	OR (95% CI)	p value	OR (95% CI)	p value
Bundle branch block	5.24 (2.05–13.42)	0.006	–	NS
NYHA III or IV	8.44 (3.00–23.70)	<0.00005	–	NS
EF (per 10% increase)	0.29 (0.15–0.57)	0.0003	0.18 (0.07–0.45)	0.0003
SDNN (per 10 ms increase)	0.72 (0.62–0.84)	<0.00005	0.67 (0.55–0.81)	<0.00005

Conclusions: HRV is independently associated with prognosis in non-ischaemic DCM pts.

P3398 Usefulness of cardiac natriuretic peptide as a neurohumoral marker of impaired coronary microcirculation in patients with dilated cardiomyopathy: relationship between coronary flow reserve and neurohumoral factors

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The abnormalities of coronary microcirculation and augmentation of neurohumoral factors, including atrial and brain natriuretic peptide (ANP and BNP), and Norepinephrine (NE) has been described in pts with dilated cardiomyopathy (DCM). The neurohumoral factor is receiving growing attention as a non-invasive marker for the failing left ventricular (LV). However there was no reports of the association between neurohumoral factors and coronary circulation. This study was designed to investigate the relationship between neurohumoral factors and the myocardial blood flow reserve in pts with DCM, using a Doppler flow wire (DFW).

Methods; We studied coronary flow velocities in 12 pts with DCM using a 0.014 inch Doppler guide wire in the proximal portion of the left anterior descending coronary artery at rest and during adenosine (AD)-induced (intravenous 150 ug/kg/min adenosin tri-phosphate infusion) hyperemia. Coronary flow reserve (CFR) was calculated as the ratio of AD-induced APV/based APV (APV; averaged peak velocity). Hemodynamic parameter of the LV was estimated as pulmonary capillary wedge pressure (PCW), measured by Swan-Ganz catheter, ejection fraction (LVEF) and end-diastolic volume index (LVEDVI) by leftventriculogram. Plasma levels of NE, ANP and BNP were sampled simultaneously. The pts was divided into two groups, group N (CFR > 2.0, n = 7) and L (CFR ≤ 2.0, n = 5), according to CFR value.

Results; Although hemodynamic parameter of the LV were similar with two groups, plasma levels of neurohumoral factors were significantly higher in group L than in group N. Plasma level of neurohumoral factors were significantly increased in group L. In group N, the plasma level of BNP is moderately elevated despite normal ANP and NE.

	CFR	Norepinephrine	ANP	BNP	LVEF	LVEDVI	PCW
Group N	2.90 ± 0.87	270 ± 81	30 ± 37	99 ± 174	39 ± 20	138 ± 72	16 ± 14
Group L	1.67 ± 0.35	521 ± 24	202 ± 102	572 ± 301	31 ± 15	162 ± 51	10 ± 5
P value	0.016	0.002	0.002	0.006	0.48	0.54	0.34

(mean ± SD.)

These data indicate that low CFR was associated with highly elevated neurohumoral factors, suggesting impaired coronary microcirculation and poor prognosis.

Conclusions, The abnormal neurohumoral factors may predict low CFR, indicating microciculatory disturbance in pts with DCM. The pts with normal CFR may have solely damaged myocardium because of moderately elevated BNP. The current study provides new insights into the interplay between the CFR and cardiac natriuretic peptide system in pts with DCM.

P3399 Mitochondrial haplotypes associated with idiopathic dilated cardiomyopathy

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Dilated Cardiomyopathy (DCM) is a recognised manifestation of mitochondrial disease (MTD) and in some cases the only clinical abnormality. Although specific mtDNA mutations affecting tRNAleu have been identified in MTD associated with DCM, it is not known whether underlying variations in mitochondrial DNA predispose to isolated DCM. In other disorders ancestrally related founder mitochondrial haplotypes associate with disease susceptibility (eg type 2 diabetes). Clustering of particular mitochondrial haplotypes with idiopathic dilated cardiomyopathy would suggest possible pathogenic founder mutations of mtDNA.

We evaluated mitochondrial variants within the variable non-coding region of mtDNA in 24 unrelated South African DCM patients aged 16–79 yrs and 19 age-matched normal South African controls. There was no apparent MTD, autosomal dominant inheritance, or diabetes. Echocardiography and right and left heart catheterisation was used to confirm diagnosis. A 400 bp hypervariable region in the large noncoding region of mtDNA was amplified from leucocyte DNA from DCM patients and controls using PCR and the products sequenced with an automated sequencer.

Sequence analyses confirmed 4 different African haplotypes in both DCM patients and controls. A polymorphism at position 16189 which is associated with diabetes was equally prevalent in DCM patients and controls. However, there was a significantly higher prevalence ($p = 0.046$) of an uninterrupted long C-tract associated with the 16189 polymorphism which frequently gave rise to length variation in DCM patients (n = 11; 46%) compared to controls (n = 3; 16%).

The co-segregation of the long C-tract haplotype with DCM suggests that there may be a founder mitochondrial DNA haplotype which predisposes to DCM and that variation in this region of mtDNA may subtly affect mitochondrial function.

P3400 Removal of cardiodepressant factor(s) in dilated cardiomyopathy by immunoadsorption

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Six patients with dilated cardiomyopathy (DCM) received immunoadsorption (IA) therapy. During IA, the cardiac index increased from 2.3 to 2.9 l/min/m^2 ($p < 0.05$), and systemic vascular resistance decreased from 1373 to 1028 dyne*s*cm^{-5} ($p < 0.05$). The underlying mechanisms of these haemodynamic effects as mediated by IA remains unclear.

Methods: In-vitro experiments were performed to determine the influence of factor(s) (>100 KD) eliminated by IA in DCM patients on the intracellular cytoplasmatic calcium transient ($[Ca^{2+}]_{i\ syt}$-$[Ca^{2+}]_{i\ dia}$) and on myocyte shortening of isolated, fieldstimulated (1 Hz; 2 ms; 10–30 V) rat cardiac myocytes. IA was also performed with the blood of 6 healthy donors (controls). We investigated the effects of factor(s) (>100 KD) in the irrigation solution (IS) of IA columns on myocyte shortening and on calcium transient of myocytes loaded with CA^{2+}-sensitive fluorescent probe, (Fluo-3AM). IS was dialysed (MWCO 100 KD, 1:100, 1:1000) and heated (56°C for 30 min) for inactivation of complement. After incubation of cardiac myocytes with IS (1:30; 1:20; 1:10; 1:5; 1:2), myocyte shortening and calcium transient were analysed by confocal laser scanning microscopy (125 images/sec).

Results: IS of DCM patients (n = 6) caused immediate and dose-related decrease of calcium transient (1:30: 88.3%; 1:2: 65.7% – $p < 0.05$) and of myocyte shortening (1:30: 80.3% 1:2: 64.8% – $p < 0.05$). In contrast, IS of controls (n = 6) did not influence calcium transient and myocyte shortening of cardiac myocytes. In IS, different cytokines (e.g., TNF-alpha, interleukin 6, 8 and 10) were not detectable.

In conclusion, IA eliminates cardiodepressant factor(s) in DCM.

P3401 Tumor necrosis factor-alpha (TNF) expression in idiopathic dilated cardiomyopathy (IDCM): correlation to extend of myocardial inflammation

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Cardiac overexpression of TNF in transgenic mouse models resulted in a phenotype of systolic dysfunction with or without infiltration by inflammatory cells. In these models myocardial expression of TNF regulated the extend of inflammatory cell infiltration.

To investigate the relationship of myocardial inflammation and TNF we determined TNF expression (mRNA and protein) in 14 consecutive patients with IDCM who underwent endomyocardial biopsy. Two groups were compared: A group of patients (n = 8) without inflammation by immunohistological evaluation and a group (n = 6) with inflammation. Myocardial TNF mRNA expression was determined by competitive RT-PCR, TNF protein was detected by immunohistochemistry, TNF serum levels were determined by ELISA. Results are summarized in the table.

Results:

	IDCM with inflammation (n = 6)	IDCM without inflammation (n = 8)	P-value
Age (yrs)	50.8 (2.7)	46.6 (5.1)	0.487
Sex (female/male)	1/5	1/7	
Ejection fraction (%)	39 (8)	43 (8)	0.711
TNF serum conc. (pg/mL)	3.0 (0.55)	1.35 (0.20)	0.017
TNF mRNA (arbitrary unit)	1.54 (0.22)	0.81 (0.09)	0.020

Data are given as mean (SEM) and were analyzed using unpaired two-tailed t-test. A $P < 0.05$ indicated that significant differences existed.

In conclusion, TNF expression and serum levels were linked to the extend of inflammatory activation within the myocardium. In analogy to transgene models, it can be speculated that TNF itself might regulate the recruitment of inflammatory cells in human idiopathic dilated cardiomyopathy, too.

P3402 Cytotoxic perforin+ and TIA-1+ infiltrates are associated with cell adhesion molecule expression in dilated cardiomyopathy

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Dilated cardiomyopathy (DCM) is etiopathogenically linked to inflammatory cardiomyopathy (InfCM), being characterized by cardiac failure with evidence for intramyocardial inflammation. We recently reported that the diagnosis of InfCM based on CD3+/CD2+ infiltrates does not reflect cytotoxic T lymphocytes (CTLs: perforin+ and TIA-1+ phenotypes).

Methods and Results: Immunohistochemically stained endomyocardial biopsies obtained from n = 97 DCM patients were evaluated for various phenotypes of infiltrates and expression of endothelial cell adhesion molecules (CAMs). Biopsies superceding >7.0 CD3+/CD2+ lymphocytes/mm^2 were considered positive for InfCM (n = 45, 46%) and those with concurrent abundance of >3 endothelial CAMs (n = 63, 65%) positive for CAMs, the two diagnostic approaches correlating significantly with one another ($p = 0.0002$). Whereas CTLs did not correlate with the InfCM criteria (perforin+: $p = 0.78$; TIA-1+: $p = 0.37$), perforin+ ($p = 0.0002$) and TIA-1+ CTLs ($p < 0.0001$) correlated with CAMs evaluation. CTLs did not correlate with CD3+, CD2+, CD4+, CD8+ lymphocytes and Mac-1+/27E10+ macrophages ($p > 0.05$), but with CD18+, LFA-1+, VLA-4+ lymphocytes and CD57+ NK-cells ($p < 0.02$). Except for HLA class I and HLA DR, CTLs correlated with endothelial CAMs (ICAM-1, VCAM-1, LFA-3, CD29, CD62E and CD62P; $p < 0.01$).

Conclusions: In contrast to the diagnosis of InfCM based on immunologically naive CD3+/CD2+ lymphocytes, the CAMs based approach does also reflect perforin+/TIA-1+ intramyocardial infiltrates in DCM. These CTLs coexpress adhesion related lymphocyte activation phenotypes (b2-integrins, VLA-4) and NK-cellular antigens. Our data are in accordance with current immunological concepts repealing the formerly postulated dichotomy of adhesion and secretory events in the lethal attack exerted by CTLs.

P3403 Human endothelial cells as tool for the detection of β1 mimetic autoantibodies in patients with dilated cardiomyopathy

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Background: Autoantibodies (AA) of β1 receptors are thought to play a pathogenic role in patients with dilated cardiomyopathy (DCM).

The β1 receptor stimulation leads to an increased level of cAMP resulting in a raised heart rate. The measurement of the modulation of beating frequency in cultured animal myocytes was used to detect the absence or presence of β1 AA. Up to now, no system was aviable which allows to test human β1 AA in human cells. It was shown that human umbilical vein endothelial cells (HUVECs) carry β1 receptors.

The aims of our study are wheather the β1 receptors in HUVECs are functionally coupled to the intracellular cAMP level and wheather in the serum of DCM patients an autoantibody could be detected which imitates a β1 stimulating effect.

Methods: We used sera from 10 human donors, 3 healthy volunteers and 7 DCM patients with markedly reduced left ventricular function (LVEF < 20%). The IgG fraction was isolated by ammonium sulfate precipitation (saturation of 33%). The precipitates were washed, dissolved in physiological buffer and dialyzed for 72 h. HUVECs of the 2nd passage were incubated with the IgG fractions for 5 min in the presence of phosphodiesterase inhibitors (IBMX 10 μM, RO-20–1724 10 μM). The cAMP level was measured by a commercial enzyme immunoassay kit. As internal standard we used isoprenalin (1 μM, 5 min), as selective β1 antagonists bisoprolol or metoprolol (1 μM, 15 min prior to stimulation).

Results: Isoprenalin stimulates the cAMP-production in HUVECs in a concentration dependend manner and is reduced to the control level by coincubation with metoprolol. The IgG fraction from 6/7 DCM patients lead to a distinct increase of the cAMP levels. The stimulation of cAMP production is reduced by preincubation with the antagonists bisoprolol or metoprolol. The IgG fraction of 2/3 healhty volunteers has no stimulating effect on the cAMP level, however, in one case an increase of cAMP level was observed.

Conclusion: A stimulating effect of β1 agonists (drugs) on the cAMP level can be measured in human endothelial cells. Therfore this cell type offers a tool to evaluate the β1 mimetic effect of AA. Indeed, IgG fractions from serum of DCM patients show distinct stimulating effects on the cAMP levels mediated by β1 receptors. These findings demonstrate in human cells for the first time the β mimetic effects of autoantibodies in DCM patients.

P3404 Polymorphisms in the β1-, β2- and β3-adrenergic receptor genes among patients with congestive heart failure

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Genetic polymorphisms have previously been defined in the β2- and β3-adrenergic receptor (βAR) genes, whereas no polymorphisms have been described in the β1AR gene. We searched for possible polymorphisms in the β1-receptor gene by PCR amplification and automated sequencing of DNA from peripheral leucocytes, and found two previously undetected mutations. 185 patients with heart failure and 76 healthy controls were genotyped for the novel β1-polymorphisms and for defined β2- and β3- polymorphisms by RFLP and hybridization. The association with long-term survival was investigated.

Results: See table.

Genotypes in patients with heart failure

	β1AR		β2AR		β3AR
	aa N-term	aa C-term	aa16	aa27	aa64
Wildtype (n)	122	10	25	54	167
Mutation (n)	61	174	159	126	18
Survival	p = 0.004	n.s.	n.s.	n.s.	n.s.

aa = aminoacid, Mutation = mutation in its heterozygote and homozygote forms

The allele frequency was not significantly different between patients and controls for any of the polymorphisms.

Conclusion: We have discovered two novel genetic mutations in the β1-receptor gene, one of which was significantly associated with improved 5-years survival. A possibly defect in the function and decreased sensitivity of the β1-receptor might explain this unexpected association.

P3405 Association of preformed IgG3 antimyosin antibodies to endocardial infiltrates after heart transplantation for patients with idiopathic dilated cardiomyopathy

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The significance and the mechanisms of endocardial infiltrates (EI) in cardiac allografts remains uncertain. Dilated cardiomyopathy patients (DCM) with statistically raised levels of preformed autoantibodies against myosin heavy chain (mhc) have previously been shown to be have a greater frequency of rejection episodes following cardiac transplantation (Tx). The relationship of these antibodies to the incidence of EI in endomyocardial biopsies (EMB) in patients has not been evaluated.

The **Objective** of the study was to determine whether the frequency of EI was related to the indication for Tx, the rejection status and to ELISA levels of preformed antimyosin antibodies at class and subclass level.

Results: - Detection of EI (no. and frequency) in EMB from patients Tx for DCM, (n = 64) was higher than in patients with IHD (n = 53); 61%, 1.54 ± 0.58 *vs* 45%, 0.90 ± 0.37 respectively. Frequency of EI in pts with and with rejection was different in the two groups; 1.86 ± 0.64 *vs* 0.58 ± 0.33, $p < 0.05$ in the DCM group and 0.9 ± 0.49 *vs* 1.0 ± 0.47, p = NS in pts transplanted for IHD. Association of patients with EI to preformed antibody +ve or −ve status in the DCM group differed from IHD patients. Frequency of EI between IgM antibody positive and negative patients did not differ in the groups transplanted for DCM or IHD. A select group of patients transplanted for DCM had a higher activity of preformed IgG3 Abs. Incidence of EMB with EI to IgG3 positive DCM patients was significantly higher than IgG3 negative pts. IgG3 Ab positive patients also had a greater incidence of ISHLT grade 3 as the initial episode of rejection than did Ab negative patients: 50% (5/10) *vs* 15% (6/40), $p < 0.05$.

Conclusion: Pro-inflammatory characteristics of preformed IgG3 Abs in serum of patients with DCM may influence the immunological response to the development of EI and the rejection process after cardiac transplantation.

P3406 Allosteric effects of domain-specific human, rabbit, and monoclonal mouse antibodies on β1-adrenergic receptor function

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Purpose: Antibodies capable of modulating the response of certain G protein-coupled receptors have been found in several human autoimmune diseases. The aim of our study was to further elucidate the possible pathophysiological significance of (auto-) antibodies targeting the *human* β1-adrenergic receptor (anti-β1-AR), which is still discussed controversially.

Methods: To investigate the possible effects of anti-β1-AR on receptor function, we generated *heterologeous* antibodies to selected domains (amino-, carboxyterminus, and 2nd extracellular loop) of the human β1-AR in rabbits (polyclonal) and mice (monoclonal). Their immunological and functional properties were characterized using synthetic receptor-peptides as well as intact recombinant *human* β1-AR, and compared with those of selected anti-β1-AR autoantibodies (n = 8), representative for a previously defined subgroup of cardiomyopathic patients.

Results: Rabbit, mouse and human antibodies targeting the 2nd extracellular receptor domain (EC_{II}) preferentially bound to a native receptor conformation, and all of them impaired radioligand [^{3}H]-CGP 12177 binding to the receptor. However, their effects on receptor-mediated signaling differed considerably: rabbit and mouse anti-β1-EC_{II} decreased both basal *and* agonist-stimulated intracellular cAMP-production (and corresponding protein kinase A activities) in a concentration-dependent manner; in contrast, all patient autoantibodies increased basal, and most of them (n = 6/8) even further increased agonist-stimulated receptor activity, *i.e.* acted as receptor-sensitizing agents. Besides, we also detected some partial agonist-like human anti-β1-EC_{II}, which *in*creased basal but *de*creased agonist-simulated receptor activity (n = 2/8).

Conclusion: Antibodies recognizing a same small epitope of the β1-AR can have very divergent allosteric effects on the full scale from inhibitory to agonist-promoting activities. Human anti-β1-EC_{II} might activate cardiac β-AR also *in vivo* and thus be of pathophysiological significance in certain heart diseases.

P3407 Dobutamine stress echocardiography in patients with dilated cardiomyopathy

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Background: Dilated cardiomyopathy (DCM) and coronary artery disease are the most common causes of congestive heart failure. Dobutamine stress echocardiography (DSE) is routinely used to evaluate the contractility in patients (P) with ischemic heart disease. The aim of this study was to investigate whether contractile reserve evaluated by DSE is a powerful prognostic predictor of P with DCM.

Methods: Therefore 41 patients (49 ± 7 years) with DCM and congestive heart failure (NYHA III) were examined. After optimal medical treatment (vasodilators, diuretics) and avoiding inotropic or β-blocking drugs for one week echocardiography (at rest and under low-dose infusion) was performed. Using M-mode echo-cardiography morphological parameters and systolic function (fractional shortening FS; %) were determined. LV diastolic function was assessed by Doppler-echocardiographic analysis of the diastolic transmitral flow: the maximal early (V_E) and late velocity of diastolic filling; the E/A-ratio; the deceleration (DT) and the isovolumetric relaxation time (IVRT). To determine the contractility reserve we measured the ejection fraction (EF), LV enddiastolic and endsystolic volume at rest and during DSE. The contractility reserve index" was calculated according to the formula: EF_{stress} minus EF_{rest} divided by the EF_{rest}. The result is multiplicated with 100.

Results: Impaired FS (15 ± 2%), increased LV cavity size (LV enddiastolic diameter: 69 ± 5 mm), diastolic dysfunction were documented in all P. After a follow-up period of 25 ± 4 months the clinical conditions were unchanged in 16 P, improved in 8 P and worsened in 17 P (2 P died of sudden cardiac death). Multivariate stepwise logistic regression analysis showed that the only the "contractility reserve index" was independently related to the prognosis of P with DCM.

Conclusion: P with DCM and a poor β-adrenergic contractile reserve ("negative contractility reserve index") had an unfavorable outcome. "Contractility reserve index" was evaluated by DSE seems to be prognostic significant in P with DCM.

P3408 Alterations in circulating plasma adenosine in dilated cardiomyopathy: a baseline and dipyridamole stress study

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Dipyridamole is a popular vasodilator stress which acts through accumulation of endogenous adenosine mainly produced by the myocardium. Heart failure is characterized by chronically increased adenosine levels, which have been putatively involved in the initiation and progression of disease.

Aim of the study was to assess whether patients with dilated cardiomyopathy (DC) have an abnormal response in terms of endogenous plasma adenosine (ADO) accumulation, to an adenosinergic stress as high dose dipyridamole when compared to coronary artery disease (CAD) patients.

Two groups of patients were studied: I (n = 9 pts, mean age 66 ± 6 years) with idiopathic DC, dyspnea NYHA class 2 to 4, EF < 35%, and II (n = 15 patients, mean age 55 ± 10), with EF>50% and known or suspected CAD. The 2 groups differed in plasma ADO at baseline (I = 281 ± 25 vs II = 211 ± 9 nM/l, $p < 0.0001$) and at peak stress (I = 422 ± 124 nM/l vs II = 756 ± 105 nM/l, $p < 0.0001$), with DC patients showing a blunted% increase in plasma ADO after dipyridamole (I = 123 ± 21% vs II = 367 ± 67, $p < 0.0001$) and an earlier time to peak stress (I = 2' vs II = 12' from onset of infusion).

In conclusion, a profound derangement in adenosinergic system is detectable in patients with DC in whom plasma adenosine levels are abnormally elevated at baseline and dipyridamole-induced plasma adenosine increase shows an earlier peak, a flat response and a lower plateau when compared to CAD patients.

P3409 The elusive link between coronary flow and myocardial contractile reserve in idiopathic dilated cardiomyopathy: a transthoracic and transoesophageal echo study

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A defect in systolic myocardial function and impairment in coronary flow reserve due to microcirculatory disturbances characterize idiopathic dilated cardiomyopathy (DC).

Aim of this study was to assess the interrelationship between contractile reserve and coronary flow reserve (CFR), assessed by TTE and TEE stress echo respectively, during dipyridamole test in DC patients.

Two groups of pts were evaluated: I, with idiopathic DC (24 patients), dyspnea NYHA class 2–4, EF < 35%, age 60 ± 13 years; and II, healthy controls (11 subjects) with EF >50%, age 57 ± 8, angiographically normal coronary arteries and chest pain syndrome of non-cardiac origin. All patients underwent transthoracic and transesophageal echocardiography monitoring during dipyridamole (DIP) infusion, up to 0.84 mg/kg over 10'. Wall Motion Score Index (WMSI) was calculated at rest and peak stress in a 16 segment model of left ventricle, each segment ranging from 1 = normal to 4 = dyskinetic. CFR was reduced in DC (Group I = 2.1 ± 0.8 vs II 3.2 ± 0.9, $p < 0.002$). Within group I there was no interpatient correlation between changes in CFR and left ventricular contractile response ($r = 0.4$, p = ns). Of the 7 functional non-responders (rest-stress variation in WMSI <0.44), 4 also were physiologic non-responders (CFR < 2); of the 17 functional responders (WMSI > 0.44), 11 also were physiologic non-responders (CFR < 2).

In conclusion, DC patients as a group show a significant impairment in coronary flow reserve in spite of normal coronary arteries. At individual patient analysis, contractile myocardial response and physiologic flow response to DIP stress are substantially heterogeneous and asymmetrically affected in DCC patients.

P3410 Stable improvement of left ventricular function after partial left ventriculectomy during medium-term follow-up: results of an invasive study

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While partial left ventriculectomy (PLV) efficiently reduces left ventricular (LV) volumes and increases EF, the duration of this effect is not known. We report medium-term effects of PLV on LV function in 16 patients (mean age 47, 13 men) with end-stage heart failure due to non-ischemic dilated cardiomyopathy. Right heart catheterization and ventriculography were performed preoperatively and at early (range 10–18 days) and medium-term (range 6–9 months) follow-up (F/U).

Results: LV end-diastolic (EDVi) and end-systolic (ESVi) volume indexes, EF, systolic LV major-to-minor axis ratio (L/D ratio) and pulmonary capillary wedge pressure (PCWP), before PLV (preOp) and at early and medium-term F/U are shown in the Table. EDVi, ESVi, EF and L/D ratio did not change between early and medium-term F/U ($p > 0.05$, for all).

Early and medium-term effects of PLV

	EDVi (ml/m²)	ESVi (ml/m²)	EF (%)	L/D Ratio	PCWP (mmHg)
Preop	166 ± 30	127 ± 25	24 ± 7	1.44 ± 0.27	20 ± 10
Early F/U	100 ± 22*	60 ± 15*	40 ± 11*	1.93 ± 0.32*	15 ± 5*
Mid-term F/U	102 ± 15*	63 ± 12*	38 ± 8*	1.86 ± 0.28*	19 ± 8

*, $p < 0.05$ vs. preop

Conclusion: PLV leads to reduction of LV volumes and stable improvement in EF and LV geometry during medium-term F/U.

P3411 Left ventricular inotropic reserve predicts improvement in ejection fraction after long-term carvedilol therapy in non-ischaemic cardiomyopathy

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In non-ischemic cardiomyopathy (NICM) chronic beta-blocker therapy is associated with significant improvement in left ventricular (LV) ejection fraction (EF). The purpose of this study was to determine whether higher baseline LV inotropic reserve, defined as the increase in LVEF in response to intravenous dobutamine infusion (DoDEF), predicts the improvement in LVEF after long-term carvedilol therapy in patients with NICM. Fifteen patients underwent baseline assessment of LVEF, at rest and after a 10-minute intravenous infusion of dobutamine at 10 microgm/kg/min, using equilibrium radionuclide ventriculography technique. Age 46 ± 12 yr, 9 males, functional class (FC) 2.6 ± 0.5, duration of CHF (Dur) 60 ± 34 mo, LVEF 18 ± 6%, DoDEF 9 ± 8. Carvedilol was started and up-titrated to the maximally-tolerated or target dose, 62 ± 30 mg daily, and maintained for 13 ± 7 mo. Resting LVEF was measured after this follow-up period. Resting LVEF increased to 29 ± 12%. Patients were divided into 2 groups based on baseline DoDEF: above and below mean. Patients with higher than average baseline DoDEF (group 2) had a significantly higher improvement in LVEF (DEF 19 ± 8) compared to patients with lower than average baseline DoDEF (Group 1, DEF 8 ± 8), p = 0.02, despite comparable other baseline characteristics.

Group 1:	n = 11			
Baseline:	Dur 68 ± 36,	EF 17 ± 5,	DoΔEF 6 ± 3,	FC 2.5 ± 0.5
Follow-up:	Dose 57 ± 30,	EF 25 ± 10,	ΔEF 8 ± 8,	p = 0.03 for EF increase
Group 2:	n = 4			
Baseline:	Dur 40 ± 19,	EF 22 ± 7,	DoΔEF 19 ± 12,	FC 2.5 ± 0.6
Follow-up:	Dose 75 ± 29,	EF 41 ± 11,	ΔEF 19 ± 8,	p = 0.03 for EF increase

Inter-group comparison: p = NS for Dur, baseline EF, FC, and dose; p = 0.02 for follow-up EF and p = 0.04 follow-up ΔEF.

Conclusion: NICM patients with higher LV inotropic reserve derive higher improvement in LVEF from carvedilol therapy.

P3412 Mutation analysis of cardiac and skeletal actin genes in dilated cardiomyopathy

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Idiopathic dilated cardiomyopathy (DCM) is a syndrome characterised by enlargement and impaired contractile function of the heart without a definable cause. It is a major cause of heart failure, and one of the most common indications for heart transplantation. DCM is familial in about a quarter of cases, suggesting that genetic factors play an important role in its aetiology.

Recently, missense mutations in the gene for cardiac actin have been identified in members of 2 small unrelated families with DCM, and a causal role postulated. However, the frequency of cardiac actin mutations in patients with DCM is unknown. Furthermore, cardiac and skeletal alpha actin genes are co-expressed in the sarcomere of cardiac myocytes; and given the predominant expression of the skeletal actin isoform in the adult human heart, we postulated that the skeletal actin gene was now implicated as a candidate gene in DCM.

Using single strand conformation polymorphism (SSCP) analysis and direct sequencing of abnormal conformers, we screened all exons of the cardiac and skeletal actin genes for mutations in 11 affected subjects from 8 families with autosomal dominant DCM, and 46 unrelated probands with idiopathic DCM. Although a number of silent polymorphisms were identified, no missense mutations were detected in either actin gene.

These results suggest that cardiac actin gene mutations are not a major cause of idiopathic DCM, and provide no support for the possible involvement of the skeletal actin isoform in this disease.

P3413 Impaired coronary vasodilating capability is a mechanism for worsening of left ventricular function during stress in early stage dilated cardiomyopathy

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Patients with early stage dilated cardiomyopathy (DCM) show a blunted myocardial blood flow (MBF) response to atrial pacing tachycardia (Pac) and i.v. dipyridamole (Dip) possibly due to coronary microvascular dysfunction. Aim of the present study was to assess whether an abnormal coronary vasodilating capability is also associated with an impaired left ventricular (LV) functional response to stress in these patients.

Methods: The study population consisted of 17 DCM patients (age 43 ± 10, 13 males) (NYHA class I-II, angiographically normal coronary arteries, LV EF < 50%) and of 8 normal subjects (age 46 ± 8, 4 males). LV function was assessed at rest (R) and durimg Pac by equilibrium radionuclide angiography. Global LV EF as well as regional LV EF in the septal (S) and in the postero-lateral (PL) walls were measured. On the same day, absolute global and regional MBF were also obtained by 13N-Ammonia and positron emission tomography at R, during Pac and after Dip (0.56 mg/kg in 4 min).

Results: Heart rate, mean arterial pressure and rate pressure product at R and during Pac were not significantly different between patients and normals. Patients, as compared to normals, showed a similar global MBF at R (0.85 ± 0.24 vs 0.91 ± 0.14, ns) but a lower MBF during Pac (1.22 ± 0.58 vs 1.96 ± 0.72, $p < 0.01$) and after Dip (2.02 ± 0.76 vs 3.64 ± 0.75, $p < 0.01$). Patients also showed a decrease of global LV EF during Pac (from 36 ± 9 to 32 ± 9, $p < 0.01$) which was not seen in normals (from 58 ± 5 to 60 ± 6, ns). There was a significant correlation between regional MBF increase (Pac/R MBF) and regional LV EF change during pacing (Pac-R LV EF) in the S ($r = 0.65$, $p < 0.01$) but not in the PL wall ($r = 0.21$, ns).

Conclusions: Impaired coronary vasodilating capability is a mechanism for worsening of regional and global LV funcion during stress in patients with early stage DCM.

P3414 Mild dilated cardiomyopathy: benign or malignant disease?

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It was suggested that mild dilatation of left ventricle (LV) or slightly decreased LV ejection fraction (EF) are the major features of mild dilated cardiomyopathy (MDC). Furthermore, it was believed that its natural history, as well as the long-term outcome are advantageous in comparison to the advanced disease. In order to elucidate this issue we studied 40 pts, 80% males, mean age 50.4 ± 12.2 yrs, LV enddiastolic dimension 6.3 ± 0.8 cm, LV endsystolic dimension 4.9 ± 1.0 cm, LV EF = 48 ± 8.9%, mean symptom duration 36.3 ± 26.5 months. At initial assessment all pts underwent extensive clinical work-up, cardiac catheterization and EMB and were followed for 132 (34.8 ± 26.3) months, considering cardiac death and heart transplantation as end-points. Complete follow-up (FU) data were obtained for 20 pts (50%); 4/20 pts (25.0%) died and none was transplanted. According to LVEF (echocardiography) at the end of FU, pts were classified into four categories: improved, stable, deteriorated, and nonsurvived. At the end of FU improved, stable, deteriorated, and non-survived pts were found in 25%, 35%, 20%, and 20%, respectively. The analysis of LVEF differences in all four groups at the entry, did not demonstrate statistical significant difference ($F = 1.5$, $p > 0.05$). Improved IDC patients had initial LVEF 47.4 ± 5.0%, while at the end of FU 58.6 ± 6.8% ($t = -3.4$, $p < 0.05$). In stable IDC patients LVEF at the entry, and at the end of FU was 48.4 ± 9.3% and 48.6 ± 9.5%, respectively ($p > 0.01$). In IDC group who deteriorated the LVEF values were 53.0 ± 7.9% at the start of the study and 40.0 ± 8.3% at the end ($t = 3.9$, $p < 0.05$). LVEF of the patients who did not survive FU was 42.2 ± 1.9% at the entry.

In conclusion, this study MDC demonstrated that MDC is malignant disease.with significant number of patients who deteriorated or died. LVEF at the entry could not predict clinical outcomes, and therefore a different mechanism in the ominous clinical course e.g. arrhythmic, need to be considered.

P3415 Existence of a third chromosomal loci responsible for pure familial dilated cardiomyopathies

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Dilated cardiomyopathies (DCM) represent the first cause of heart transplantation. At least 25% of cases have a familial inheritance. Previous studies have demonstrated the genetic heterogeneity of the disease. Indeed, eight chromosomal locations accounting for pure forms (1q32, 9q13-22) or associated with cardiac and/or muscular disorders (1p1-q1, 2q11-22, 3p22-25, 6q23, 10q21-23) have been identified as well as mutations in cardiac actin gene in two unrelated families. Genetic linkage analysis were carried out on eight families from the French panel (157 individuals including 39 affected members and 25 unknown) with 26 microsatellite markers located in the eight known morbid loci in order to check the potential linkage between these loci and the disease in the families. Two families (18 and 15 members) are potentially linked to the 10q21-23 locus and one family (10 members) to the 3p22-25 locus. A linkage to the markers analyzed in the 6q23 and 9q13-22 regions was excluded for the eight families. For two families (21 and 45 members), all the known morbid loci can be excluded. Moreover, the involvement of the cardiac actin gene in the disease was excluded by SSCP analysis in these eight families. We can, therefore, conclude that there is at least one new chromosomal region responsible for DCM. So, a genomewide scan was carried out with 342 microsatellite markers on the most informative family (45 members including 10 affected). Ninety percent of the genome of this family has been excluded. The identification of the third locus responsible for pure DCM is ongoing.

P3416 Immunohistochemical changes in dilated cardiomyopathy during immunoadsorption therapy

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Seven patients with dilated cardiomyopathy (DCM) received a immunoadsorption (IA) therapy. During IA, the cardiac index increased from 2.2 to 2.8 l/min/m^2 ($p < 0.05$). The aim of this study was to analyse changes of chronic inflammatory process in myocardium induced by IA.

Methods: 7 patients with dilated cardiomyopathy (NYHA III–IV, ejection fraction <30%, stable medication) received one-time IA therapy at one-month intervals until month 3. Before and after (<7 d) IA therapy five right ventricular biopsies were obtained from all patients from the interventricular septum. Biopsies were fixed in 4% formalin and embedded in paraffin. The sections were 1 μm thick. In all cases, we excluded acute myocarditis according to the Dallas criteria. In addition to conventional histology, immunohistochemical staining was performed. The immunohistochemical staining procedure with the Labelled StreptAvidin-Biotin (LSAB) method was used for identification of inflammatory cells. The number of the cells were counted under high power magnification (400×) by two observers. The number of cells (cells/mm^2) was described as the mean value of ten counted high power fields. The following antibodies were used: anti CD3; -CD4; -CD8, CD45RO, HLA-DP.

Results:

	CD 3	CD 4	CD 8	CD45 RO
Pre IA	4.6	1.5	2.4	23.7
	(SE 1.2)	(SE 0.4)	(SE 0.6)	(SE 10.0)
Post IA	1.3	0.3	0.8	9.5
	(SE 0.4)	(SE 0.15)	(SE 0.2)	(SE 5.8)
	$p < 0.05$	$p < 0.05$	$p < 0.05$	$p < 0.05$

The reduction of inflammatory cells was paralleled by a decline of HLA-DP activation.

In conclusion, IA reduces the inflammatory process in myocardium of DCM patients.

P3417 Probing the immunological properties of the extracellular domains of the human beta1-adrenoceptor

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The human beta1-adrenoceptor is an immune target for autoantibodies with functional activity in cardiovascular disease such as idiopathic dilated cardiomyopathy and Chagas' disease. Different epitopes on the extracellular domains are involved. To study the immunological and pharmacological properties of three different epitopes on the extracellular domains of the human beta1-adrenoceptor, rabbits were immunized with peptides corresponding to a large domain in the N-terminal part of receptor and to its first and second extracellular loops. In contrast to the two other peptides, the first extracellular loop did not have immunogenic properties but acted as a hapten. Antibodies, affinity-purified with the three synthetic peptides were able to significantly ($p < 0.001$) immunoprecipitate the solubilized receptors from transfected Sf9 cell membranes, confirming that they recognize the target receptor. While antibodies against the N-terminal domain did not inhibit the binding of a radiolabeled antagonist to the receptor, those against the first and second extracellular loop showed non-competitive inhibition ($p < 0.05$). Similarly, only the two latter antibodies against the first ($p < 0.01$) and second ($p < 0.001$) extracellular loops of the receptor exerted a specific agonist-like effect on the receptor as assessed on neonatal rat cardiomyocytes in culture. Our results are in accordance with those found for human anti-receptor autoantibodies with functional effects. We conclude that not all extracellular epitopes give raise to functional autoantibodies. We also suggest that the cross-linking between the loops is necessary for functional activity.

P3418 Angiotensinogen gene polymorphism in Caucasian probands with hypertrophic cardiomyopathy

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Genetic polymorphisms in components of the renin angiotensin system (RAS) have been implicated in the expression of several cardiovascular diseases. The angiotensinogen (AGT) gene mutation with methionine to threonine substitution at codon 235 (M235T) has been associated with left ventricular hypertrophy in hypertension and in Japanese patients with non-familial hypertrophic cardiomyopathy (HCM). The aim of this study was to determine the effects of this polymorphism on Caucasian probands with HCM.

Methods: We conducted an allelic association study for angiotensinogen gene M235T polymorphism in 204 unrelated patients with HCM (44.6 ± 14.6 years, 40.2% females). Of these 92 (45%) had familial disease and 112 (55%) had no family history of HCM. As a control population we studied 244 healthy volunteers, without hypertension or left ventricular hypertrophy, matched to cases by ethnicity, age and gender. DNA was extracted from peripheral blood leukocytes and the exon 2 region of the AGT gene was amplified by PCR using allele-specific oligonucleotide primers, followed by restriction endonuclease digestion and gel electrophoresis.

Results: The AGT genotypes TT, MT and MM were present respectively in 18.6%, 49% and 32.4% of patients with HCM and in 17.2%, 52.9% and 29.9% of controls. The mean maximal left ventricular wall thickness of the three groups was 21.7 ± 5.6 mm, 20.7 ± 5.9 mm and 21.9 ± 6.3 mm respectively, p (ANOVA) = 0.348. Compared with a frequency of 44% among controls, the T allele frequency was 43% among all patients with HCM (chi2 = 0.024, p = 0.89), 45% in patients with non-familial HCM (chi2 = 0.041, p = 0.84) and 42% in subjects with familial HCM (chi2 = 0.111, p = 0.74) There was no significant difference between T allele frequency in patients with and without familial disease (chi2 = 0.242, p = 0.62). The T allele frequency in patients with HCM and a family history of hypertension was 27% vs 44% in patients with HCM and no family history of hypertension, chi2 = 1.671, p = 0.20. The relative risk of HCM between subjects with the TT genotype vs either the TM or MM genotype (odds ratio) was 1.1 [95% CI 0.6–1.7] for all HCM patients, chi2 = 0.1 and 0.9 [95% CI 0.5–1.8], chi2 = 0.001 in patients with familial HCM.

Conclusions: (a) Among Caucasian patients the M235T variant of the AGT gene is associated neither with familial nor non-familial HCM.

(b) The M235T polymorphism does not influence the degree of hypertrophy in Caucasians with HCM.

P3419 Intra-procedural myocardial contrast echocardiography: a routine procedure in catheter treatment for hypertrophic obstructive cardiomyopathy

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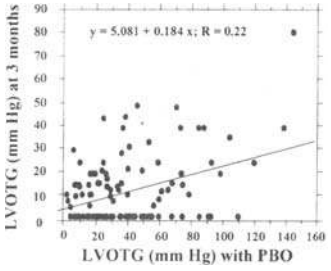
Introduction: Catheter treatment (PTSMA) for HOCM requires the exact definition of the septal myocardium to be ablated. We compared the predictive value of MCE and probatory balloon occlusion (PBO) of the presumed target vessel (TV) in 128 patients (pts.) in whom both approaches were used.

Results: A satisfactory reduction of the left ventricular outflow gradient (LVOTG) was achieved in 117 of these pts. (91%; from 59 ± 33 to 13 ± 15 mm Hg; $p < 0.0001$). LVOTG with PBO was 40 ± 30 mm Hg ($p < 0.001$). There was only a weak correlation between the LVOTG with PBO and the LVOTG after 3 months (See figure). PBO-induced reduction of the LVOTG was >30% in 76 pts. (65%) and >50% in only 55 pts. (47%). In 2 pts. the TV had to be changed after MCE because of echo contrast remote from the septal target area, i. e. papillary muscles or left ventricular free wall segments.



Conclusions: In case of a positive intra-procedural MCE study, PBO adds little information with respect to target vessel selection in PTSMA for HOCM. Furthermore, MCE is able to exclude alcohol necrotization of myocardium remote from the septal target area.

RESULTS OF OPERATIONS AND INTERVENTIONS IN CONGENITAL HEART DISEASE

P3420 Predictors of the right ventricular failure in patients after atrial switch for complete transposition

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Systolic function of the anatomic right ventricle (RV) to sustain systemic pressure long term after Mustard or Senning procedure in patients (pts) with TGA is a main concern in long-term follow-up.

Aim: To assess RV impairment, and to find factors predicting RV failure in pts. with TGA after atrial switch.

Material and methods: 61 asymptomatic pts aged 8-25 years with simple TGA, in mean time 10.5 ± 2.6 years after Mustard or Senning procedure. In all pts chest X-ray, 12-lead ECG and 24-hour ECG Holter monitoring, 2-D and colour coded Doppler echocardiography were performed. Systemic RV function was assessed by radionuclide first-pass angiography; exercise capacity by treadmill test according to modified Bruce protocol.

Results: Mean rest RV ejection fraction (EF) was 36.1 ± 7.7% and left ventricular EF was 52.1 ± 9.4%. 17 pts had rest RVEF < 32% (mean 27.4%) and 44 pts had RVEF ≥ 32% (mean 39.6%). Exercise capacity in both groups was good (mean 10 METs). Univariate analysis showed that pts with lower RVEF (<32%) had enlarged heart size on X-ray (CTR 0.50 vs 0.47, p = 0.03) longer QRS duration (111.3 vs 96.8 ms, p = 0.006), and more frequently rhythm disturbances (nodal rhythm, atrial flutter, paced rhythm) (p = 0.009). Also the group with RVEF < 32% more often had moderate or severe tricuspid regurgitation. There was no correlation with LVEF, age at the surgery, follow-up time, exercise capacity. Multivariate logistic analysis revealed close correlation with rhythm disturbances (p = 0.009) and QRS duration (p = 0.026, odds ratio-0.95, and 95% confidence interval 0.91–0.99).

Conclusions: RV function is significantly impaired in more than 1/3 of asymptomatic pts after atrial redirection procedure for TGA.

The best variables predicting RV failure were rhythm disturbances and QRS duration.

P3421 Exercise capacity, ventricular function and myocardial perfusion 10-years after arterial switch operation

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22 children (age 12.3 ± 2.2 years) with transposition of the great arteries (TGA) were investigated in mean 11.2 ± 2.9 years after arterial switch operation. Spiroergometry (treadmill, Bruce protocol) was performed in all patients; there was no significant difference in cardiopulmonary exercise capacity (anaerobic threshold, max. oxygen uptake) between patients and normal matched volunteers. On stress echocardiography there was a normal exercise induced increase of ventricular function in all patients; two of them had dyskinetic areas within the left ventricular myocardium. There was a significant increase of glycogenphosphorylase activity as a marker for myocardial ischaemia after exercise in five patients; four of those had adenosine induced perfusion defects in positron emission tomography (PET). Coronary flow reserve (CFR) was significantly reduced on PET scanning in all patients compared to normal healthy volunteers.

Conclusion: Children after arterial switch operation have a normal cardiopulmonary exercise capacity; nevertheless exercise induced ischaemia is apparent in some patients, whilst being clinically asymptomatic. Coronary insufficiency, reduced CFR and exercise induced perfusion defects may cause major problems in adulthood.

P3422 Evaluation of cardiac anatomy and function after long-term surgical repair of tetralogy of Fallot by magnetic resonance imaging

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Magnetic Resonance Imaging (MRI) represents a particularly useful diagnostic tool for the evaluation of cardiac malformations. After surgical repair, Tetralogy of Fallot (TOF) patients show several anatomical and functional abnormalities that mainly involve the right ventricle (RV) and therefore are not easy to be studied by conventional imaging tools. MRI seems to represent an ideal technique for the follow-up of such patients.

Methods: We studied 15 pts (11 males, 4 females), aged 22 ± 11 years (range 5–30), who were operated on 16 ± 8 years (range 2–21) before. All of them had been treated by a transannular patch. We also studied 15 age-matched controls. MRI was performed by using a conventional 0.5 T scanner. The study protocol included a spin-echo anatomical study, a gradient-echo functional evaluation of both ventricles, and a flow sensitive sequence positioned through the ascending part of the pulmonary artery. The functional examination included the evaluation of RV volumes, ejection fraction (EF) and mass.

Results: In all the pts MRI depicted the cardiac anatomy with an high image quality. Significantly higher RV volumes and masses than normals were seen in TOF pts. RV EF was preserved in 8 out of 15, while severely depressed function was seen in 4. These also had the greatest RV mass and exhibited a significant residual infundibular stenosis. Pulmonary regurgitation was a common feature (10 out of 15 pts) but was significant only in 3 pts (>1 Lt/min).

	Patients	Controls	p
RV diastolic volume (ml/m^2)	107 ± 41	83 ± 24	0.001
RV mass (g/m^2)	61 ± 8	28 ± 4	0.001
RV EF %	45 ± 11	58 ± 6	0.001
LV diastolic volume (ml/m2	86 ± 28	82 ± 18	0.05
LV EF %	58 ± 6	59 ± 3	0.05

Conclusions: Several unique anatomical and functional information can be detected by MRI in surgically treated TOF patients. RV function and mass appear to be strictly related to the degree of residual pulmonary stenosis and presence of pulmonary regurgitation.

P3423 Influence of surgical closure of atrial septal defects in adults on tachyarrhythmias

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There is controversy about the benefit of surgery for atrial septal defects (ASD) in adults and its effect on the incidence of atrial flutter/fibrillation.Surface and 24 Holter ECGs before, early (3–7 days) and late (>6 months) after ASD closure performed at age 42.2 (18.5–74.9) years in 211 patients were examined.All consecutive patients seen for a 10 year period with ASD and pulmonary to systemic flow ratio >1.5:1 were reviewed.The age of ASD patients with no preoperative dysrhythmia was 39 ± 13 years, those with flutter were 54 ± 12 and those with fibrillation 59 ± 8 years old (p < 0.05).38 (19%) had atrial flutter/fibrillation as presenting symptom. There was no correlation between shunt size and incidence of flutter/

fibrillation. 4 patients (2 with flutter and 2 with fibrillation) had a stroke before ASD closure and 2 with fibrillation had transient ischemic attacks. The number of patients with atrial flutter decreased from 18 to 10(p = 0.04), whereas ASD closure did not lead to significant decrease in atrial fibrillation (28 before versus 21 patients after ASD closure). 1 patient with fibrillation had a stroke after ASD closure.Irrespective of rhythm ASD closure lead to an improvement in NYHA functional class (p = 0.001) but was associated with a 1% mortality.

Our data show that ASD closure in adults leads to signifanct decrease of atrial flutter and is thus beneficial as the risk for stroke is also decreased. In patients with atrial fibrillation, however, ASD closure late in adult life does not reduce incidence of atrial fibrillation so that in selected adults a right-sided Maze procedure at time of ASD closure may be warranted.

P3424 Transcatheter occlusion of the patent ductus arteriosus using the Amplatzer duct occluder: immediate and indermediate-term results

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In this study we report our immediate and intermediate-term results of transcatheter closure (TC) of patent ductus arteriosus (PDA) with the Amplatzer Duct Occluder (ADO). The design of other devices is not ideal for this purpose and their use has been associated with several drawbacks, especially in large PDA's.

Methods: Forty patients (pts), aged 4 months to 33 years, (mean = 6.4 ± 6.7 years) with a moderate to large, type A to E, PDA underwent attempted TC using the ADO. The device is a plug-shaped repositionable occluder made of 0.004 in nitinol wire mesh. It is delivered through a 6F long sheath. The mean PDA diameter (at its pulmonary end) was 3.9 ± 1.1 mm (range = 2.2–6.2 mm). All pts had color flow echocardiographic follow-up (FU) (6–24 months) at 24 hours, 1 and 3 months after closure, and at 6 month intervals thereafter.

Results: The mean ADO diameter was 5.9 ± 1.4 mm (range = 4–8 mm). Complete angiographic closure was seen in 26/40 (65%) pts. The remaining pts had a trivial angiographic shunt through the ADO. At 24 hours color flow mapping revealed no shunt in all pts. An 8F long sheath was required for repositioning of a misplaced into the pulmonary artery. 8 mm device. The mean fluoroscopy time was 7.8 ± 1.4 min (range = 4.6–12 min). There were no complications. No obstruction of the descending aorta or the pulmonary artery branches was noted on Doppler FU studies. Neither thromboembolization nor hemolysis or device failure was encountered.

Conclusions: Our data support previous preliminary experience that ADO is an effective and safe device for TC in the majority of pts with patency of the arterial duct.

P3425 Where are the limits of transcatheter closure of atrial septal defects with the Amplatzer septal occluder?

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Purpose: The secundum type of atrial septal defect (ASD) is open to transcatheter closure techniques using different investigational devices. When attempting the transcatheter closure technique it is very important to recognize the variability in morphology of the defects to avoid incorrect outcome of the procedure like device embolization, residual shunting or AV valves incompetence. We report 114 patients who underwent transcatheter closure of secundum ASD with the Amplatzer septal occluder (ASO), 75 of these pts (85%) presented with morphological variation of secundum defect.

Patients: Between September 1995 and January 1999 114 pts (age 0.9–43 years, median 10) underwent transcatheter closure with ASO. 39 patients had centrally placed, fossa ovalis type of defect. 75 pts had morphological variations of secundum defects: 56 pts had partial (<3 mm) or total deficiency of antero-superior septal rim. 8 pts with multiple ASD's, 7 patients with aneurysm of atrial septum associated with single communication and 4 pts with multiperforated aneurysm.

Methods: All defects were closed with the Amplatzer septal occluder (ASO), the implantation procedure was monitored by transoesophageal echocardiography (TEE).

Results: The diameter of the defect measured by TEE ranged from 4–26 mm (median, 12) mm and balloon stretched diameter from 4–35 mm (14) mm. Size of implanted devices ranged from 4–34 (15) mm. Reexamination after one month (114 pts) one year (67 pts) and two years (28 pts) showed all defect closed except for two trivial leaks being of no hemodynamic significance.

Conclusion: ASO significantly extends the limits of usual criteria for transcatheter treatment and allowed to close majority (up to 80%) of all secundum atrial septal defects.

ANATOMIC AND FUNCTIONAL ASSESSMENT BY IMAGING

P3426 Atrioventricular function long after Mustard operation for transposition of great arteries: influence of atrial flutter

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Right ventricular (RV) failure and atrial flutter are known long term complications and thus contribute to mortality after Mustard repair for transposition of the great arteries. There is no uniform definition for the resulting RV dysfunction but the qualitative assessment of 2D echoes.

Methods: Electromechanical atrial and ventricular function was assessed in 22 (female 10) patients aged 27 ± 5 years, 10–29 (mean 24) years after initial Mustard operation using transthoracic Doppler echocardiography. Patients were divided into 2 groups: *Group I* included 12 patients with previously recorded atrial flutter and *Group II* involved 10 patients without history of atrial arrhythmia. All patients were studied while in sinus rhythm except 3 (2 in *Group I* and 1 in *Group II*) who were paced for complete heart block and 2 in *Group II* with junction rhythm.

Results: There was no difference in age, gender or age at surgery between the 2 patient groups. RV end diastolic dimension was increased in both groups while left ventricular fraction shortening was reduced (20 ± 10%) only in *Group I* patients. Although right sided total long axis excursion was equally reduced in the 2 patient groups (1.0 ± 0.3 cm), that of atrial 'A' wave of the same side was reduced only in *Group I* patients (0.14 ± 0.13 cm vs 0.26 ± 0.09 cm), $p < 0.01$. Total long axis excursion of the left (1.35 ± 0.37 cm) and septal (0.63 ± 0.23) sides were both significantly reduced in *Group I* patients compared to *Group II* patients (1.8 ± 0.3 cm, 0.95 ± 0.31 cm), $p < 0.05$, $p < 0.001$ respectively as was septal 'A' wave (0.11 ± 0.10 vs 0.33 ± 0.12 cm), $p < 0.001$. The onset of right atrial shortening was significantly delayed in *Group I* compared to *Group II* (110 ± 14 ms vs 84 ± 25 ms, $P < 0.001$), but that of left atrial shortening was not different in the 2 patient groups.

Conclusion: Biventricular dysfunction may occur in patients long after Mustard correction for transposition of great arteries. The consistent association of atrial flutter with the disturbed atrial and ventricular electromechanical behaviour suggests a causal relation with atrial arrhythmia.

P3427 Mitral regurgitation, T-wave abnormalities and development of impaired left ventricular function after treatment with anthracyclines

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It is well documented that the anthracycline antibiotics are cardiotoxic. However, with current cardiac monitoring it is not possible to detect early changes that may be predictive of myocardial damage. Current practice in our department includes serial 12 lead electrocardiogram(ECG)and echocardiography for the assessment of left ventricular function. During routine examination mitral regurgitation was noted as a new finding in a number of cases with normal fractional shortening. The purpose of this study is to investigate the development of mitral regurgitation and its relationship to other indicators of myocardial damage in patients receiving anthracycline chemotherapy.

Patients and Methods: 333 patients (169 males, 164 females). Ages ranged from 2–31, median 13 years. All were treated with anthracyclines for childhood malignancy. Cumulative doses of anthracyclines were between 80–450 mg/m^2,median 180 mg/m^2. Left ventricular function was assessed using both M mode echocardiography (systolic and diastolic internal dimensions and fractional shortening) and 12 lead ECG. Mitral regurgitation was detected using colour flow Doppler.

Results: 33 patients (10%) developed ultrasound detectable mitral regurgitation which was not apparant clinically. All had normal systolic function. 15 of these patients developed non specific T wave abnormalities. Subsequently 3 of these patients developed impaired left ventricular systolic function. This occurred at 5, 11 and 20 months following the initial finding of mitral regurgitation.

Conclusion: The combination of subclinical mitral regurgitation and non specific electrocardiographic changes could be an early predictor of anthracycline cardiomyopathy.

P3428 Three-dimensional images of congenital heart disease using electron beam CT

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The purpose of this study is to assess usefulness of three-dimensional (3D) images of congenital heart disease using electron beam CT (EBT). Ninety cases including eleven bronchial abnormalities were studied.

Method: After injection of contrast medium from peripheral vein, ECG-synchronized scanning was started in early phase. The scan time was 100 msec in all cases and the slice thickness was 3 or 6 mm with 2–7 mm of the table movement. Two-dimensional (2D) images obtained by EBT were transmitted to workstations on line. It took about twenty minutes to reconstruct a 3D image from 2D images. The 3D images were compared with the angiograms and the echocardiograms.

Result: The position of ventricular septal defect, two great arteries, infundibular septum and atrioventricular valves were showed clearly in the sections of the 3D images. They were useful to estimate a route from the left ventricle to the aorta in order to perform a biventricular repair in complex heart disease such as Double outlet right ventricle and corrected transposition of great arteries. They were also useful for evaluate possibility of separation in univentriculr heart. The relationship between the lesions and the surroundings were easily showed in pulmonary sling, abnormal origin of coronary artery and bronchial abnormality. The 3D images of Peripheral pulmonary stenosis and pulmonary valvular stenosis after external conduit repair were showed more apparently than the angiograms observing the sections at various angles.

Conclusion: The 3D image using EBT gave us new information and was useful to understand anatomy of congenital heart disease and decide a surgical method.

P3429 Echocardiographic parameters of left ventricular systolic and diastolic function in infants, children and adolescents with congenital aortic valve defects before and after cardiosurgery

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The analysis of left ventricular (LV) systolic and diastolic function has diagnostic and prognostic values in patients with congenital aortic valve defects.

Methods. The purpose of this investigation was Doppler echocardiographic (ECHO) quantify LV systolic and diastolic function in 141 patients aged between 3 and 24 with aortic stenosis (AS; n = 92) and aortic stenosis + aortic insufficiency (AS + AI; n = 49) before and 6 years after cardiosurgery. ECHO measurements were performed according to the guidelines of the American Society of Echocardiography. This parameters were compared with similar variables in healthy children (N; n = 150).

Results. Before surgery. The diastolic function parameters were the peak mitral flow velocity in early diastolic (E) (AS – 83.9 ± 6.0 cm/s; AS + AI – 79.7 ± 13.1 cm/s; N – 88.1 ± 8.9 cm/s), peak mitral flow velocity in late diastole (A) (AS – 81.2 ± 6.8 cm/s AS + AI – 89.3 ± 9.9 cm/S; N – 45.3 ± 6.3 cm/s), ratio of peak early to late atrial filling velocity (E/A) (AS – 1.04 ± 0.08, AS + AI – 1.03 ± 0.02; N – 1.96 ± 0.17), isovolumetric relaxation time (IVRT) (AS – 100 ± 10 ms; AS + AI – 96 ± 32 ms; N – 71 ± 6 ms) and deceleration time (DT) (AS – 237 ± 14 ms, AS + AI – 222 ± 97 ms; N -149 ± 21 ms). The systolic function parameters were LV shortening fraction (LVSF) (AS – 44.5 ± 2.8%; AS + AI – 28.8 ± 3.1%; N – 34.4 ± 2.9%), LV ejection fraction (LVEF) (AS -79.9 ± 1.9%; AS + AI – 57.0 ± 10.9%; N = 61.2 ± 2.9%).

After surgery. The diastolic function parameters were E (AS – 82.4 ± 7.1 cm/s; AS + AI – 81.2 ± 8.8 cm/s; N – 88.1 ± 8.9 cm/s), A (AS – 77.8 ± 7.1 cm/s; AS + AI – 81.7 ± 9.8 cm/s; N – 45.3 ± 6.3 cm/s); E/A (AS – 1.0 ± 0.5, AS + AI – 1.0 ± 0.4; N – 1.96 ± 0.17), IVRT (AS – 91 ± 5 ms; AS + AI – 89 ± 10 ms; N – 71 ± 6 ms) and DT (AS – 231 ± 28 ms, AS + AI – 197 ± 53 ms; N – 149 ± 21 ms). 2 patients died after cardiosurgery. Their diastolic function parameters were E (94.2 ± 5.4 cm/s). A (49.8 ± 3.4 cm/s), E/A (1.89 ± 0.06), IVRT (69 ± 11 ms), DT (117 ± 28 ms). The systolic function parameters were LVSF (AS – 42.0 ± 2.8%; AS + AI – 30.9 ± 2.1% N – 34.4 ± 2.9%), LVEF (AS – 70.3 ± 4.2%; AS + AI – 59.5 ± 4.0%; N – 61.2 ± 2.9%).

Conclusions. In AS and AS + AI patients the disturbances of LV diastolic function were observed both before and after cardiosurgery. These disturbances should be indication for early cardiosurgery. Pseudonormalization of LV diastolic function parameters was observed in patients that died. The parameters of LV systolic function were worse in AS + AI patients than in AS patients both before and after cardiosurgery.

P3430 The use of ultrasound in the evaluation of cyanosis following bi-directional cavopulmonary shunt

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Some of the major causes of increasing cyanosis in children who have undergone bidirectional cavo-pulmonary shunt (Glenn) operation include: 1) the development of pulmonary arteriovenous fistulas; 2) development of upper to lower body venous communications and 3) the normal relative decrease in pulmonary blood flow in relation to the child's growth. We suggest that contrast echocardiography can easily identify the relevant mechanism for decreasing saturation.

Methods: A contrast injection of agitated saline into an intravenous catheter in the upper extremity was performed in 5 patients (aged 1–12 yrs) evaluated for gradually increasing cyanosis during 1998. All patients had undergone the Glenn operation 1–10 yrs earlier. When microbubbles were identified in the heart, an attempt was made to identify the cardiac connections of the vessels carrying the microbubbles.

Results: 4/5 patients were found to have microbubbles in the heart. In two patients, the contrast fluid entered the heart via the pulmonary veins and left atrium, indicating the presence of pulmonary arteriovenous fistulas. In one patient the contrast entered the heart via the Inferior Vena Cava, indicating the presence of upper to lower body venous communications. This diagnosis was verified on cardiac catheterization and the collaterals occluded with multiple coils. One patient was found to have contrast in both systemic and pulmonary venous systems, indicating the presence of pulmonary arteriovenous fistulas as well as upper to lower body venous communications. One patient was found to have neither, again this diagnosis was verified on cardiac catheterization.

Conclusions: The use of contrast echocardiography facilitates easy and accurate definition of the mechanism leading to desaturation following the Glenn operation.

P3431 The prevalence and characteristics of physiological left sided regurgitation in children and adolescents

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Most studies of valve regurgitation in normal subjects have been in adults.In this study we aimed to prospectively determine the prevalence of echocardiographically detectable left sided valvular regurgitation in normal children and adolescents.

Patients and Methods: Healthy volunteers between the ages of 3 and 18 years were recruited from a local school.The study group consisted of 324 subjects (192 males, 132 females).Mitral and aortic flow was assessed using colour and continuous wave doppler techniques.Regurgitation was said to be present when high velocity colour flow, directed into the proximal chamber was detected after valve closure.

Results: The prevalence of mitral regurgitation for the whole group was 1.85% (6/324 subjects,age range 7–18 years).In each case mitral regurgitation was confined to the proximal half of the left atrium. In all but one case(83%)the regurgitant jet arose from the posteriomedial aspect of the mitral valve.The mean jet area was 1.4 cm^2 (range 1.1–1.9 cm^2). None of these patients had clinically detectable valve regurgitation.In addition to the above,one patient had mitral regurgitation on colour doppler but a continuous wave trace that was not holosystolic. The prevalence of aortic regurgitation was 0.3% (one female, 11 years). The jet was confined to the immediate region of the valve and was 0.44 cm^2 in area.

Conclusion: True left sided physiological regurgitation in the paediatric population is rare.Previous studies in normal adults have reported prevalence rates for aortic and mitral valve regurgitation of up to 71 and 89% respectively. This supports the popular theory that valve regurgitation is a wear and tear phenonenon becoming more common with advancing age.

P3432 Dobutamine stress echo in patients repaired with Fontan

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Several investigators have reported that patients (pts) after the Fontan procedure (FP) have a subnormal cardiac output (CO) including those doing well clinically. Dobutamine stress echocardiography (DSE) has been used as an alternative stress test for detecting the cardiac reserve in coronary and valvar heart disease as well as in cardiac failure. In this study we aimed at clarifying the hemodynamic response during DSE in pts after FP.

Methods: The study group was comprised by 10 patients (pts) (22 ± 4 years old, 14 ± 6 years s/p FP), and by 10 sex, age and body surface (BS) matched controls (C). Five of the pts were on sinus rhythm (SR) and the other five on atrial fibrillation (AF) and on digitalis. All pts and C were evaluated by 2D and doppler echo at rest and at peak of (5, 10, 20, 30, 40 μg/kg/min) 3 minute period of dobutamine infusion. End terminating point for stopping dobutamine infusion (DI) was the target of 130 beats/min. Stroke volume (SV), CO and CO index (COI) were estimated for all subjects using the equations: SV = LVOT cross sectional area X velocity time integral of LVOT, CO = SVx HR and COI = CO/BS.

Results Mean dose of DI for pts and C was (26 μgr/kgr/min, 35 μgr/kgr/min) respectectively. Systolic blood pressure (SBP) increased slightly but statistical significant (SS) in both C and pts In pts, SV, CO and COI at rest throughout the exercise were SS lower compared to C ($p < 0.001$) No SS difference was found between pts with and without AF. The% increase in SV, CO and COI from rest to the peak of exercise was higher in C than in pts ($p < 0.05$)

Conclusions: Pts s/p FP who are asymptomatic have lower CO at rest and show a less favorable hemodynamic response to DI than C. Although, pts with AF do not differ compared to those without AF.

PAEDIATRIC CARDIAC SURGERY

P3433 Pulmonary blood flow distribution after the total cavopulmonary connection

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Background Although the total cavopulmonary connection (TCPC) has been proposed as a rational alternative to atriopulmonary connection for Fontan operations, pulmonary blood flow distribution after TCPC is unkown.

Methods To clarify the pulmonary blood flow distribution after TCPC, we selected 11 patients (8.1 ± 10.1 yrs) performed TCPC and achieved the lung scanning by administrating ^{133}Xe saline solution from their arms, and then from their legs. Radionuclide counts on both lungs were obtained. Because TCPC candidates have many anatomical variations, we divided them into 3 groups. Group R: SVC-PA anastomosis is right side to the site of in IVC-PA anastomosis in 4 patients. Group L: SVC-PA is left in 3. Group B: IVC-PA is between bilateral SVC in 4.

Results The right to left ratio when ^{133}Xe was perfused from SVC was 77.9%:22.1% (±11.6), that from IVC was 45.1%:54.9% (±6.3), and SVC flow speed is equal to IVC's in Group R. That ratio from SVC was 23.6%:76.4% (±11.2), that from IVC was 70.8%:29.2% (±11.6), and SVC to IVC flow ratio is 0.9:1 in Group L. That from the right arm was 75.6%:24.4% (±1.5), that from the left arm was 33.8%:66.2% (±28.4) and that from IVC was 54.4%:45.6% (±10.3) in Group B.

Conclusion ^{133}Xe perfusion scan could reveal pulmonary blood flow distribution quantitatively in the patients after TCPC. The pulmonary blood flows from SVC and IVC perfused to the each anastomotic side predominantly. In the patients whose SVC-PA is left side to IVC-PA, the right and left balance of the pulmonary blood flow distribution was more even than another option, and less mixing of pulmonary blood flow was obtained.

P3434 Acute peritoneal dialysis after surgery for congenital heart defects

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In patients (pts.) with acute renal failure after surgery for congenital heart defects (CHD) peritoneal dialysis (PD) is the preferred elimination method because of limited vascular access, risks given by anticoagulation, frequent hemodynamic instability and technical simplicity. The purpose of this study was to evaluate risks and benefits of PD in this patient population.

Methods: From 1991 to 1997 PD was used in 70/2437 (2.9%) pts. after surgery for CHD. Data were available from 68/70 pts. aged 1 day–25.1 years (median 1.8 months). 54/68 pts. (79.4%) were infants. Preoperative renal dysfunction was present in 16 pts. (23.5%). At time of PD initiation 32 pts. (47.1%) had low cardiac output (LCO) and/or adrenaline >0.1 mcg/kg/min., 25 (36.8%) had capillary leak syndrome and 19 (27.9%) an open chest. PD was started because of refractory fluid retention in 67 pts. (98.5%, anuria in 25/67 pts.), hyperkalemia in 12 pts. (17.6%) and high urea level (>30 mmol/L) in 2 pts. (2.9%). Some pts. had more than 1 indication. Average PD duration was 3.4 (<1–14) days.

Results: 39/68 pts. (57.4%) died in the intensive care unit (ICU). In this group, LCO and/or adrenaline support >0.1 mcg/kg/min. were more frequent than in survivors (61.5 versus 27.6%, $p < 0.01$). Main causes of death were heart failure (25 pts.), multiorgan failure (6 pts.) a sepsis (5 pts.). In terms of PD fluid removal there was no difference between survivors and non-survivors (42.3 ± 32.1 versus 50.4 ± 54.7 mL/kg/day, NS). There was, however, a significant difference in total fluid balance during PD between both groups (−7.3 ± 55.8 versus +38.2 ± 76.9 mL/kg/day, $p < 0.05$). PD was functional (removed fluid >20 mL/kg/day) in 46/59 pts. (78%) with PD duration > 24 hours. PD was complicated by catheter block necessitating exchange in 27 pts. (39.7%), positive peritoneal cultures in the absence of PD related sepsis in 10 pts. (14.7%) and leak around catheter in 4 pts. (5.9%). Renal function was assessed in 26/29 pts. discharged from ICU and was normal in 24 (92.3%) and slightly decreased in 2 (7.7%).

In conclusion, drug refractory fluid retention was the main indication for PD after surgery for CHD. High mortality of dialysed pts. was caused by intractable heart failure and its sequelae. In surviving pts. PD helped to maintain a negative fluid balance and led probably to lower morbidity and mortality caused by hyperhydration. No serious PD complications were observed. Renal function recovered in the survivors.

P3435 Aortic root replacement with pulmonary autograft in the young age group

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Pulmonary autograft has been considered to be the preferred aortic valve replacement in the young age group because no anticoagulation is required; no degeneration; excellent haemodynamics; and growth. The operation is technically demanding, and we therefore reviewed the results of pulmonary autograft procedure at Great Ormond Street over the last 5 years.

Methods: The records of 36 patients, aged 18 days to 26 years (median age 178 months), were reviewed. All the patients underwent root replacement with coronary reimplantation. Follow-up was complete (median 24.5 months, range 1 month to 5 years). Echocardiographic assessment at late follow-up was available in all the patients.

Results: Aortic stenosis was the primary diagnosis in 2, aortic insufficiency in 4, a combination of these in 26, and aortic stenosis with left ventricular outflow tract obstruction in 4 patients. 33 patients had previous aortic valve interventions (26 valvuloplasties, 17 open valvotomies, 1 valve replacement). There were 2 early deaths and 1 late death (arrhythmia). There were no reoperations for autograft or homograft dysfunction, or valve-related events. Echocardiographic evaluation of the autograft revealed no significant obstruction, moderate insufficiency was found in one, and severe insufficiency in another patient. Evaluation of the homograft showed mild stenosis in 2, and mild insufficiency in 6 patients. All patients have a normal, active lifestyle.

Conclusions: The results are encouraging and the use of tile pulmonary autograft in children requiring aortic valve replacement appears to be justified.

CATHETER INTERVENTION IN CONGENITAL HEART DISEASE

P3436 Intravascular ultrasound assessment of morphologic changes of coarctation of the aorta following balloon angioplasty

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Balloon angioplasty has been widely accepted as a procedure-of-choice for the treatment of coarctation of the aorta. The morphologic changes of arterial wall in the coarcted segment following angioplasty has seldomly been reported. We conducted this study to investigate the morphologic changes of the arterial wall following balloon angioplasty using intravascular ultrasonography (IVUS).

Methods: During a 28-month period, angioplasty for coarctation of the aorta was performed in 22 patients, of whom 12 underwent IVUS study to assess the morphologic changes of arterial wall. A 8 F, 10 or 20 MHz IVUS (CVIS) catheter were used. The IVUS imagings was performed prior and immediately following balloon angioplasty. Of the 12 patients, their ages ranged from 4.5 to 18 years. Three had Turner syndrome and 3 had recurrent coarctation following surgical angioplasty. Of the 12 patients, the pressure gradient reduced significantly from 35.8 ± 7.3 to 8.7 ± 7.2 mm Hg ($p < 0.01$). Intimal tear and dissection were detected with IVUS in all 12 patients, which were seen in 3 patients on angiogram. All had dissections less than one fourth of the vessel circumference. No one had aortic aneurysm on IVUS images or angiogram. The mean narrowest diameter increased from 8 ± 2.4 to 12 ± 2.5 mm following angioplasty. ($p < 0.01$) After a follow-up period ranging from 4 to 32 months, the mean pressure gradient estimated with echocardiography was 13.3 ± 4.3 mm Hg.

In conclusion: Intimal tears and dissections were generally present in patients with effective angioplasty for coarctation of the aorta. IVUS is useful in evaluation of morphologic changes following balloon angioplasty.

P3437 Transcatheter closure of large atrial septal defect in adults

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Introduction: Transcatheter closure of atrial septal defect (ASD) with Amplatzer Septal Occluder (ASO) was well documented and become treatment of choice in selective patients.

The aim of our two centers study was to determine feasibility of ASO for closure of large ASD more than 20 mm in diameter, in children and adults.

Patients and Methods: From 9/95–01/99, 188 patients (age 5.1–58.9, median 25) with ASD underwent transcatheter occlusion with ASO. Among them 34 with stretched diameter larger than 20 mm.

Results: The median size of the ASD measured by transesophageal echocardiography (TEE) was 19.5 mm (range, 14–26 mm) and the median stretched diameter was 24 (19–35 mm). Size of implanted devices ranged from 20–36 mm (25 mm). All patients had RV volume overload with a median Qp/Qs of 2.59 (1.7–3.27). The median fluoroscopy time was 14 min (6.8–60 min). As assessed by TEE and cine, there was immediate complete closure (C) in 9/34 (25%). At 24 hour follow-up transthoracic echocardiogram with color revealed C in 24/34 (70%), 27/30 (90%) at one month and at 3 months follow up 29/30 (96%) had C. There has been no major complications related to the closure. On median follow up interval 10 months (range, 1 week–3 years), there has been no episodes of endocarditis, thromboembolism or wire fracture. Only one patient was treated due to premature atrial extrasystoles.

Conclusion: We conclude that the new self-expandable, repositionable ASO is effective method to close large secundum ASD's with C in the majority of patients. Further clinical trials are underway.

P3438 The results of the repair of atrial septal defect with or without partial anomalous pulmonary venous connection in patients over 40 years old

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Objective: We aimed to determine the value of surgical closure of atrial septal defect (ASD) and partial anomalous pulmonary venous connection (PAPVC) in patients (pts) over 40 years of age.

Methods: We analyzed 88 consecutive pts over 40 years of age operated because of ASD (76 pts) and PAPVC (12 pts) and followed up for 1 to 17 years. Patient quality of life, clinical status, NYHA class, ecg, chest x-ray and echocardiography were studied before operation and at the end of follow up.

Results: There were 16 men and 72 women aged 40–62 (mean 46.5 ± 6.8 years). Before operation 64% of pts were in III and IV NYHA class, 7 pts had atrial fibrillation. Antiarrhythmic drugs were used in 37% of pts, diuretics in 34% and anticoagulants in 5% of pts. The average pulmonary to systemic flow ratio was 2.48 ± 0.61.

We noted 1 operative and 3 late deaths during follow up. On examination 82% of pts were in I and II NYHA class. The clinical improvement was quantified as significant by 69% of pts. No improvement or deterioration was reported by 12% of pts. Antiarrhythmic drugs were used in 51%, diuretics in 11% and anticoagulants in 12% of pts. 11 pts suffered from atrial fibrillation. Echocardiographic examination revealed significant decrease of the right ventricular diastolic diameter in both groups (4.15 ± 0.89 vs 3.02 ± 0.35 cm, $p < 0.001$ in ASD pts and 3.99 ± 0.86 vs 2.91 ± 0.58 cm, $p < 0.05$ in PAPVC pts), decrease of tricuspid insufficiency and maximal velocity of tricuspid diastolic flow as compare to preoperative examination.

Conclusion: Surgical repair of ASD with or without PAPVC in pts over 40 years of age can significantly improve the clinical status as well as prevent the right ventricular dilatation and insufficiency.

P3439 Neonatal aortic balloon valvuloplasty – early and intermediate results(up to 9 years)

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Primary balloon valvuloplasty was performed in 27 consecutive neonates with severe aortic stenosis. Approach was via the axillary artery(23),femoral artery(3)or antegradely via a ventricular septal defect (1). Median age was 4 days (range 1–30), median weight 3.6 kg (range 1.1–4.5). Balloon: aortic annulus ratio was 1.01 ± 0.12. Valvuloplasty significantly reduced the peak systolic pressure gradient from 58 ± 38 to 20 ± 15 mmHg, whilst increasing aortic regurgitation by a mean of 2.2 ± 1.2 grades. Overall mortality was 41%(7 early and 4 late deaths-after 1 month), but was higher in the subgroup of 17 neonates undergoing valvuloplasty in the first week of life (53% vs 12%). Arterial complications occurred in 4 patients (femoral avulsion-2, femoral thrombosis-1, axillary thrombosis-1). 10 children have required 1 or more reinterventions; Ross proceedure (3 and 43 months),homograft valve replacement (6 months), open valvotomy (1 and 3 months) and repeat balloon valvuloplasty (1, 1, 1 and 8 months). Of the 14 children requiring angioplasty in the first week of life and surviving 1 month, 38% required reintervention compared with 25% of the group requiring angioplasty after 1 week of life. The median Doppler gradient at follow up was 33 mmHg (range 9–50).

Conclusion: Neonatal balloon valvuloplasty is technically successful in terms of gradient reduction. However the mortality in those requiring treatment in the first week of life appears to exceed the mortality rate for alternative therapies such as the Norwood proceedure. Reintervention is common in those surviving (38%). This high mortality is contrasted with a much better prognosis in patients treated afer the first week of life, who have a survival rate of 88% and a reintervention rate of 25% at a median follow up of 76 months (range 6–106).

P3440 Reduction of right ventricular systolic pressure results in disappearance of retrograde right coronary artery systolic flow in patients with pulmonary valve stenosis

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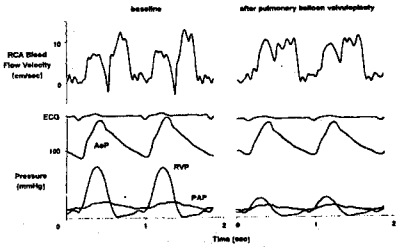
Previous studies in animals have shown an alteration of right coronary artery (RCA) blood flow as a result of elevated right ventricular systolic pressure (RVSP) secondary to pulmonary artery constriction or pulmonary emboli. The impact of the elevated RVSP and its changes on the RCA blood flow have not been well studied in humans.

Methods: Towards this end, in 9 patients with severe isolated pulmonary valve stenosis (mean age 30.8 ± 10.6 years), proximal RCA blood flow velocity (BFV) was measured, using an intracoronary Doppler velocimeter, along with hemodynamic parameters before and after pulmonary balloon valvuloplasty (PBV).

Results: The pre-valvuloplasty phasic RCA BFV pattern was predominantly diastolic with an obvious systolic retrograde (SR) wave (Fig. Left panel). The level of RVSP had a negative correlation with the peak systolic antegrade (SA) BFV (r = −0.71), the SA RCA BFV curve area (r = −0.73) and the volumetric RCA flow (r = −0.83) and a positive correlation with the SR BFV curve area (r = 0.97). PBV caused a significant reduction in both the transvalvular pressure gradient (by 59 ± 29 mmHg) and the RVSP (by 55 ± 19 mmHg). The peak SA BFV, the SA BFV curve area, the ratio of total systolic to diastolic BFV curve area and the RCA volumetric flow increased significantly while the SR BFV curve area decreased significantly (Fig. Right panel). The decrease of RVSP had a negative correlation with changes in the peak SA BFV (r = −0.60), in the ratio of peak SA to diastolic BFV (r = −0.51) and in the RCA volumetric flow (r = −0.53) and a positive correlation with changes in the SR RCA BFV curve area (r = 0.91).



In conclusion, RCA BFV pattern is strongly dependent on the RVSP level and its changes after PBV. PBV-induced reduction in RVSP results in a dissapearance of retrograde systolic componet of the RCA BFV pattern.

P3441 Atrial septal defect in the adult: is routine surgical closure always beneficial?

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Atrial septal defect (ASD) can be recognized firstly in adult age, mostly in asymptomatic or mildly symptomatic patients (p), in whom benefits of surgical closure are still debated.

Methods: Clinical histories of 87 p with first diagnosis of ASD when older than 30 years (59 females-68%; mean age 50 ± 13 years, range 30–81) observed at our Institution since 1978 for a mean follow-up of 96 ± 69 months (range 12–240) were revised. Clinical decision (medical treatment:48 p, 55%, group A; surgery;39 p, 48%, group B) resulted either from individual cardiologist's opinions and indications and/or from patients' personal choices. At first evaluation, group A and B did not differ significantly for any clinical, echocardiographic or hemodynamic parameter; p of group A were older (54 ± 14 vs 45 ± 11 years; $p < 0.0001$); 46 p in group A (95%) and 36 p in goup B (92%) were in I-II NYHA class.

Results: During follow-up NYHA class worsening was observed in 4 p (8%) in group A and 3 p (8%) in group B. Major complications (cardiac death, cerebral emboli, infective endocarditis, severe mitral regurgitation, re-operation) were virtually the same in the two groups: 8 p (16%) in group A and 8 p (20%) in group B. New onset complex supraventricular arrhythmias occurred less frequently in group A (5 p, 12%) vs group B (15 p, 38%; $p < 0.01$).

In conclusion, in a population of adult p with ASD, most of whom mildly or a-symptomatic at first evaluation, serendipitous indication to surgery seeems to be uneffective on mid-term mortality and morbidity.

P3442 Which ASD secundum are not suitable for transcatheter closure?

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Amplatzer septal occluder (ASO) is new self-centering device for transcatheter closure of ASD secundum. The purpose of the study was to determine the echocardiographic characteristic of ASD secundum that can not be closed with ASO.

Between 9/95 and 6/98 we examined 220 patients with ASD at median age 6.7 (range 9 months to 43 years) and median weight 32 kg (range 6.9 to 82 kg). We found with TTE 14 (6%) patients, with TEE 23 (11%) patients and during catheterization one patient that were not suitable for transcatheter closure. 91 (27 male/55 female) had the implantation of ASO and the others are on waiting list.

The characteristic of the ASDs not suitable for transcatheter closure with ASO were: 1) ASD secundum with rims < 5 mm (19 pts), 2) ASD secundum with PAPVD (4 pts), 3) associated sinus venosus with PAPVD (13 pts) and 4) ASD secundum with diameter > 30 mm (1 pts). We found 43 patients with insufficient rims: 12 inferior rim (rim toward IVC), 7 posterior rim (direction toward coronary sinus) and 24 anterior-superior rim (toward aorta), but all patients with insufficient anterior-superior rim had successful ASO implantation.

Conclusions: 18% of ASDs are not suitable for transcatheter closure with ASO. TEE is essential for patients' selection. It allows better detection of defect's location, rims length and PAPVD. The most important are rims towards the IVC, SVC, right upper pulmonary vein and AV valves that should be at least 4 mm. Aortic rim is not important for ASO deployment. We also found that inferior and posterior defects are not suitable for transcatheter closure with ASO.

P3443 Severe hypoxaemia due to atrial right-to-left shunt in adult patients with normal pulmonary artery pressure. percutaneous transcatheter occlusion

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Hypoxemia due to atrial right-to-left shunt through a patent foramen ovale (PFO) and/or atrial septal defect (ASD) with normal pulmonary artery pressure is an uncommon diagnosis. We report here 8 consecutive cases.

From August 1995 to September 1998, 8 patients (age: 59–78 years), were referred to our institution for severe hypoxemia (oxygen saturation of 70–85%) and dyspnea due to an interatrial right-to-left shunt. Half of the patient had platypnea and orthodeoxia. In 5 patients, symptoms were present for a period of 1 month to 3 years. In 3 patients, hypoxemia appeared suddenly: 2 after surgery (1 pneumonectomy and 1 ventral hernia). The diagnosis was confirmed in all by contrast transoesophageal echocardiography.

Cardiac catheterization revealed normal right-sided pressures. Angiography in the inferior vena cava showed the right-to-left shunt through a PFO (n = 4) or a small ASD (n = 4) and rotation of the heart in a counterclockwise direction distorting the position of atrial septum relative to caval inflow. This latter was explained by enlargement of the ascending aorta noticed in 7 patients or heart tilting secondary to pneumonectomy.

All patients underwent percutaneous occlusion of the PFO/ASD under local anaesthesia using the inverted Sideris device (n = 5), the Cardioseal device (n = 2) and the Amplatzer device (n = 1). Immediately after implantation, a significant rise in oxygen saturation was observed (oxygen saturation > 95%). The closure succeeded in all patients but one. In one patient, the introducing sheath could not be advanced due to tortuous inferior vena cava and patient remained hypoxic. Two complications were observed after closure: 1 atrial fibrillation and 1 transient cerebrovascular accident. During follow-up (1 to 30 months), the 7 patients had no oxygen desaturation or dyspnea and contrast echocardiography showed no atrial shunt (n = 6) and tiny residual shunt (n = 1).

Hypoxemia due to interatrial right-to-left shunt without pulmonary hypertension is an uncommon pathology that is probably underestimated due to the prevalence of PFO in the general population. Correction can be easily performed by percutaneous closure. This latter should be regarded as the treatment of choice for the occlusion of PFO/ASD and a good alternative to surgical closure.

PATHOPHYSIOLOGY AND DIAGNOSIS OF CONGENITAL HEART DISEASE

P3444 Echocardiographic morphologic and geometric variations of the left ventricular outflow tract: possible role in the pathogenesis of discrete subaortic stenosis

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Although the clinical features and natural course of discrete subaortic stenosis (DSS) are well defined, the etiology remains speculative. The purpose of this study was to identify the echocardiographic morphologic and geometric variations of the left ventricular outflow tract associated with DSS in children and to determine whether these variations had role in the pathogenesis of DSS. The aortoseptal angle (ASA), mitral-aortic valve separation (MAS), and the size of the aortic annulus were determined in two groups of children. Group 1 comprised 11 patients with isolated DSS, who were compared with an age- and body surface area- (BSA) matched healthy children (Group 1A, n: 20). Group 2 comprised 10 patients with DSS and ventricular septal defect (VSD). Group 2 was compared with an age- and BSA- matched patients with isolated perimembranous VSD (Group 2A, n: 22). Measurements were carried out from previously recorded echocardiographic studies. The ASA was steeper (119.3 ± 6.1° vs 137.5 ± 5.6°, $p < 0.001$), and the MAS was wider (6.1 ± 1.6 mm vs 3.2 ± 0.7 mm, $p < 0.001$) in patients with isolated DSS than in healthy control subjects. Similar differences were found between patients in Group 2 and Group 2A; the ASA was steeper (122.2 ± 6.5° vs 141.3 ± 5.0°, $p < 0.001$), and the MAS was wider (5.8 ± 1.5 mm vs 3.8 ± 1.1 mm, $p < 0.001$). The size of the aortic annulus was not different among four study groups. Although the MAS was significantly wider in patients with DSS there was significant overlap in MAS between patients and controls. However, if an ASA < 130° was chosen as a predictive variable, it was found to be highly sensitive, specific, and positive predictive marker for the development of DSS. This study demonstrates that DSS is associated with a steeper ASA, and a wider MAS, in patients with or without associated VSD. These morphologic abnormalities, especially a steeper ASA may be risk factors for the development of DSS.

P3445 Tilt training for neurocardiogenic syncope in paediatric patients

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Head up tilt testing is a standardised and sensitive test for diagnosing neurally mediated syncope in patients with a history of syncope. In adult patients who underwent repeated diagnostic tilt tests, we have observed an improved tilt tolerance. Therefore we hypotesised that repeated and prolonged exposure of the cardiovascular system to orthostatic stress might have therapeutic effects in the management of patients with this disorder. The purpose of the present study was to analyse whether the same results could be obtained in pediatric patients with neurocardiogenic syncope. **Methods:** 12 pediatric patients (mean age: 12.7 ± 3.7, min 6 years) with a history of syncope and positive tilt test, performed a program of tilt training. 6 patients were diagnosed as vasodepressor type of syncope, 4 with cardio-inhibitory (CI) type and 2 with mixed type. In the patients with the cardio-inhibitory type of syncope the duration of asystole ranged from 10 to 15 s (mean 12.4 ± 2.5). The patients were tilted daily until syncope occurred or until 45 min. After discharge from the hospital the patients continued tilt training at home for 1 or 2 periods of 30 min per day. They were instructed to lean against a vertical wall, under the supervision of a family member. **Results:** A significant increase in tilt duration was observed during one week of in hospital therapy, with disappearance of syncope in all patients (tilt duration during diagnostic test: 21 ± 13 min (minimum: 3.5 min) vs >45 min at discharge from the hospital. After 2 to 6 sessions all patients were able to sustain the tilt test for 45 min. In the patients with the CI type of syncope, asystole during tilt disappeared within 2 days. In all pts syncope during daily life disappeared completely. **Conclusion:** A daily program of tilt training is a satisfactory therapy also for pediatric patients with neurocardiogenic syncope, since it abolishes the abnormal and excessive autonomic reflex activity.

P3446 Young adult Marfan patients: aortic stiffness and the influence of beta-blocker medication

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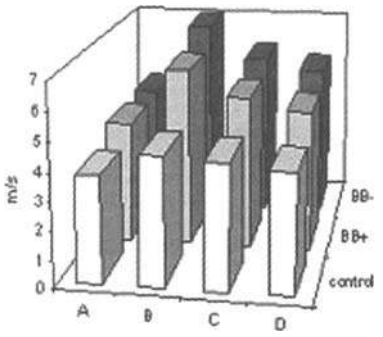
Objective: To investigate aortic stiffness in young adult Marfan patients with and without β-blocker medication.

Methods: 69 Marfan patients (age range 18–40 yrs) without a history of aortic aneurysms necessitating surgery and 21 matched controls were studied with magnetic resonance velocity mapping, perpendicular to 4 levels in the aorta: 1) ascending aorta, 2) descending aorta (level: pulmonary bifurcation), 3) descending aorta (level: diaphragm), and 4) (level: above the aortic bifurcation). Modulus/phase image pairs with a spatial resolution of 1 mm/pixel, at a temporal resolution of 25 ms, were generated. Aortic flow curves at the 4 levels were calculated. Flow wave velocity (FWV) was calculated from the onset of the flow waves and the distances between two levels. FWV from (A) level 1 to 2, (B) level 2 to 3, (C) level 3 to 4, and (D) level 1 to 4 were compared between 21 controls, 48 Marfan patients using and 21 Marfan patients not using β-blockers.



Results: Significant differences in FWV between Marfan patients and controls were demonstrated in all segments (A: 4.3 ± 1.1 vs 3.8 ± 0.7 ms^{-1}, B: 6.5 ± 2.2 vs 4.5 ± 0.8 ms^{-1}, C: 5.5 ± 1.6 vs 4.4 ± 1.0 ms^{-1}, D: 5.1 ± 0.8 vs 4.2 ± 0.5 ms^{-1}, respectively,$p < 0.03$. Significant differences in FWV between Marfan patients using and not using β-blockers (5.0 ± 0.7 vs 5.4 ± 0.9 ms^{-1}, $p = 0.04$) and between the both groups and the controls (4.3 ± 0.5 ms^{-1}, $p < 0.0001$) could be demonstrated in segment D. Furthermore, a significant difference in mean blood pressure between the groups using and not using β-blockers was demonstrated (78 ± 7 vs 83 ± 8 mmHg, $p = 0.02$).

Conclusions: Young adult Marfan patients show increased stiffness of the entire aorta. Aortic stiffness differences between patients using and not using β-blockers may be related to a reduction in blood pressure.

P3447 Mechanisms for aortic arch gradients unmasked by isoprenaline

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Purpose: A subgroup of patients have persistent upper limb hypertension at rest, and left ventricular hypertrophy (LVH) following coarctation repair, despite the absence of resting pressure gradients. The aim of the study was to assess the changes in catheter pullback pressure gradients following iv isoprenaline infusion.

Methods: In 14 pts (7 M, 7 F; median weight 12 [range 5–70] kg; median age 13.9 [3–192] months) who had previously undergone aortic arch repair (coarctation N = 10; interrupted arch N = 2; Damus procedure N = 2; interval from surgery to catheterization 6 [3–48] months), iv isoprenaline (0.1 mcg/kg/min) was administered at cardiac catheterization. Indications for catheterization were resting hypertension (N = 5), echo-Doppler gradients of >30 mm Hg at rest or during exercise (N = 7), or prior to planning further surgery (N = 2).

Results: During isoprenaline infusion, the median heart rate increased from 93 [70–140] to 130 [110–165] beats/min. The pullback gradient across the repaired segment increased from 10 [0–35] to 43 [13–75] mm Hg ($p < 0.05$). In all 5 patients with resting upper limb hypertension there was an exaggerated increase in gradient from 18 [0–35] mm Hg at baseline to 55 [35–75] mm Hg. In 3 others, all with LVH, upper segment hypertension was recorded only during isoprenaline infusion. In these patients, this was the mechanism for the development of a pressure gradient across the aortic arch. The remaining 6 patients had normal upper segment pressures during isoprenaline infusion, but developed gradients (median 5 [2–10] mm Hg at baseline to 24 [13–48] mm Hg with isoprenaline), due to a decrease in distal vascular resistance.

Conclusion: Two distinct mechanisms (increased degree of obstruction with upstream hypertension, or decreased distal vascular resistance and impaired pulse transmission) account for the development of pressure gradients following aortic arch repair. Isoprenaline may unmask clinically significant arch obstruction following previous aortic arch reconstruction.

CORONARY ARTERY PROBLEMS IN CONGENITAL HEART DISEASE

P3448 Myocardial perfusion and coronary flow reserve in children with transposition of the great arteries 10 years after anatomical correction

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Children after anatomical correction of TGA are subsequently largely asymptomatic. However, the final outcome and possible coronary insufficiency remains unclear. It has been considered that coronary flow reserve (CFR) may be reduced in this population.

Methods: Myocardial blood flow (MBF) was assessed at rest and during maximal hyperemia using N-13 ammonia PET before and after intravenous adenosine infusion in 22 children (mean age 12 ± 2 years). MBF and CFR were compared with a group of healthy volunteers.

Results: A stress-induced perfusion defect was noted in 4 patients. Mean resting MBF was higher in patients than in volunteers (0.97 ± 0.27 vs. 0.74 ± 0.14, $p = 0.04$), while stress MBF was reduced (2.74 ± 0.44 vs. 3.48 ± 0.59, $p = 0.001$). CFR in patients was significantly lower than in controls (2.96 ± 0.60 vs. 4.75 ± 0.81, $p < 0.0001$). Myocardial vascular resistance (MVR) was lower at rest in patients (97.87 ± 21.3 vs. 125.08 ± 25.06, $p = 0.006$), while stress MVR tended to be higher.

Conclusion: Patients with surgically corrected TGA show reduced coronary flow reserve compared with healthy young adults. Quantitative PET assessment of CFR may thereby reveal functional abnormalities in these patients prior to the appearance of perfusion defects.

P3449 Coronary anatomy and long-term outcome of the arterial switch

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Background: Abnormal coronary artery anatomy (CAA) is thought to have a significant influence on mortality and late coronary morbidity after the arterial switch (ASO) and an alarming incidence of late coronary obstruction is reported. This study determines the impact of CAA on the long term outcome of the ASO and occurrence of late coronary obstruction.

Methods: CAA of 147 pts after ASO (1977–98) was determined based on operative reports and pre-operative angiograms. Current status and coronary related morbidity were evaluated using EKG's, echocardiograms, scintigraphy and post-operative coronary angiograms.

Results: In 117 pts CAA consisted of an anterior descending (LAD) and circumflex artery (Cx) from the left cusp and the right coronary artery (RCA) from the right or posterior cusp, 12 pts had LAD from the left and Cx and RCA from the right cusp, 7 LAD and RCA from one cusp and Cx from the other, 4 pts had single ostium and 3 pts had 3 separate ostia. 3 pts had complex patterns with double branches, one of whom had double Cx arteries from either cusp, crossing over in the myocardium and one pt had supra commisural coronary. Overall mortality was 20%. Late coronary related incidents were seen in 3 pts: 2 arrhythmia (1 fatal) and 1 severe LV dysfunction. All 3 pts had the most common anatomy, ischaemia was noted in the early postoperative period. In 2 of these pts coronary angiograms are normal, suggesting failure of myocardial protection during ASO. The 3rd pt has obstructed left ostium. 1 pt has asymptomatic stenosis of the right coronary ostium, and 1 pt has multiple tortuous collaterals from all 3 main coronary branches without stenosis. No significant difference was found between CAA and early mortality as well as late morbidity.

Conclusions: Contrary to previous reports did CAA prior to ASO not influence outcome in our patients. Late coronary abnormalities were found in 3 pts, two of whom are asymptomatic.

P3450 Thrombi in the heart and in coronary arteries in children: successful thrombolytic therapy with rt-PA

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The aim of the study was to evaluate the effectiveness of thrombolytic therapy with rt-PA in cardiac thrombi and coronary arteries thromboses in children.

Material: 13 children aged 3 month (mo) to 17 years (y), (9 boys, 4 girls) were diagnosed in Department of Cardiology between 1996–1998. 5 patients (pts) had myocarditis/dilated cardiomyopathy (CMP) and severe heart failure (SF = 6.8–16%), 1 patient (pt) was after pacemaker implantation because of complete atrioventricular heart block, 2 pts with mechanical prosthetic valve (St. Jude) in mitral position, 2 pts with Kawasaki disease and 3 pts with complex congenital heart disease. In all pts localization of thrombi were evaluated by echocardiography: LV – 6 pts, LV and LA – 3 pts, RA – 1 pt, in coronary arteries – 2 pts (LPA and RPA – 1, RPA – 1), SV – 1 pt. All pts were treated with rt-PA (Actylise) in doses 0.03 to 0.1 mg/kg/h given to systemic vein or directly to occluded coronary arteries in 3 boluses of 1 mg. Duration of treatment was from 1 to 9 days. The PT, PTT, fibrynogen, FDP levels and complete blood cell count were monitored during thrombolytic therapy. Size and localization of thrombi were monitored by echocardiography. After completed rt-PA treatment heparine or Fraxiparine and Sintrom were given.

Results: Very good results – complete resolving of thrombi were achieved in 9 pts (69.2%), in 4 pts with myocarditis/CMP size of thrombi decreased but persisted until death.

Conclusions: 1. Rt-PA (Actylise) is very effective and safe thrombolytic drug in children with cardiac and coronary arteries thromboses given in dose 0.03–0.1 mg/kg/h to systemic vein or directly to coronary arteries in bolus 2. Short time bleeding from respiratory tract was the only complication observed in 1 pt.

P3451 Anomalous origin of the left coronary artery from the pulmonary artery: diagnosis and postoperative follow-up

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Purpose: to review our experience with the diagnosis of anomalous left coronary artery (ALCA) from the pulmonary artery (PA) and to assess short to midterm surgical results.

Methods: between 1992 and 1998, 12 infants and children (2 mo to 15 yrs) were treated for ALCA at the SCMCI. Eight were diagnosed during the first year of life; 4 were diagnosed later, the oldest being 15 years of age. Eleven patients (pts) were operated on in order to establish dual coronary artery system: 6 underwent the Takeuchi procedure and 5 reimplantation of the ALCA.

Results: All pts diagnosed during the first year of life were symptomatic and had severe dysfunction of the left ventricle. One died shortly after diagnosis before surgical repair was attempted from multiorgan failure and severe neurologic damage. Older pts had preserved myocardial function. Echocardiographic diagnosis was accepted only if flow was clearly demonstrated within the LCA and into the PA. Using these criteria, 5/12 required catheterization to establish diagnosis (one infant and all older patients). Surgery was performed shortly after diagnosis and surgical technique chosen to best fit the anatomy. There were no operative or late deaths on follow up. Three pts needed additional surgery. The most recent evaluation revealed good global LV function in all patients operated on until November 1998, with normal fractional shortening as assessed by M-mode; 2 pts are still within recovery phase showing gradual improvement

Conclusions: (1) a diagnosis of ALCA can be established echocardiographically when flow is documented from the LCA into the MPA, (2) the preferred surgical method appears to be reimplantation of the ALCA and (3) even though global LV function recovers to a great extent, abnormal myocardial features can be identified even years after surgery.

CONGENITAL HEART PROBLEMS IN ADULTS AND ADOLESCENTS

P3452 Long-term results (30 years) after coarctation of aorta repair

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Backround: Even after successful operation of coarctation of aorta (COA) the patients are not cured.

Methods: We examined 21 pts (mean age 41 ± 9 years) who were operated for COA in the age of 11 (3–18) years, 30 ± 8.7 years ago. The type of operation was in 95% resection and anastomosis end-to-end, one patient had Dacron graft. We performed clinical examination, echocardiography, exercise test and MRI.

Results: Bicuspid aortic valve was present in 63%, in 19% with moderate or severe dysfunction, in 28% with mild dysfunction, mitral valve disease was found in 19%, one patient had Ebstein anomaly of tricuspid valve, one patient aneurysm of ascending aorta. Left ventricle hypertrophy ≥ 12 mm was in 57%, left ventricle systolic dysfunction with EF ≤ 50% was found in 14%. Rest hypertension had 48% of patients, exercise hypertension ≥ 200 mmHg 57% of patients. Recoarctation with arm-leg pressure gradient ≥ 20 mm Hg was in 19%, stenosis > 30% on MRI was in 52%. Most patients (67%) were in functional class NYHA I, 14% in NYHA II, 19% in NYHA III. Patients with stenosis > 30% on MRI had NYHA 1.8 ± 0.87, patients with stenosis ≤ 30% with exclusion of moderate or severe valvular disease were all in functional class NYHA I ($p < 0.01$). Hypercholesterolemia > 5.5 mmol/l was found in 38%.

Conclusion: In spite of good clinical outcome, there are many residual findings in patients 30 years after COA repair. With respect to the increased risk of coronary artery disease and progression of valvular disease, these patients should be followed up closely.

P3453 Effect of phlebotomy on haemostatic parameters in adults with cyanotic congenital heart disease

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Hemostatic abnormalities affecting both platelets and coagulation factors are known in patients (pts) with cyanotic congenital heart disease (CCHD) and are associated with an increased risk for bleeding. Phlebotomy (P) has been recommended to reduce the perioperative risk of serious bleeding. The aim of this study was to evaluate the impact of P on hemostatic parameters in pts with CCHD.

Methods: 13 pts (3 females), mean age 36.0 ± 11.5 yrs, oxygen saturation 82.5 ± 3.6%, underwent 20 P because of hyperviscosity symptoms. Isotonic saline (750 ml) was administered prior to withdrawal of 500 ml of whole blood. Whole blood was collected in sodium citrate tubes adjusted for packed cell volume (PCV) before P, 100 and 200 minutes after the end of P (E100, E200) and on day 3 and 10. Hemoglobin (HB, g/L), PCV (%), platelet count (PLT, bil/L), international normalized ratio (INR), activated thromboplastin time (aPTT, sec), thrombin time (TT, sec) and fibrinogen (F, g/L) were measured. Parameters before P were compared to those after P.

Results:

HB	PCV	PLT	INR	aPTT	F	
Before P	221 ±18	68 ± 6	140 ± 52	1.14 ± 0.09	31.3 ± 3.3	3.3 ± 0.7
E 100	209 ± 23*	63 ± 7*	140 ± 55	1.16 ± 0.10	35.9 ± 23.8	3.0 ± 0.6†
E 200	209 ± 23*	63 ± 7*	144 ± 54	1.15 ± 0.10	31.5 ± 3.1	3.1 ± 0.8
Day 3	206 ± 20*	62 ± 6*	149 ± 51	1.12 ± 0.08	30.3 ± 2.6	3.3 ± 0.8
Day 10	204 ± 20*	63 ± 6*	169 ± 52#	1.12 ± 0.07	29.3 ± 3.7‡	3.7 ± 0.6‡

TT is comparable: 16.6 ± 1.9 *vs* 16.3 ± 1.6 *vs* 16.8 ± 2.1 *vs* 16.9 ± 2.0 *vs* 16.7 ± 1.3 sec. p-value *vs* before P: *p < 0.001; #p = 0.013; ‡p = 0.003; †p = 0.001

Conclusion: Phlebotomy results in a mild increase in platelet count and fibrinogen and in a slight decrease in aPTT on day 10. Extrinsic coagulation pathway is not affected by P. P may be justified at least 10 days before major surgery in this population to improve hemostasis and to donate autologous blood.

P3454 Prevalence, risk factors and clinical consequences of thrombus formation detected by transoesophageal echocardiography after "Fontan type" operations

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Intracardiac thrombus formation in patients after "Fontan-type" operations are well known as a risk factor. We performed serial transoesophageal echoexaminations (TEE) in such patients, as transthoracic echocardiography (TTE) often does not detect thrombus formation. To evaluate risk factors for thrombogenesis we compared age, sex, underlying cardiac malformation, type of Fontan operation, clinical-, laboratory-, echo- and haemodynamic data between the thrombus and non thrombus group.

Results: 67 TEE's were performed in 43 patients, mean age 19.4 years (range 7.3 y), mean age at operation 9.0 y (range 5.5 y). 16 patients showed thrombus formation in the right atrium, in one of them a thrombus was suspected on TTE. After a mean interval of 5.3 months in five patients the thrombus was resolved, 3 had a residual thrombus and in five thrombus was unchanged despite thrombolytic therapy with alteplase and consecutive oral anticoagulation. There was no difference in age at operation, sex distribution, age at TEE, underlying cardiac malformation and presence of arrhythmias between both groups. Laboratory (Hct, albumine, pTT, protein C and S), echocardiographic (spontaneous echocontrast, ventricular function, atrioventricular- and/or semilunar regurgitation)- and haemodynamic findings (right atrial pressure, pulmonary artery pressure, transpulmonary gradient, systemic and pulmonary flow ratios systemic and pulmonary resistance) did not differ between thrombus and non thrombus group.

Conclusion: All patients with "Fontan-type" operations seem to be at risk for thrombogenesis and therefore should have serial TEE. As there are no predictive risk factors concerning laboratory, haemodynamic and echocardiografic findings all patients should have oral anticoagulation lifelong.

P3455 Prevalence and clinical outcome of hepatitis C infection after cardiac surgery in childhood

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Hepatitis C (HCV) has been known as the main cause of posttransfusion hepatitis since 1989. Worldwide very few data exist on the prevalence of HCV-infection in pediatric patients after major cardiac surgery. We revaluated a study population comprising 486 pts. (mean age 18 years) under medical attendance of the German Heart Center Munich, having undergone operation before 1990. Since 1991 all blood products are routinely tested for anti-HCV.

Method: Serum samples werde collected and examined for anti-HCV antibodies by means of enzyme immuno assay (Abbott EIA II) and westernblot (Mikrogen, Munich) and directly for HCV-RNA by RT-PCR. In addition RNA positive samples were genotyped (RFLP) and quantitated (HCV Amplicor Roche). In all seropositive pts. tests for liver enzymes and auto-antibodies were performed.

Results: Of the 486 pts. examined 14.8% were anti-HCV positive after a mean interval of 17.5 years after the operation compared to 0.65% in an age and sex matched control group. In 55% of the patients HCV-RNA could be detected. Genotype distribution was as follows: 1 a (acc. to Simmonds) 40%, 1 b – 60%, 3 a < 1%. RNA concentration ranged between 250 000 and 1,200 000 genome equivalents/ml. All pts. were clinically stable with only slightly elevated liver enzymes (ALT, AST < 60 U/L) in the positive group.

Summary: These results show a anti-HCV prevalence among the cardiac surgery pts. being 18 times higher than in the normal German population. Despite beeing clinically well in the moment, these pts. are considered to be at risk for chronic liver disease

P3456 Emergency hospital admission of adults with congenital heart disease

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The number of patients (pts) with congenital heart disease (CHD) reaching adulthood is continuously growing. Naturally also the emergency hospital admission quantity in this patient population is rising. The aim of this study was to determine the reason and the nature of the emergency situation that lead to an unscheduled hospital admission into a specialized centre.

During 11 consecutive months a total of 61 pts aged 16 to 58 ys (median 27.0 ys) were acutely admitted to the hospital. The distribution of the underlying CHD was as follows: Fallot's Tetralogy/pulmonary atresia (n = 21), univentricular heart after Fontan procedure (n = 15), atrial switch in complete transposition of the great arteries (n = 10), Eisenmenger syndrom with atrioventricular septal defect (n = 1), truncus arteriosus, or ventricular septal defect (n = 4), congenitally corrected transposition of the great arteries (n = 3), atrial septal defect (n = 2), others (n = 5). 51 of the admitted pts had been previously operated.

The reasons for hospital admission (more than one reason possible) were: atrial or ventricular arrhythmia (n = 31), acute heart failure (n = 16), transient cerebral ischemia or cerebral abscess (n = 3), syncope (n = 3), acute abdomen (n = 2), dissecting aortic aneurysm (n = 1), resuscitation (n = 1), respiratory failure (n = 1), suspected pulmonary embolism (n = 2), endocarditis (n = 1), infected pacemaker electrode (n = 1).

All pts needed immediate emergency care. 18 cases had to be admitted directly to the intensive care unit, 9 pts underwent urgent surgery (heart, brain, or gastrointestinal surgery). 9 pts died. The survivors were hospitalized for 12 ± 10 days.

In conclusion: adults with CHD can experience a broad number of serious emergency situations. Therefore management of this patient population is just successful if all associated specialities cooperate in a supraregional full service referral centre.

ARRHYTHMIAS AND ELECTROPHYSIOLOGY

P3457 Signal-averaged electrocardiography in healthy children: influence of age, gender and anthropometric data

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Signal-averaged electrocardiographic (SAECG) abnormalities provide valuable information in risk stratification of children with various heart diseases culminating in fatal arrhythmias and heart failure. Childhood cancer therapy was also shown to be associated with increased incidence of SAECG abnormalities. Establishing normative data for the pediatric age groups therefore is imperative.

We determined the influence of body characteristics such as height, weight, body surface area (BSA), left ventricular mass, age and gender on SAECG signals and obtained normative data for standard SAECG parameters in a healthy pediatric population.

One hundred healthy children (52 females, 48 males) aged 10.4 ± 3.9 years were studied with high resolution ECG. The study group was divided into three age groups; each age group was divided in two subgroups according to gender. Parameters studied were the signal-averaged QRS duration (QRSd), the duration of the terminal portion of the QRS < 40 micro V of amplitude (LAS40), the root-mean-square voltage of the total QRS complex (RMS-QRS), and the root-mean-square voltage of the last 40 ms (RMS40). Means, standard deviations, minimum and maximum values were determined for each parameter at 25–250 and at 40–250 Hz filtering for the six subgroups. The relation between SAECG parameters and anthropometry was determined by linear regression analysis.

QRSd is significantly influenced by BSA (r = 0.58, p = 0.0001), height (r = 0.58, p = 0.0001), weight (r = 0.56, p = 0.0001),left ventricular mass (r = 0.56, p = 0.0001) and age (r = 0.51, p = 0.0001). There is a weak positive correlation between LAS40 and BSA (r = 0.27, p = 0.01), height (r = 0.26, p = 0.007), weight (r = 0.27, p = 0.01), left ventricular mass (r = 0.27, p = 0.006) and age (r = 0.26, p = 0.01). RMS40 and RMS-QRS are negatively correlated to anthropometric data. QRSd, LAS40 and RMS-QRS are significantly influenced by gender. In boys, LAS40 is influenced by weight (p = 0.04) and left ventricular mass (p = 0.02), in girls by age (p = 0.005), BSA (p = 0.03) and height (p = 0.02). The relation between SAECG parameters and body characteristics is more pronounced in females. Significant differences exist when results are compared to adult normal values.

These data provide a basis for interpretation of SAECG in children. Parameters are influenced by body surface area, height, weight and left ventricular mass. Age and gender also contribute significantly to the variation of some SAECG parameters. In the analysis of SAECG in children, adjustments of results for anthropometric characteristics, age and gender are mandatory.

P3458 Radiofrequency catheter ablation for all types of tachyarrhythmias in children and in patients with congenital heart disease

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Since 1995, we have treated pediatric patients, and patients with congenital heart disease of any age with recurrent tachyarrhythmias (TA), with radiofrequency ablation. The purpose of this study was to present the results of this mode of therapy for all types of TA. Seventy four patients (pts), 48 males, 26 females were treated. There were 68 children, {2.5–18 (mean 12.09 ± 3.8) yrs} and 6 adults (21–45 yrs). Types of TA included: AV nodal reentry tachycardia (AVNRT) in 19 pts, AV reentry tachycardias (AVRT) in 43 pts (20 left, 6 right and 20 septal-3 pts had two pathways), ectopic atrial tachycardia (EAT) in 4 pts, ventricular tachycardia in 6 pts {idiopathic right ventricular (RV) tachycardia in 4, postoperative tetralogy of Fallot (TOF) in 1, RV dysplasia in 1} junctional automatic tachycardia (JAT) in 1 and incisional atrial reentry tachycardia (IART) in 2 pts. One pt had both AVNRT and EAT. Congenital heart disease was present in 12 pts (Ebstein's anomaly in 5, postoperative TOF in 2, and congenitally corrected transposition, common AV canal, tricuspid atresia, transposition of the great arteries after Senning operation, and crisscross heart in 1 each). General anesthesia was used in 38 patients and conscious sedation in the rest. Success rates were 100% for IART, 95% for AVNRT and for AVRT, 75% for EAT, 50% for VT and the procedure was unsuccessful in the JAT pt. Fluoroscopy time was 8–117 min (mean 33.7 ± 27.4). Tachycardia reccurred in 11 pts (14%) and a successful repeat procudure was performed in 6 pts, whereas the rest are controlled with medications. Permanent complete AV block occurred in 1 pt (1.4%) with AVNRT and transient AV block in a pt with a posteroseptal accessory pathway. During follow-up of 1–40 months no other complications were noted.

In conclusion, radiofrequency catheter ablation is a highly efficacious form of therapy for pediatric and congenital heart patients that can be applied to all types of TAs. Highest success rates are expected for supraventricular TAs. The number of acute complications is extremely low and most can be avoided with careful technique. Medium term follow-up is remarkable for paucity of late side effects.

P3459 The effects of cisapride on ventricular repolarization in children

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Life-threatening ventricular arrhythmias mainly attributed to QTc prolongation have been reported in adults and children using cisapride, a prokinetic agent that facilitates gastrointestinal motility. We prospectively studied infants and children receiving cisapride without any concomitant drug, to analyze the time-related effects of cisapride on ventricular repolarization.

Standard 12-lead resting ECGs were obtained from 20 patients (mean age: 6.1 ± 4.1 years; range 2 months–13 years) before cisapride (0.8–1.2 mg/kg per day) therapy, and after 3rd, 7th days and 1 month of therapy. The corrected QT interval (QTc) was calculated by the method of Bazett. Dispersion of QT and QTc (QTD, QTcD) were defined as the difference between the maximum and minimum QT and QTc intervals occurring in any of the 12 leads. Data from these patients were compared with a control group of 372 normal children.

Baseline QTc, QTD and QTcD measurements were not different from control group. Mean QTc values at 7th day and 1 month of cisapride therapy were significantly higher from control group ($p < 0.01$ and < 0.001). Mean QTc at 7th day and 1 month of therapy were also found significantly higher than that of baseline value ($p < 0.05$ and < 0.01)). Mean QTD and mean QTcD values during the cisapride treatment were not different from baseline values and controls. Only two patients (2 and 8 months old) had prolongation of QTc (>450 ms) at 1 month of therapy.

The results of this study suggest that cisapride treatment may cause prolongation of ventricular repolarization without causing increased heterogeneity of repolarization (QT dispersion). Small infants may be more vulnerable to this effect because of reduced activity of p-450 enzyme system. However, clinical significance of these findings is unclear, because all the patients in this study group have been asymptomatic without signs of arrhythmia.

P3460 Ventricular arrhythmia, late potentials, QT dispersion and heart rate variability 5 to 18 years after surgery of tetralogy of Fallot: an increase of risk factors?

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Sudden death (SD) due to late complex ventricular arrhythmia (cVA) is important problem in patients (pts) after surgical repair of Tetralogy of Fallot, and may increase with longer interval after operation. We thus investigated, whether longer (≥10 years) time after surgery can have influence on occurrence of factors, which were proposed to be related to the risk of SD, i.e. cVA, late potentials (LP), QT dispersion (QTd) and heart rate variability (HRV).

Methods: We distinguished 2 groups of pts: group A (<10 years after operation, mean 7.6 [± 1.3] years) – 21 pts, aged 7 to 12 years (mean 7.9 ± 1.5 years), and group B (≥10 years after operation, mean 12 [± 2.6] years) – 23 pts, aged 13 to 20 years (mean 16.3 ± 2.4 years). All subjects were in good hemodynamic status assessed by clinical and non-invasive examination. In all pts standard resting, ambulatory (48 h), exercise, signal-averaged ECGs, and short-term ECG for HRV spectral analysis were performed. According to HRV standards: total power (TP), low-frequency (LF), high-frequency (HF), and additionaly power coherent with respiration (CRP) were calculated by Berger's and validated by the autoregressive method. Statistical evaluation was performed by use of logistic and linear regression analyses.

Results: In pts operated more than last decade the risk of occurrence of cVA (couplets in 7 pts, a non-sustained VT in 1 pt) was more than 3-times higher (odds ratio = 3.2, $p > 0.13$, 95% confidence interval 0.71 ÷ 14.42) and risk of occurrence of LPs was 5-times higher (odds ratio = 4.7, $p > 0.07$, 95% confidence interval 0.84 ÷ 25.77) than in those operated less than 10 years. There were significant ($p < 0.05$) correlations between time from repair and QTd (r = 0.30), LF/HF (r = 0.42), normalized HF power (r = −0.42) and CRP (r = −0.43).

Conclusion: Accumulation, with time after surgery of Tetralogy of Fallot, of risk factors having influence on the electrical stability of the heart were observed in pts operated more than last decade.

P3461 Usefulness of the P-wave triggered signal-averaged ECG in predicting risk of paroxysmal supraventricular arrhythmias among children with atrial septal defect

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Paroxysmal supraventricular arrhythmias (SVA) often complicate the natural history of atrial septal defect (ASD). In a group of 50 consecutive children and adolescents (age: 11 ± 7 yrs) with ASD we applied the P-wave triggered signal-averaged ECG (ASAECG) to investigate atrial electrophysiologic properties and to assess whether this method could be useful in detection those at risk of the development of SVA. Eighteen sex- and age-matched healthy children (age: 12 ± 5 yrs) formed a control group (C). The following ASAECG parameters were calculated: the root-mean-square voltage for the terminal 10, 20, 30 ms of filtered P-wave (RMS10, 20, 30) and time duration of filtered P-wave (PWD).

Results. In the whole group of ASD pts we found longer duration of the PWD and lower values of RMS10 compared to controls (106 ± 13 vs 94 ± 14 ms, 5.2 ± 2.1 vs 6.4 ± 2.0 μV, ASD vs C, $p < 0.05$). None of the ASAECG parameters significantly correlated with the baseline clinical characteristics, the right ventricle diameter (RVD) and the ratio of pulmonary to systemic flow (Qp:Qs). Eight (16%) ASD pts revealed paroxysmal SVA (atrial fibrillation in 8 pts and supraventricular tachycardia in 2 pts) on 24 h Holter monitoring. They demonstrated more compromised haemodynamic status (table), but also a decreased value of RMS10 and RMS20 compared to pts without paroxysmal SVA. The PWD and RMS30 did not differ between groups.

	PWD (ms)	RMS10 (μV)	RMS20 (μV)	RVD (mm)	Qp:Qs
SVA+ (n = 8)	109 ± 11	3.8 ± 1.0*	6.3 ± 1.6	24 ± 6*	2.9 ± 1.0*
SVA− (n = 42)	106 ± 14	5.5 ± 2.2	8.0 ± 3.0	20 ± 5	1.7 ± 0.6

*- $p < 0.05$ SVA+ vs SVA−; $p = 0.09$ for RMS20

Conclusions. Children and adolescents with ASD and paroxysmal SVA demonstrate unfavourably altered atrial electrophysiologic properties which do not simply reflect impaired haemodynamic status. P-wave triggered SAECG could be a useful technique for detecting children with ASD at risk of paroxysmal SVA.

P3462 Management and outcome of atrial flutter in the perinatal age group

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Background: Perinatal atrial flutter is a potentially lethal arrhythmia. Management of this rhythm disorder in the perinatal period is difficult and controversial.

Methods: A group of 44 pts with documented atrial flutter was studied retrospectively.

Results: Atrial flutter was diagnosed prenatally in 43 fetuses and immediately postnatally in one neonate. Fetal hydrops was seen in 19 pts, of whom 16 received matemal therapy. Two were delivered and one not treated, because of a severe non-treatable cardiac malformation. In the non-hydropic group of 24 pts 16 were treated and the remaining 8 were delivered immediately. In the hydropic group 10 received single-drug therapy (digoxin or sotalol), 6 multiple-drug therapy. In the non-hydropic group 12 received a single drug (digoxin or sotalol) and 4 multiple drugs. One pt with rapid 1:1 atrio-ventricular conduction (heart rate 480/min) died in utero. Of the 43 liveborn infants 12 were in atrial flutter at birth. Electrical cardioversion was successfull in 8 of 9 pts. Transvenous overdrive atrial pacing was successfull in one of 2 pts where it was used. No recurrences in atrial flutter have occurred beyond the neonatal period. Neurological damage of prenatal origin, however, was encountered in 4 pts, including ischaemic damage, intra-ventricular hemorrhage and infarction.

Conclusions: Fetal atrial flutter is a serious and threatening rhythm disorder and particularly when it causes hydrops. It may be associated with fetal death or neurological damage. Treatment is required primarily aimed at reaching an adequate ventricular rate and preferably conversion to sinus rhythm. Digoxin failed in prevention of recurrence at time of delivery in a quarter of our pts, while with sotalol no recurrence of atrial flutter has been reported. Therefore class III agents may be the future therapy. Once fetuses with atrial flutter survive without neurological damage, their future is good and prophylaxis beyond the neonatal period is unnecessary.

P3463 Haemodynamically optimized temporary cardiac pacing after surgery for congenital heart defects

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Disturbance of normal AV synchrony and dyssynchronous ventricular contraction may have deleterious effect on pts with otherwise compromised hemodynamics. This study evaluated the effect of hemodynamically optimized temporary dual-chamber pacing in pts after surgery for congenital heart disease.

Methods: Pacing was performed in 23 children with various postoperative dysrhythmias, low cardiac output and/or high inotropic support aged 5 days to 7.7 years (median 7.3 months) and optimized to achieve highest systolic and mean arterial and lowest mean central venous and/or left atrial pressures. Following pacing modes were used: 1. Atrial triggered or AV sequential pacing with individually optimized AV delay in 12 pts with 1st–3rd° AV block. 2. AV sequential pacing using transesophageal atrial pacing in combination with a temporary VAT pacemaker for atrial tracking and ventricular pacing in 2 pts with 3rd° AV block and poor signal and exit block on atrial epicardial pacing wires. 3. R wave triggered atrial pacing in 8 pts with junctional ectopic tachycardia and impaired antegrade AV conduction precluding the use of atrial overdrive pacing. 4. Atrio-biventricular sequential pacing in 2 pts. Implantable pulse generators customized for temporary pacing were used to improve atrial sensing and allow for high synchronization rates combined with long AV delays necessary for R wave triggered atrial pacing.

Results: Optimized pacing led to a significant increase in arterial systolic (mean) pressure from 71.5 ± 12.5 (52.3 ± 9.0) to 80.5 ± 12.2 (59.7 ± 9.1) mmHg ($p < 0.001$ for both) and decrease in central venous (left atrial) pressure from 12.3 ± 3.4 (10.5 ± 3.2) to 11.0 ± 3.0 (9.2 ± 2.7) mmHg ($p < 0.001$ and < 0.005, resp.) (compared to spontaneous rhythm, VVI pacing or dual-chamber pacing with empirically set AV delays at identical heart rates). Optimal AV delay settings during AV synchronous pacing ranged from 15 to 140 ms (15–50 ms in 13/16 pts). Atrio-biventricular pacing added further hemodynamic improvement to AV sequential univentricular pacing in both evaluated pts.

In conclusion, individually optimized temporary dual chamber pacing was successfully used to improve hemodynamics in pts with poor ventricular function and various dysrhythmias after congenital heart surgery. Very short AV delays during AV synchronous pacing were necessary in the majority. Biventricular pacing carried an additional hemodynamic benefit to optimized AV synchrony. Technical limitations could be overcome by customized pacing equipment.

P3464 Fetal complete atrioventricular block: perinatal outcome

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The clinical course and outcome with complete atrioventricular (AV) block detected prenatally were studied to identify factoes that affect the natural history of this lesion.

Methods: We used Fetal echocardiography to study complete AV block. The study included 27 fetuses with complete AV block between 19–38 week's gestation. In 14 fetuses (52%) complete AV block was associated with complex structural heart defects, usually left atrial isomerism (n-8) or discordant AV connection (n-3). The other 13 fetuses had normal cardiac anatomy; in 9 cases the mother had connective tissue disease or tested positive for antinuclear antibodies. Three fetuses showed progression from sinus rhythm or second degree block to complete AV block. Of the 27 pregnancies, 3 were terminated and 12 fetuses or neonates died; at the and of the neonatal period 13 fetuses were still alive. Fetal or neonatal death correlated significantly with the presence of structural heart defects (2 of 14 surviving, $p < 0.001$), hydrops (0 of 11 surviving, $p < 0.001$), an atrial rate < 120 beats/min (1of 6 surviving, $p < 0.005$) or a ventricular rate < 55 beats/min (1 of 10 surviving, $p < 0.001$). Mean atrial and ventricular rates were higher in surviving than in nonsurviving fetuses (142 ± 8 vs. 127 ± 21 beats/min, $p < 0.002$; 64 ± 6 vs. 52 ± 8 beats/min, $p < 0.001$, respectively). A slow atrial rate, however, was frequently associated with left atrial isomerism. In fetuses without left isomerism, mean atrial rate was not significantly different in surviving and nonsurviving fetuses (142 ± 8 vs. 144 ± 15 beats/min, $p = 0.66$), whereas ventricular rate remained different (64 ± 8 vs. 53 ± 8 beats/min, $p < 0.001$). In two cases transplacentar treatment by administering sympathomimetic drugs to the mother was attempted. Although ventricular rate increased variably, only one of these four fetuses, which had no additional structural defect, survived. Effective forms of fetal therapy are not established. A postnatal prmanent pacemaker was implanted in 6 neonates; 4 survived the neonatal period.

In conclusion: Fetal echocardiography must be considered a useful in the study of greater undestanding factors that influence the natural history of fetal complete AV block.

CONGENITAL HEART DISEASE IN FOETUSES AND NEWBORNS

P3465 Impact of fetoscopic versus open fetal surgery on fetoplacental blood flow and outcome in human foetuses

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Introduction: The outcome of human fetal cardiac interventions may be influenced by the impact of the operative approach on fetoplacental blood flow. Therefore, the purpose of our study in human fetuses was to assess the effects of a fetoscopic versus an open operative approach on fetoplacental blood flow, neurological damage and fetal demise.

Methods: Fetoplacental blood flow was studied in 21 human fetuses before and on the day after fetoscopic (n = 6) or open (n = 15) fetal surgery for a noncardiac lesion by 2-dimensional and pulsed-Doppler ultrasound. Hemodynamic variables measured or calculated were umbilical arterial (UA) systolic, diastolic and mean flow velocities. Neurologic damage was assessed with prenatal head ultrasound and/or postnatal evaluation. Variables were analyzed using Bonferroni's paired samples t-test and individual samples t-tests and are presented as mean and SD considering a $p < 0.05$ as significant.

Results: Before fetal surgery, systolic, diastolic and mean umbilical arterial blood flow velocities were similar in the fetuses undergoing fetoscopic versus open fetal surgery (systole 40.0 ± 7.0 cm/sec vs. 36.2 ± 5.0 cm/sec, $p = 0.17$; diastole 11.3 ± 5.1 cm/sec vs. 9.7 ± 1.7 cm/sec, $p = 0.31$; mean 22.3 ± 5.3 cm/sec vs. 21.8 ± 3.1 cm/sec, $p = 0.82$). On the day after fetal surgery, systolic, diastolic, and mean umbilical arterial flow velocities were significantly higher after the fetoscopic than the open operative approach (systole 43.1 ± 13.1 cm/sec vs. 28.2 ± 8.4 cm/sec, $p = 0.009$; diastole 16.1 ± 15.0 cm/sec vs. 6.3 ± 2.8 cm/sec, $p = 0.047$; mean cm/sec 26.9 ± 12.1 vs. 14.2 ± 4.2 cm/sec, $p = 0.005$). There was a strong trend to lower mortality and less neurological damage after the fetoscopic approach versus the open operative group (29% vs. 64%, $p = 0.12$; 14% vs. 43%, $p = 0.2$).

Conclusion: In human fetuses, a fetoscopic operative approach preserves fetoplacental blood flow better than an open one. This finding may explain the trend for lower mortality and less neurological damage following the minimally invasive fetoscopic approach and strengthens its value for fetal cardiac interventions.

P3466 Homeometric autoregulation enables the right ventricle of the newborn animal to maintain cardiac output during infant respiratory distress syndrome and subsequent partial liquid ventilation

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Infant Respiratory Distress Syndrome (IRDS) causes increased pulmonary vascular resistance with a raised afterload. Subsequent Partial Liquid Ventilation (PLV) improves respiratory conditions but may further raise pulmonary vascular resistance. We investigated the effects of artificially induced IRDS and subsequent PLV on RV and LV systolic pump function and on pulmonary and systemic hemodynamics in the newborn lamb.

Methods: IRDS was induced by lung lavages in nine newborn lambs that were subsequently treated with PLV for 30 min (PLV-30) and 60 min (PLV-60). RV and LV contractilities were assessed using indices derived from RV or LV end-systolic pressure-volume relations, obtained by micromanometric and conductance catheters during inferior vena cava occlusion.

Results: Pulmonary function deteriorated during IRDS with a significant decrease in P_AO_2/FiO_2 whereas pulmonary artery pressure (P_{AP}) and pulmonary vascular resistance increased significantly. Cardiac output (CO) and stroke volume (SV) did not change. RV contractility showed a significant increase during IRDS: the slope of the end-systolic pressure-volume relation ($RV\text{-}E_{ES}$) increased while its volume intercept at 5 kPa ($RV\text{-}V_5$) decreased. Pulmonary function recovered during PLV whereas P_{AP} and pulmonary vascular resistance remained high. RV contractility showed a sustained significant increase. Indices for LV pump function and contractility were always unchanged.

	Baseline	IRDS	PLV-30	PLV-60
P_AO_2/FiO_2	0.60 ± 0.13	$0.10 \pm 0.06^*$	$0.35 \pm 0.13^\#$	$0.26 \pm 0.16^\#$
P_{AP} (kPa)	2.22 ± 0.58	$3.60 \pm 1.32^*$	$3.40 \pm 0.86^*$	$3.52 \pm 0.84^*$
$RV\text{-}E_{ES}$ (kPa/ml)	1.22 ± 0.58	$1.88 \pm 0.64^*$	$2.07 \pm 0.71^*$	1.69 ± 0.86
$RV\text{-}V_5$ (ml)	1.88 ± 0.64	$0.91 \pm 0.46^*$	$1.15 \pm 0.35^*$	$1.01 \pm 0.63^*$

$^*P < 0.05$ compared with baseline. $^\#P < 0.05$ compared with IRDS

Conclusion: IRDS increases pulmonary vascular resistance and right ventricular contractility without significantly changing left ventricular contractility. With subsequent partial liquid ventilation, lung function improves but pulmonary vascular resistance remains high with no further change in cardiac performance. It is shown that with the increased pulmonary vascular resistance, the right ventricle of the newborn heart is able to maintain cardiac output through homeometric autoregulation.

P3467 Prenatal diagnosis of congenital heart disease prevents pre-operative lact-acidosis in the newborn patient

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Background: Duct-dependent congenital heart disease may not cause problems during fetal life but can in immediate postnatal life. Prenatal detection and immediate postnatal care, including prostaglandin administration, might improve management of the disease, lead to better blood gas control and thus prevent severe pre-operative lact-acidosis.

Methods: Patients operated upon for congenital heart disease during the first 31 days of life (n = 164) were studied retrospectively, 16 were diagnosed prenatally (group A) and 148pts had not been diagnosed prenatally (group B). The prenatally diagnosed pts were delivered within the University Hospital, received prostaglandin immediately and were intubated and ventilated if needed. The other 148 pts were all born in outlying hospitals or at home and were transported in after congenital heart disease was suspected.

Results: differences were noted in post-op intensive care duration (group A vs. B: 4.40 ± 1.54 vs. 9.51 ± 2.29 days, $p = 0.48$), pre-op pH (7.30 ± 0.03 vs. 7.27 ± 0.01, $p = 0.30$), BE (-5.10 ± 0.78 vs. -6.16 ± 0.55 mmol/l, $p = 0.54$) and *lactate* 3.14 ± 0.57 *vs.* 6.33 ± 0.58, $p < 0.001$), indicating a significant difference in blood lactate in favor of the prenatally diagnosed group.

Conclusions: Prenatal diagnosis of congenital heart disease and the resulting immediate postnatal care prevent lactate increase in the pre-operative period of these patients. This decreases the risk of cerebral damage and brings the patient in better condition at surgery.

P3468 Electron microscopic and morphometry data does not correlate with the functional and haemodynamic response to growth hormone in patients with dilated cardiomyopathy

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Seven men with idiopathic dilated cardiomyopathy were selected on the basis of normal angiography, normal growth hormone secretion, HYHA Class II-III, and an ejection fraction of less than 40%. All patients had hormonal, functional (gated blood pool scan to assess LVEF and exercise test), haemodynamic (right heart catheterization) and endomyocardial biopsy (EMB) (myofibrillar volume/cell volume%) at baseline, 3 momths therapy with human growth hormones at 14 IU/per week.

Results: Administration of growth hormone improved clinical symptoms and exercise capacity in all the patients. LVEF% improved from 35 ± 1.3 to 48 ± 1.7, $p < 0.001$) and decreased both SVR and PVR (2580 ± 1200 to 1929 ± 500 dyne/s/cm^{-5}, $p < 0.001$ and 200 ± 120 to 158 ± 108 dyne/s/cm^{-5}, $p < 0.01$)respectively. There was no change in PCWP. However, electron microscopy and morphometry of 7 EMB showed no change in myofibrillar content before and after 3 months of GH administration (myofibrillar volume/cell volume, from 29 to 32%).

Conclusion: The myofibrillar content of myocardium from patients with dilated cardiomyopathy does not change in response to GH administration inspite of functional and haemodynamic improvement. The efficacy of GH administration in patients with dilated cardiomyopathy should be revised and mechanisms other than increased myofibrillar content should be explored.

CORONARY VASOREACTIVITY AND FLOW RESERVE

P3469 Effects of simvastatin and enarapril on vasomotion of resistance coronary artery

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Background: Management for hypercholesetrolemia and/or hypertension to prevent coronary artery disease, has great clinical significance, but remains to be pathophysiologically investigated. This study was conducted to evaluate clinical effects of simvastatin and/or enarapril upon vasomotion of resistance coronary artery.

Methods: Thirty-seven hypercholesterolemic and/or hypertensive patients were enrolled into the study to test the effects of simvastatin (S) and/or enarapril (E) on vasomotion of coronary artery and randomized to the four groups, where the patients were treated with S (Group-S, n = 8), with E (Group-E, n = 10), or with S and E (Group-SE, n = 7), and followed without S or E (Group-C, n = 12). We administered S, E, S and E (5–10 mg per day) for more than 6 months. We quantified endothelium-dependent or -independent response to acetylcholine (Ach) or ATP into the study left coronary artery (coronary flow reserve (CFR): maximal hyperemic flow – baseline flow/baseline flow), by coronary angiography and intracoronary doppler guidewire. Changes in flow reserve were evaluated in the four study groups.

Results: CFR to Ach or ATP showed no significant change in Group-C (CFR to Ach: from 55 ± 28% to 52 ± 28%, CFR to ATP: from 200 ± 66% to 204 ± 63%, n.s.). CFR to Ach not ATP was significantly improved in Group-S (from 35 ± 19% to 56 ± 22%, p = 0.03, from 198 ± 61% to 202 ± 62%, n.s., respectively). CFR to not ACh but ATP was improved in Group-E (from 50 ± 23% to 73 ± 38%, n.s., from 170 ± 64% to 198 ± 56%, p = 0.03, respectively). CFR to Ach and ATP were improved in Group-SE (from 34 ± 23% to 83 ± 54%, p = 0.02, from 149 ± 84% to 198 ± 115%, p = 0.01, respectively).

Conclusion: This study suggests that simvastatin and enarapril, alone or together, improve vasomotion of resistance coronary artery and may have beneficial potentials for management of coronary artery disease.

P3470 Unexplained myocardial lactate production as an acute result after intracoronary calcium-antagonist application in patients with syndrome X

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Calcium-antagonists are often used in patients with chest pain and normal coronary angiograms. The acute coronary and myocardial reactions of calcium-antagonists in patients with syndrome X remain unclear.

Methods: Average peak flow velocity (APV) in the LAD was in-vestigated 12 patients with Syndrome X (mean age: 50 years [range 25 – 69 years]). Lactate concentration and oxygen saturation (SaO_2) were measured in the aorta (A) and coronary sinus (CS) simultaneously before and after an intracoronary bolus of the calcium-antagonist verapamil (1 mg).

Results: After verapamil APV increased from 16.0 ± 4.4 cm/s to 40.17 ± 11.2 cm/s ($p < 0.001$). Besides a difference in lactate concentration in A and CS before and after verapamil application, there is a change from an initial myocardial lactate consumption to a lactate production after verapamil (table 1). At the same time SaO_2 increased significantly in the CS due to a decrease in O_2 extraction.

table 1

	SaO_2 baseline	Lactate baseline	SaO_2 verapamil	Lactate verapamil
A	94.9 ± 3.2#	1.09 ± 0.36*	96.4 ± 1.5#	0.89 ± 0.43*
CS	40.2 ± 19.4***	1.03 ± 0.39*	73.3 ± 3.0***	1.21 ± 0.36*
A-CS	54.8 ± 19.1***	0.07 ± 0.24***	23.2 ± 2.4***	−0.31 ± 0.30***

#not significant, *p < 0.05, ***p < 0.001; SaO_2 [%], Lactate [mmol/l]; A-CS: Difference in lactace concentration between aorta (A) and coronary sinus (CS)

Conclusion: There is an unexplained increase in coronary sinus lactate concentration after verapamil in patients with syndrome X. These findings have not been reported before and may be due to an altered myocardial metabolism with lactate production during ischemia, a wash out effect, or steal phenomenon.

P3471 Can intravenous administraiton of adenosine produce the maximal hyperaemic response in patients with acute myocardial infarction? Comparison to intracoronary adenosine during Doppler flow wire

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Studies have shown that intracoronary and intravenous administration of adenosine produces a similar augmentation in coronary blood flow in normal coronary circulation. This study was designed to compare the hyperemic response between intracoronary (IC) and intravenous (IV) adenosine tri-phosphate (ATP) in the reperfused legion of myocardial infarction (MI) using a Doppler flow wire (DFW).

Methods: Coronary flow reserve (CFR) was obtained using DFW from 25 patients (pts) with MI who underwent reperfusion therapy by direct percutaneous transluminal coronary angioplasty. A 0.014-inch DFW was placed in the distal portion of the reperfused coronary artery lesion immediately (Group A), 3 weeks (Group R) and 3–6 month (Group O) after reperfusion. A CFR of non-infarcted artery was also measured in the pts with MI (Group N). The hyperemic response to IC and IV ATP was compared (150 μg/kg/min intravenous vs. 50 μg in LCA or 25 μg in RCA intracoronary injection). A CFR was calculated as the ratio of ATP-induced to baseline averaged peak velocity (APV).

Results: Immediately after reperfusion (Group A), IC ATP produced greater hyperemic response than IV ATP. Hyperemic response between IC and IV ATP was similar both in non-infarcted (Group N) and in infarcted coronary artery 3–6 month (Group O) after reperfusion. The pts were devided into two groups according to the ratio of IC to IV CFR, group L (IC/IV CFR < 1.5) and group H (IC/IV CFR ≥ 1.5). Group H has significantly smaller basal APV than group L (APV; 9.8 ± 2.1 vs. 17.5 ± 6.8, p = 0.012).

	Group A	Group R	Group O	Group N
CFR (iv)	1.62 ± 0.50	1.98 ± 0.46	2.33 ± 0.64	2.76 ± 0.85
CFR (ic)	2.25 ± 0.95	2.25 ± 0.64	2.47 ± 0.67	2.87 ± 0.77
P value	0.016	0.086	0.52	0.48

(mean ± SD.)

Conclusions: IC ATP produced greater hyperemic response than IV ATP in the infarcted coronary artery bed immediately after reperfusion in pts with MI. Intravenous ATP could not produce maximal hyperemia in the reperfused coronary circulation specifically with low coronary flow velocity derived by DFW. These results indicate that intravenous drug administration for detecting flow reserve is inadequate route for pts with MI immediately after reperfusin, especially with low flow velocity.

P3472 Computational fluid dynamics analysis in a coronary artery bifurcation stenosis model

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Background: A Computational Fluid Dynamics (CFD) analysis of a coronary bifurcation model, under different stenoses, was performed, using a 2D, steady, laminar, unstructured grid. The effects of stenoses on the static pressure, wall shear stress, velocity and molecular viscosity were examined.

Methods: An unstructured grid program was used to analyze the non-Newtonian blood flow in a LAD bifurcation with several degrees of stenosis. The initial geometry coordinates were taken from a normal subject. The stenoses coordinates follow the traces of low velocity and low shear stress regions. Various blood flow velocities were applied namely 0.17 m/s, 0.34 m/s and 0.68 m/s which correspond to rest condition, moderate and strenuous exercise, respectively. Static pressure, wall shear stress, velocity and molecular viscosity distribution were computed for all three branches and for all available stenoses.

Results: From the CFD analysis of the normal coronary bifurcation model results show that low wall shear stress and low velocity values occur at regions opposite to the flow divider result which agrees with preferred sites of atherosclerotic lesions in human. In the stenosis region, as the flow velocity increases, the pressure decreases and subsequently the wall shear stress increases. In the maximum degree of tested stenosis (over 70.0%) and under the maximum inflow velocity, 0.68 m/s, the maximum wall shear stress value was 225.0 N/m^2, which far exceeds the reported experimental value of 37.9 N/m^2 for endothelial denudation. Under all stenoses tested cases, static pressure distribution in the upstream to the flow divider area, increases at high blood velocities.

Conclusion: The wall shear stress increases with stenosis. At extreme flow velocity (rigorous exercise) the wall shear stress value far exceeds the endothelial denudation point.

P3473 Sympathetic stimulation using cold pressor test increases coronary collateral flow

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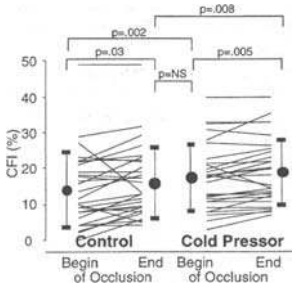
Background/Methods: Little is known about the function of coronary collateral vessels. The purpose of this study was to examine the collateral flow under a strong sympathetic stimulus (cold pressor test, CPT). In 30 patients (62 ± 12 years) with coronary heart disease two coronary occlusions were performed. In a randomized order, a CPT was performed in one occlusion. Two minutes before and during the 1 minute-occlusion, one of the patient's hands was submerged into ice water. For the calculation of a perfusion pressure-independent collateral flow index (CFI), the aortic (Pao), the central venous (CVP) and the coronary wedge pressure (Poccl) were measured (CFI = (Poccl − CVP)/(Pao − CVP)).

Results: The CPT lead to an increase of Pao from 98 ± 14 mmHg to 105 ± 15 mmHg (p = 0.002). CFI increased during occlusion from 14% ± 10% to 16% ± 10% and from 17% ± 9% to 19% ± 9% without and with CPT, respectively.



Conclusions: During ballon occlusion collateral flow increases due to collateral recruitment independently of sympathetic stimulation. The CPT additionally increases collateral flow. This may reflect a coronary collateral vasodilation mediated by the sympathetic nervous system. This collateral flow increasing effect is comparable to the effect of the occlusion itself.

P3474 Effects of electrical neurostimulation on coronary haemodynamics

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Neurostimulation reduces anginal complaints and myocardial ischemia in patients with angina pectoris refractory to conventional strategies, putatively by altering the microcirculation in the heart. To test this hypothesis, we studied 14 patients, scheduled for an elective angioplasty (PTCA) with single vessel disease in the left anterior descending coronary artery (LAD). Prior to the PTCA the effect of Transcutaneous Electrical Nerve Stimulation (TENS; Lifecare LTD, Shnuel Israel) was studied on average peak flow velocity (APV; Doppler flow wire, Flomap, Cardiometrics, Mountainview, Ca USA) and coronary diameter (quantitative coronary angiography, QCA) simultaneously in the stenotic LAD and smooth circumflex coronary artery (LCX) (10 patients). Four patients served as a control group. Volumetric flow was calculated from these measurements.

Results (mean ± S.E.M.):

	LAD		LCX	
	Baseline	Sham	Baseline	Sham
QCA (mm)	2.95 ± 0.02	2.94 ± 0.03	2.60 ± 0.16	2.65 ± 0.19
APV (cm/s)	27.7 ± 8.5	27.9 ± 8.7	20.6 ± 4.8	20.0 ± 4.9
Flow (ml/min)	89.8 ± 26.7	90.6 ± 27.5	48.4 ± 5.1	48.2 ± 5.5

	LAD		LCX	
	Baseline	Tens	Baseline	Tens
QCA (mm)	2.92 ± 0.18	2.80 ± 0.15*	3.24 ± 0.26	3.41 ± 0.23*
APV (cm/s)	25.2 ± 3.5	24.4 ± 3.3	21.6 ± 2.8	21.5 ± 3.0
Flow (ml/min)	49.9 ± 8.1	44.8 ± 7.4*	54.5 ± 11.5	60.5 ± 11.2*

*$p < 0.05$ versus baseline

TENS increased coronary flow in the non-stenotic artery and decreased flow in the stenotic coronary artery. Considering that neurostimulation reduces ischemia, the beneficial effect is likely to be explained by an improvement of micro-collateral flow to the ischemic myocardium.

P3475 Post-ischaemic coronary flow reserve impairment and changes induced by α1- and α2-adrenergic blockade

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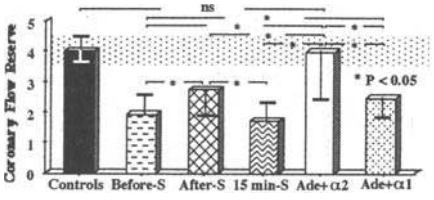
The capacity of coronary arteries to dilate is impaired in the presence of ischemia, and it is controversial whether coronary flow reserve (CFR) may normalize shortly after coronary stenting (S). Accordingly in 30 patients undergoing S for an 85 ± 5% stenosis and in 15 normal controls we evaluated CFR with intracoronary flow wires (Cardiometrics) and 24-μg IC adenosine (Ade). In addition we investigated if α 1-(urapidil 10-mg IC) or α 2- (yohimbine 2-mg IC) adrenergic blockade superimposed to 140-μg/kg for 5 min IV adenosine infusion might improve or normalize CFR. CFR was measured in patients before-S, soon after-S, 15-min later (15 min-S) and after superimposing α1- and α2-blockers on top of adenosine IV infusion. Epicardial coronary diameters were measured at the level of the wire tip by quantitative angiography. The results are shown in figure (mean ± SD).



Conclusions: Coronary stenting transiently improved but did not normalize CFR (2.73 ± 0.9). CFR became normal only superimposing α2-adrenergic blockade (4.09 ± 1.4) on top of Ade, i.e. inducing additional microvascular dilation, whereas the higher increase in blood flow obtained with α1-blockade as compared with α2-blockade was mainly due to conduit coronary arteries dilation.

P3476 Coronary collateral flow and its protective potential against future myocardial infarctions

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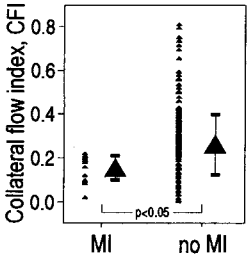
Purpose: The purpose of this prospective study was to determine whether collateral flow has a protective function against future myocardial infarctions.

Methods: In 263 patients (pts) the occurrence of myocardial infarction (MI) was monitored during a follow-up period of 3 to 34 months following invasive study of collaterals. All the pts underwent coronary angioplasty (PTCA) and a collateral flow index (CFI) determination using intracoronary (i.c.) pressure- or Doppler-guidewires. Mean aortic (P_{ao}) and distal occlusive (P_{occl}) pressure during PTCA or distal flow velocity integral during (Vi_{occl}) and after ($Vi_{0\text{-}occl}$) PTCA were measured continuously. The pressure derived CFI was calculated as follows: $(P_{occl} - 5)/(P_{ao} - 5)$. Doppler-derived CFI: $Vi_{occl}/Vi_{0\text{-}occl}$ The angiographic collateral degree was also assessed accoding to the extent of epicardial coronary artery filling through collateral channels (Rentrop 0–3). Based on the absence or presence of ST-segment changes (< or ≥1 mm) on i.c. ECG during PTCA, the patients were considered to have sufficient or insufficient collaterals.

Results: During the follow-up period (mean 13 ± 5 mounths), 12 patients had a MI.

	Myocardial infarction	No myocardial infarction	P
n	12	251	
Age	64 ± 12	59 ± 10	NS
%-Stenosis	81 ± 12%	82 ± 13%	NS
CFI	0.14 ± 0.06	0.24 ± 0.17	<0.05
Rentrop (0–3)	0.5 ± 0.5	1.1 ± 0.9	<0.05
insufficient	100%	72%	< 0.05

%-Stenosis: %-stenosis before PTCA; CFI: Collateral flow index; insufficient: ST-segment shift during PTCA



Conclusions: In this relatively large population with coronary artery disease and quantitatively assessed coronary collaterals, their effectiveness against future myocardial infarction can be clearly demonstrated.

P3477 Acute effects of intravenous amlodipine on coronary microcirculation in humans. Results from the pressure/flow curve analysis

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Many studies suggest that non-ischemic heart failure is associated with impaired coronary microcirculatory function stimulating much interest on drugs potentially able to dilate the coronary microcirculation. Experimantally, amlodipine (Aml) has powerful coronary vasodilating properties; however, it is not known whether and to which extent it is able to dilate the coronary microcirculation in man. In this study the vasodilating effects of Aml on human coronary microcirculation were tested in comparison with adenosine (Ado), one of the most effective coronary vasodilating agents.

Methods: In 10 normal subjects (4 men, mean age 51 ± 15 yrs, range 25–67), coronary flow velocity (CFV) (Doppler flowire into the left anterior descending coronary artery) and left coronary perfusion pressure (2F Millar catheter at the ostium of the left main) were measured at baseline, during Ado (0.5–2 mg intracoronary bolus) and 30 min after i.v. Aml (10–20 mg according to blood pressure response). Data were acquired on a PC and processed offline. Coronary flow reserve (CFR) was obtained as the ratio of CFV during vasodilation (Ado or Aml) and at baseline. The slope of the istantaneous diastolic CFV/pressure curve (IDVPS) (cm/sec/mmHg) was used to measure coronary conductance which, in the absence of epicardial coronary stenosis, reflected the maximal vasodilation achieved by the coronary microcirculation during Ado and 30 min after Aml.

Results: Mean CFV was 16 ± 7 cm/sec at baseline and significantly increased to 50 ± 12 cm/sec during Ado ($p < 0.01$) and to 22 ± 8 cm/sec during Aml ($p < 0.05$). CFR was higher during Ado than during Aml (3.5 ± 0.8 vs 1.5 ± 0.4; $p < 0.01$). However, the IDVPS was not different in the two study conditions (1.7 ± 0.7 vs 1.4 ± 0.7, respectively; ns).

Conclusions: Aml induces a significant coronary vasodilation in normal subjects. The vasodilatory effect of Aml, in terms of CFR, is lower than that of Ado while the effetcs of the two drugs on diastolic coronary conductance, i.e. their abilities to dilate the coronary microcirculation, are similar. These results suggest that Aml may be beneficial in pts with non-ischemic heart failure due to its powerful vasodilatig effects on the coronary microcirculation.

P3478 Non-invasive measurement of blood flow in the left anterior descending artery and great cardiac vein

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Purpose: With magnetic resonance (MR) flow mapping it is possible to quantify flow velocity and volume flow in the coronary vessels in a noninvasive way. The close anatomic relationship of the Left Anterior Descending Artery (LAD) with the Great Cardiac Vein (GCV) allows imaging both in one view. We examined the feasibility to discriminate between these two vessels and to measure the flow quantitatively.

Methods: Nine individuals with a normal LAD and 6 patients with a diseased LAD [3 after anterior myocardial infarction (MI) of whom 1 with occluded LAD and collateral supply] underwent MR imaging to quantify the flow in the LAD and GCV. From MR images, using connectivity to the aortic root, differentiation between the LAD and GCV was made. Perpendicular to the LAD MR phase contrast velocity mapping was performed within a breath-hold. A Region of Interest (ROI) was drawn around the LAD, GCV and myocardial tissue, to analyze the flow data.

Results: After correction for cardiac motion of the vessel, differentiation can be made between the GCV and the LAD using the flow pattern. The flow in the GCV is mainly systolic and points in the inverse direction as the flow in the LAD, which is mainly diastolic. These criteria appeared valid in all individual subjects, even in cases of highly stenotic arteries. Volume flow measurements corrected for BSA;

	LAD (ml/min/m^2)	GCV (ml/min/m^2)
Normal (n = 9)	32 ± 17	−24 ± 21
Diseased (n = 5)	26 ± 7	−17 ± 18
Occluded LAD and collaterals	-	−7

Conclusion: Magnetic resonance is a unique tool for noninvasive, simultaneous measurement of the flow pattern and volume flow in the GCV and the LAD. A possible clinical application of measuring venous coronary flow is the assessment of collateral supply.

P3479 Impairment of coronary vasodilator reserve after successful angioplasty is prevented by α_1-adrenoceptor blockade

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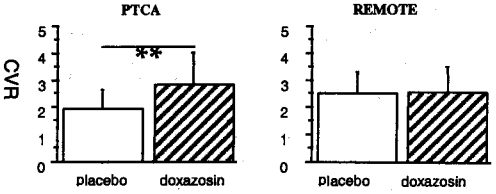
Background Coronary vasoconstriction after coronary angioplasty (PTCA) is abolished by i.c. phentolamine. An impairment of coronary vasodilator reserve (CVR) has been observed up to 7 days after successful PTCA. To ascertain if pretreatment with the α_1 blocker doxazosin could improve CVR after the procedure, we carried out a randomized, double blind study on 26 patients with >75% single vessel stenosis undergoing PTCA.

Methods G1, (n = 12) received doxazosin od on top of their treatment at: 1 mg for 3 days; 2 mg for 7 days and 4 mg for 7 days before and after PTCA; G2 (n = 14) received matching placebo. Myocardial blood flow (MBF) at baseline (bas) and after iv dipyridamole (dip, 0.56 mg/kg) was measured within 5 days of PTCA using PET with $H_2^{15}O$. CVR was calculated as dip/bas MBF.

Results The main hemodynamic parameters were comparable in the 2 groups at bas and after dip. In the PTCA territory bas MBF was 0.92 ± 0.2 and 1.05 ± 0.3 ml/min/g in G1 and G2 (p = ns). Dip MBF tended to be higher in G1 than G2 (2.46 ± 0.9 vs 1.99 ± 0.6 ml/min/g; p = 0.09). CVR was higher in G1 than G2 (2.78 ± 1 vs 1.95 ± 0.7; ** = $p < 0.01$).



Conclusion Pre-treatment with doxazosin prevented the impairment of CVR after PTCA. We suggest that the reduced CVR, after a successful PTCA, is due to increased α_1 adrenoceptor constriction of coronary resistive vessels.

P3480 Evidence of microvascular dysfunction in patients with normal coronary angiograms

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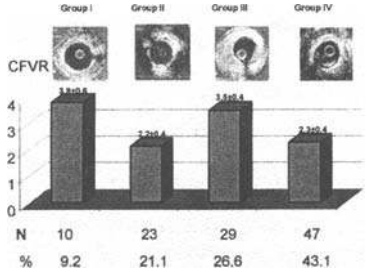
The purpose of the study was to investigate the incidence and severity of microvascular dysfunction in patients with chest pain but with normal coronary angiograms. A total of 126 patients who showed a normal coronary angiograms were examined with intracoronary ultrasound (ICUS) and Doppler (ICD). A 3.2 F or 2.9 F, 30 MHz ultrasound catheter (CVIS, Boston Scientific) was used for ICUS and a 0.014 inch FloWire (Cardiometrics) was used for ICD. Coronary flow velocity reserve (CFVR) was compared to the presence or absence of plaque formation based on ICUS.

Reduction of CFVR was found in 82/126 (65%) patients. No significant difference of the CFVR was found between patients with and without hypertension (2.69 ± 0.65 vs. 2.73 ± 0.80, p = 0.77). A significant difference exists between patients with and without diabetes mellitus (2.30 ± 0.47 vs. 2.80 ± 0.68, p < 0.05). ICUS was available in 109 patients. Based on the presence and absence of plaque formation on ICUS and with and without reduction of CFVR, patients were divided into four groups.



Conclusion: Microvascular dysfunction exists in a majority of patients with chest pain but with normal coronary angiograms. Among which, a large proportion had early signs of coronary artery disease and only one-fifth had true syndrome X.

P3481 Pressure variability after intracoronary adenosine injection as a pitfall for the determination of fractional flow reserve based on minimum distal pressure

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Background: Fractional flow reserve (FFR) is measured at the time of minimum distal pressure(Pd-min) which is assumed to coincide with the time of maximum hyperemia. Pressure variability after intracoronary (i.c.) administration of adenosine may hamper the selection of data for calculation of FFR.

Methods: In 19 intermediate coronary lesions (53.9 ± 10.9% by diameter) we simultaneously measured distal coronary blood flow velocity and pressure with two 0.014" sensor-tipped guide wires. Maximum hyperemia was induced by a bolus of 12–18 mg i.c. adenosine. FFR was calculated from average pressure ratios at different times during the hyperemic response,corresponding to the cycle of Pd-min, maximum pressure drop (dP-max), maximum flow velocity (IPV-max), and the lowest per-beat value of FFR (FFR-min). The mean time difference in beats and the range in beats, of the selected cycle was determined in relation to the beat of IPV-max.

Results: Due to breathing artifacts and a significant decline in aortic pressure (Pao), the timing of Pd-min is more variable than that of dP-max or FFR-min with respect to the time of IPV-max. Because FFR was close to the threshold of 0.75, two of the 19 patients would have been referred to PTCA on the basis of using Pd-min, but not when using FFR-min or dP-max to indicate maximum hyperemia.

Table

Hyperemic parameter	Beats to IPV-max	Range (beats)	Pao	FFR
Pd-min	−0.59 ± 5.1	−10 to 10	90 ± 14**	0.75 ± 0.09
dP-max	0.07 ± 1.27*	−4 to 3	95 ± 14	0.74 ± 0.09
FFR-min	0.07 ± 1.82*	−4 to 4	93 ± 14	0.74 ± 0.09
IPV-max	0	0	96 ± 15	0.74 ± 0.08

** p < 0.03 compared to AOP = 98.7 ± 14.8 at baseline (Student's t-test). *p < 0.05 compared to variance of beats for Pd-min (ANOVA).

Conclusion: After i.c. adenosine, distal coronary pressure is subject to variations that are not induced by flow elevation and Pd-min does therefore not reliably identify the time of maximum hyperemia. Pressure-based evaluation of functional stenosis severity should therefore be based on data at the time of maximum pressure drop or minimum per-beat FFR.

P3482 Coronary flow reserve measurement using the TIMI frame count method: correlation with the Doppler wire (Flowire)

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Background: The estimation of the coronary flow reserve (CFR) has significant clinical implications. However, it requires expensive devices.

Methods: We prospectively studied 23 coronary arteries (6 left anterior descending, 7 left circumflex and 10 right coronary arteries) in patients undergoing diagnostic catheterization or coronary angioplasty. Seven arteries had >50% diameter stenosis and 13 had non significant luminal narrowing. All studies were performed following intracoronary administration of 200 μg nitroglycerine. We investigated whether CFR can be calculated by: a) the TIMI frame count (TFC) method (CFR defined as the ratio of the number of frames required to opacify standard coronary artery landmarks at baseline over the number of frames 15 seconds after intracoronary bolus of adenosine) and correlated with, b) The CFR calculated with the 0.014" angioplasty Doppler guidewire (Flowire) with adenosine as hyperemic stimulus (CFR defined as the ratio of averaged peak velocity [APV] in hyperemia over APV at baseline).

Results: The changes of the TFC and APV at baseline and during byperemia were as follows (values mean ± SD):

	TIMI frame count	APV (cm/sec)
Baselne	21.7 ± 10.9	18.7 ± 9.8
Hyperemia	12.0 ± 8.4	40.7 ± 20.0
p	0.001	0.001

A significant correlation was observed between the CFR values obtained by the TFC method (2.2 ± 1.0) and the Flowire (2.3 ± 0.8) (p = 0.0001, r = 0.87). Similarly, the percent changes of TFC and APV from baseline to hyperemia correlated significantly to each other (p = 0.0001, r = 0.89).

Conclusions: The coronary flow reserve during coronary procedures can be easily and reliably estimated using the TIMI frame count method, which is inexpensive, simple and readily available.

P3483 Pressure-derived fractional flow reserve post stent implantation: no difference in epicardial conductance between coil and slotted tube stents

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The aim of coronary stenting is restoration of epicardial conductance. Pressure derived Fractional Flow Reserve (FFR) is a specific index of epicardial conductance. In this study, we performed FFR measurements pre and post stent implantation, both in coil and in slotted tube stents.

Methods and Results: A total of 98 stents were implanted, 49 coil stents, 49 slotted tube stents, in 98 patients. The maximum inflation pressure used was 9.8 ± 2.3 for the coil stents and 10.7 ± 3.3 for the slotted tube stents (NS), respectively. FFR improved from 0.53 ± 0.17 before to 0.94 ± 0.06 after the procedure, 0.93 ± 0.06 for the coil stents and 0.94 ± 0.05 for the slotted tube stents (NS). Optimal stent deployment, defined as FFR ≥ 0.94 (equivalent to the absence of any noticeable hyperemic pressure drop across the stent), was achieved in 66% of the coil stents and 69% of the slotted tube stents respectively (NS).

Conclusions: In 67% of the patients optimal stent deployment, according to coronary pressure measurement, was achieved. No differences were observed between coil stents and slotted tube stents.

P3484 Effects of coronary angioplasty on coronary adenosine concentrations

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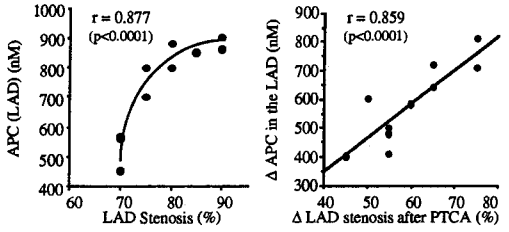
Purpose: We studied the adenosine plasma concentrations (APC) relatively to the degree of coronary stenosis and compared the APC before (B) and after transluminal coronary angioplasty (PTCA).

Methods: APC were mesasured both in the LAD below the stenosis using the PTCA catheter and in the great coronary vein (GCV) in 10 patients presenting a single stenosis of the LAD.

Results:

Stenosis (%)		APC (LAD) (nM)		APC (GVC) (nM)	
B	PTCA	B	PTCA	B	PTCA
79 ± 31	19 ± 1*	736 ± 50	152 ± 20*	846 ± 60	174 ± 22*

(m ± esm), (*P < 0.0001)



Conclusions: We found a close relationship between the stenosis and APC mesured both in the LAD and the GCV. Successfull PTCA is followed by a considerable decrease in APC (ΔAPC) which are linearly correlated with the improvement of the stenosis (Δ LAD).

P3485 Reduction of coronary blood flow during distension of urinary bladder in patients with early atherosclerosis

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Coronary blood flow is regulated to a large extent by adrenergic mechanisms. Distension of the urinary bladder reflexly causes an increase in sympathetic and a decrease in vagal fiber activity. The effect of distension of the urinary bladder on the coronary circulation in patients with early atherosclerosis remains unknown.

To assess the effect of bladder distension on coronary dynamics, we measured epicardial and microvascular responses in 40 patients with early atherosclerosis (<50% diameter stenosis). Patients were randomized into two groups on the basis without (group 1, n = 20) or with (group 2, n = 20) pretreatment of α-1 adrenergic receptor blocker (oral doxazosin 2 mg). Percent change in coronary artery diameter was measured by quantitative coronary angiography, and percent change in coronary blood flow was calculated using intracoronary flow Doppler. In response to bladder distension (intravesical pressure 20 mm Hg) coronary diameter was significantly decreased from 3.20 ± 0.46 mm to 2.70 ± 0.42 mm ($P < 0.001$), coronary blood flow from 82.1 ± 25.8 to 62.4 ± 25.6 mL/min ($P < 0.001$), and coronary resistance was increased from 1.40 ± 0.73 to 2.36 ± 1.50 mm Hg/mL/min ($P < 0.001$) compared with baseline values, in group 1 patients. Intracoronary nitroglycerin significantly lessened the severity of urinary bladder distension-induced epicardial coronary vasoconstriction below baseline values ($P < 0.001$). In group 2 patients during bladder distension, although there were significant decrease in epicardial coronary diameter, and increased coronary resistance, coronary blood flow did not show significant changes, compared with baseline values. Rate-pressure product similarly increased during bladder distension in the 2 groups. There were significant differences of coronary diameter ($P = 0.04$), coronary blood flow ($P = 0.01$), and coronary resistance ($P = 0.008$) between the 2 groups during bladder distension.

The present study showed that urinary bladder distension caused a reduction in coronary blood flow that involved mechanisms related to α-1 adrenoceptors. The reduction of coronary blood flow during bladder distension can be relieved after nitroglycerin administration. Pretreated administration of doxazosin had reversed the decreased coronary blood flow during bladder distension towards baseline.

P3486 Patients with elevated large endothelin-1 plasma concentration have increased intimal hyperplasia and decreased blood flow velocity in coronary arteries

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Transplant vasculopathy (TVP) is the major limitation of the longterm outcome of heart transplantation (HTx) and can be detected by intravascular ultrasound (IVUS) at a very early stage. Endothelin-1 (ET-1) is a vasoconstrictive peptide found to increase in plasma after HTx. Since it has also been shown to stimulate proliferation of smooth muscle cells we hypothesized that elevated ET-1 levels are associated with both increased intimal hyperplasia and slower coronary blood flow.

Methods: Eighteen patients (pts) (11 to 150 mo after HTx) underwent routine cardiac catheterization. The average peak flow velocity (APV) in the LAD was measured by intracoronary Doppler at baseline as well as after injection of adenosine (peak APV), and the coronary flow reserve (CFR) was calculated as a ratio of both. In IVUS the intimal area (IA) at the most severely affected region of the vessel was measured. The concentration of the precursor peptide Big ET-1 was determined by a radioimmunoassay. Mean IA, APV and CFR were compared between pts with elevated plasma Big ET-1 levels (>2 fmol/ml), and those with normal values by one-way ANOVA.

Results: Pts with elevated Big ET-1 had significantly larger IA than those with normal concentrations (6.79 ± 3.07 vs. 3.28 ± 2.39 mm^2, p = 0.012). They also had lower APV at baseline (15.57 ± 5.31 vs. 20.67 ± 6.71 cm/s, p = 0.08), and a significantly decreased peak APV (41.11 ± 12.24 vs. 57.56 ± 18.91 cm/s, p = 0.04). However, mean CFR did not differ between groups (2.89 ± 0.81 vs. 2.93 ± 1.01, p = 0.92), and was in normal range.

Conclusion: Our data suggest an important role of ET-1 in the development of TVP. Its association with slower blood flow seems to be secondary to intimal hyperplasia, since vasodilatation after adenosine as expressed by CFR was not impaired.

P3487 The superiority of TIMI frame count in detecting flow velocity changes after coronary stenting compared to TIMI flow classification

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We compared the qualitative, categorical TIMI Flow Classification with a new quantitative method, the TIMI Frame Count, to investigate the differences of both systems in detecting coronary flow velocity changes after stent implantation.

Methods: TIMI Flow grades and the corrected TIMI Frame Counts (CTFC) were determined in 102 patients before, after stent implantation and at 6 months angiography. The qualitative analysis of the TIMI Flow grade was performed following the criteria of the Thrombolysis in Myocardial Infarction (TIMI) Study Group introduced in 1985. The quantitative measurement of CTFC was performed as published by Gibson 1996. The CTFC is defined as the number of cineframes required for the contrast material to reach a standard distal coronary landmark at a film speed of 30 frames per second, corrected by the longer length of LAD compared to the other coronary arteries. The CTFC is calculated by division of the actual measured frame counts of the LAD through a correction factor of 1.7, which was calculated – as described by Gibson – by the division of the mean value of LAD frame count through the mean values for RCA and LCX in a normal collective. The frame counts for the circumflex artery and the right coronary artery are used as measured without correction.

Results: Comparing changes in TIMI flow grades and the CTFC (>5 frames) before and after stent implantation, CTFC measurement detected flow velocity changes in 46% of the patients, which were not detected with the TIMI Flow Classification. Comparing the results after stent implantation and the 6 months angiography, CTFC detected flow velocity changes in 40% of the patients, where TIMI Flow Classification was not able to detect any flow changes. The rate of agreement between TIMI Flow Classification and CTFC is very poor (concordance analysis for the comparison of both methods: kappa value = 0.14 ± 0.06 for CTFC versus TIMI Flow changes before and after stent implantation and kappa value = 0.21 ± 0.06 for CTFC versus TIMI Flow changes after stent implantation and at 6 month control angiography).

Conclusion: The quantitative TIMI Frame Count method is superior to the qualitative TIMI Flow Classification in detecting coronary flow velocity changes. After therapeutic interventions CTFC measurements are able to demonstrate alterations in coronary flow, which are not detected by using the TIMI Flow Classification.

P3488 Coronary Doppler measurements do not predict progression of cardiac allograft vasculopathy: serial intracoronary flow measurements in heart transplant recipients in comparison with dobutamine stress echocardiography and intravascular ultrasound

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Coronary flow reserve can be measured by intracoronary Doppler analysis. The aim of this study was to evaluate whether intracoronary Doppler flow measurements are useful to assess the progression of cardiac allograft vasculopathy (CAV). Doppler data were compared to dobutamine stress echocardiography (DSE), a useful non-invasive method to detect functionally relevant CAV. As a reference for morphological assessment of CAV, intravascular ultrasound (IVUS; quantitative analysis of intimal hyperplasia) was used.

Methods: 35 patients (mean age 49 ± 12 years) were serially studied 13 ± 26 months after heart transplantation (baseline) and 1 year thereafter (follow-up) with Doppler, DSE and IVUS. Coronary flow reserve (CFR, max./bas. flow velocity, 16 μg adenosine) was assessed with a 0.014 in. Doppler guide wire. With DSE (5–40 μg/kg/min), wall motion abnormalities (WMA) were analyzed using a 16 segment model. Newly developed or increasing WMA at follow-up were considered a progression of CAV. Mean intimal index (MII, mean intimal area/vessel area) in each patient was determined with IVUS. A 15% increase in intima index was defined as significant CAV progression.

Results:

		Coronary flow reserve	
		baseline	follow-up
DSE progression	(n = 11)	2.7 ± 0.9	3.8 ± 0.8*
DSE no progression	(n = 14)	3.0 ± 1.0	3.3 ± 0.9*
IVUS progression	(n = 12)	2.7 ± 0.7	3.2 ± 0.6*
IVUS no progression	(n = 13)	2.9 ± 0.9	4.0 ± 0.9*

* = $p < 0.05$

In conclusion, the increase in CFR could be observed in all subgroups. Thus, serial intracoronary Doppler flow measurements are not useful to predict morphologic or functional progression of CAV as assessed by IVUS or DSE.

P3489 Coronary flow reserve assessment using transthoracic Doppler echocardiography detects functional status of internal mamaria artery bypass

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Transthoracic Doppler echocardiography (TDE) has been used for noninvasive visualization of coronary artery flow. Measurement of flow velocity changes with TDE after coronary vasodilatation in internal mamaria arteries (IMA) after coronary bypass grafting (CBG) could be used for noninvasive assessment of coronary flow reserve (CFR).

Methods: The value of CFR determined by TDE (Acuson, Sequoia) for the noninvasive assessment of the functional status of IMA after CBG was evaluated in 40 patients (pts). From supraclavicular view average maximal systolic-diastolic flow velocity in IMA after CBG was measured at rest and during maximal hyperemia induced by i.v. Adenosine (140 μg/kg/min). CFR was obtained by the ratio of hyperemic to resting flow velocities. All pts underwent coronary angiography after echo studies were performed, CFR was recorded invasively in 17 pts using Flow wires.

Results: Coronary angiography showed stenosis (>50% diameter) of IMA after CBG in 16/36 pts (group I), no relevant stenosis was detected in 20/36 pts (group II). In 9 pts of group I and 8 of group II CFR was measured invasively. IMA CFR could be measured in all pts by TDE.

	IMA stenosis	CFR (TDE)		CFR (invasive)	
Group I	>50% diameter	1.5 ± 0.4	⟶ n.s. ⟵	1.4 ± 0.5	} p < 0.05
Group II	<50% diameter	2.7 ± 0.7	⟶ n.s. ⟵	2.5 ± 0.6	

Conclusion: TDE assessment of IMA flow velocity changes after coronary vasodilatation allows noninvasive measurement of CFR in IMA after CBG in all pts. Invasive and noninvasive measurements showed no relevant differences. CFR < 2.0 predicted with a sensitivity of 88% and a specifity of 83% significant stenosis of IMA after CBG.

P3490 DEBATE II: "DESTINI-sation" of the DEBATE II trial data

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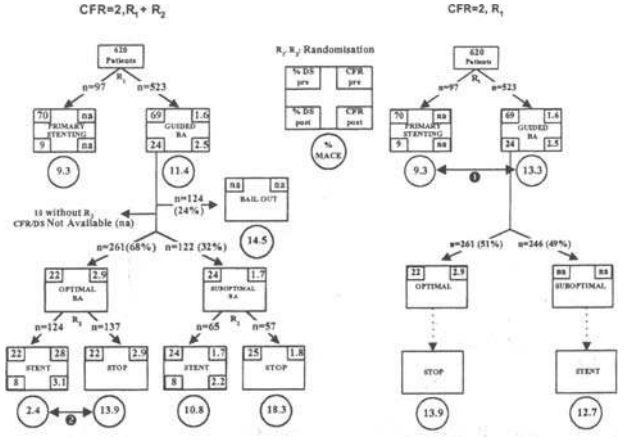
Abstract: DESTINI and DEBATE II, two contemporary randomised trials addressed the same issue, namely the value of optimal balloon angioplasty (OBA), guided by QCA and intra-coronary Doppler as compared to primary stenting; however, trial design (2nd randomisation in DEBATE II) and CFR criteria for OBA (2 vs 2.5 CFR) differ. Therefore, we have re-analysed our data according to the DESTINI criteria and design.



Conclusions: "DESTINI-sation" of the DEBATE II data confirms that primary stenting and guided balloon angioplasty do not differ in clinical outcome (MACE 9.3 vs 13.3%, p (Fe = 0.32, 1). Implementation of the 2nd randomisation in the DESTINI design also confirms that stenting post-OBA further improves the outcome of OBA (2.4 vs 13.9% = the additional value of stenting, p (FE) < 0.001, 2).

P3491 Colour-coded blood flow – new diagnostic options in intravascular ultrasound: first clinical experience

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Background: The ChromaFlo is a new intravascular ultrasound technique for color coding of the blood flow. The flow is detected by rating the movement of the tissue as they transverse the ultrasound beam. The faster moving tissue (blood) will be colorized in red, the slower moving tissue (vessel wall) will not. Both color and 2D IVUS will be obtained from the same image plane and is displayed simultaneously. ChromaFlo is available for the Endosonics imaging system and catheter.

Method: We compared the information of standard digital 2D-images, with and without contrast agent injection, versus ChromaFlo of the same region regarding lumen/plaque differentiation and the overall lumen assessment in 65 lesions of 42 pts..

Results: The signal quality of ChromaFlo is depending on various factors. We obtained good signals or a better ratio between true signals and artifact more in: small lumen, high blood pressures, big guiding catheters; that results into a good and more bad ChromaFlo signal. In contrast to small lumen the blood flow close to the outer vessel wall can not be assessed completely in most big lumen. In pts. with a good signal ChromaFlo is helpful in differentiation of lumen vs. plaque, ring down artifact, detection of dissection as well as assessing the overall lumen area, especially in complex lesions. In one case the diagnosis of a resisting flow between a graft stent and the vessel wall due to a not fully apposed stent could only be made by ChromaFlo.

Conclusion: The signal quality of the ChromaFlo is variable from pt. to pt.. In vessels with a good signal the value of information seems to be, in part, superior to standard 2D IVUS with or without contrast injection. ChromaFlo is a promising new technique in intravascular ultrasound for better lumen detection.

P3492 Assessment of flow reserve and patency status of coronary artery bypass grafts by transthoracic Doppler echocardiography

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To test the hypothesis that blood flow velocity and flow reserve in coronary artery bypass grafts (CABG) could be recorded by transthoracic Doppler echocardiography 45 consecutive patients with prior CABG (28 internal mammary artery (IMA) to left anterior descending, 33 saphenous vein grafts (SVG) to right coronary artery and 22 SVG to circumflex branches) were evaluated before coronary angiography using an Acuson Sequoia C 256™ platform at rest and after vasodilation induced by dipyridamole (DIP) infusion (0.56 mg/kg/4 min). Detection rate for not occluded IMA was 100% with 100% sensitivity and 100% specificity for graft occlusion. Detection rate for not occluded SVG was 80% with 83% sensitivity and 78% specificity for graft occlusion. Flow velocity parameters of not occluded CABG at baseline and under hyperemia were as follows:

	MA grafts		Saphenous vein grafts	
	Patent	Stenotic	Patent	Stenotic
Baseline SPV	75 ± 38*	78 ± 31*	38 ± 18	11 ± 8
Baseline DPV	41 ± 15*	25 ± 15*	11 ± 15	8 ± 3
DIP SPV	98 ± 25*	131 ± 75*	49 ± 15	18 ± 10
DIP DPV	125 ± 18*†	28 ± 14*	38 ± 17†	7 ± 3
Flow reserve	2.1 ± 1.5†	1.2 ± 0.9	1.9 ± 0.7†	0.9 ± 0.8

* = $p < 0.05$ vs SVG; † = $p < 0.05$ vs stenotic; DPV = Diastolic peak velocity (cm/s); SPV = Systolic peak velocity (cm/s); Flow reserve = DIP DPV/Baseline DPV.

None of the Doppler parameters at baseline could discriminate between patent and stenotic grafts. The best correlation was observed for flow reserve. The calculated flow reserve "cut point" values for patent IMA and SVG were assessed prospectively in a test group of 22 consecutive patients. Flow reserve ≤ 1.9 had 100% sensitivity and 88% specificity for detection of IMA graft stenosis $\geq 70\%$, and flow reserve ≤ 1.6 had 84% sensitivity and 65% specificity for detection of significant SVG stenosis.

In conclusion transthoracic Doppler echocardiography is a feasible and accurate means for obtaining a completely noninvasive assessment of CABG flow reserve and accurately predicts graft patency status.

P3493 Effect of captopril in coronary arterial distensibility as assessed by intravascular ultrasound in atherosclerotic lesions

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It has been shown that bradykinin contributes to the regulation of coronary vascular tone by causing endothelial release of nitric oxide, which in part may be responsible for normal coronary arterial distensibility. It has also been shown that even mild atherosclerosis decreases arterial distensibility. The aim of the present study was to assess the effect of captopril (which increases bradykinin levels) on arterial distensibility in atherosclerotic coronary vessels.

Methods: We have studied by intavascular ultrasound (IVUS-20 MHz, 3.5 F) 27 patients (16 men and 11 women aged 46.5 ± 7.8 years) having an angiographically non-significant isolated stenosis of the left anterior descending coronary artery (<70%). Lumen and vessel dimensions as well as plaque burden were measured at the lesion site. Coronary artery distensibility (CAD) was assessed by IVUS and simultaneous measurement of intracoronary pressure with a 2 F micromanometer catheter located at the left main coronary artery was performed. CAD was expressed by the coronary distensibility index which was calculated as 10-fold the ratio of luminal area change to intracoronary pressure change during cardiac cycle. All patients included received captopril (12.5 mg twice daily) for a 6-month period and patients were reassessed by IVUS. Statistical elaboration of the results was performed with Student's t-test. P values < 0.05 were regarded as statistically significant.

Results: Our results are shown in the table below.

	Before treatment	After treatment	
% Plaque burden:	47.59 ± 4.1	47.75 ± 4.2	P = NS
Distensibility index:	0.148 ± 0.039	0.154 ± 0.036	P = 0.012
DP*:	5.21	5.17	p = NS

*DP = Difference between systolic and diastolic intracoronary pressure.

In conclusion, captopril seems to improve coronary arterial distensibility in sites of atherosclerotic lesions despite its non significant effect on plaque progression.

P3494 Intracoronary infusion of magnesium sulfate dilates human coronary arteries in vivo

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Magnesium (Mg) is considered a natural, physiological calcium blocker, but the vasoresponse of human coronary arteries to Mg is still unknown. Therefore, we performed the present study to examine whether the coronary response to Mg changed in a dose-dependent manner and which segments of the coronary arteries were affected by intracoronary Mg infusion.

Methods: Seventeen patients with normal coronary arteries were enrolled for this study. Magnesium sulfate ($MgSO_4$) (0.02 mmol/min and 0.2 mmol/min over 2 min) was infused into the left coronary ostium. The diameter of proximal and distal segments of epicardial coronary arteries were quantitatively measured and coronary blood flow (CBF) was calculated by quantitative angiography and Doppler flow velocity measurements.

Results: At the dose of 0.02 mmol/min, $MgSO_4$ did not significantly affect the vascular response (percent change from baseline, mean ± SEM, proximal segments: +1.3 ± 0.7%; distal segments: +2.4 ± 0.9%; CBF: +5.8 ± 3.0%). At the dose of 0.2 mmol/min, $MgSO_4$ caused significant dilatation of epicardial coronary arteries (proximal segments: 4.3 ± 0.7%, $p < 0.0001$; distal segments: 8.3 ± 0.9%, $p < 0.0001$) and increase in CBF (31.1 ± 0.8%, $p < 0.0001$).

Conclusions: These findings suggest that Mg may dilate coronary arteries in a dose-dependent manner and the response of coronary arteries to Mg may be more dominant in the resistance coronary arteries than in the epicardial coronary arteries.

P3495 Favourable modulation of coronary blood flow and vasomotor responses during atrial pacing in postmenopausal women induced by the administration of oestrogen

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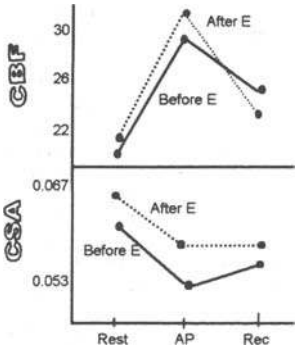
Short-term administration of 17 β estradiol (E) has been shown to improve exercise induced myocardial ischaemia in postmenopausal women with CAD.

Methods: In 12 postmenopausal women (mean age 60 ± 5 yrs) with minimal coronary irregularities, as evidenced by angiography or IVUS, we evaluated coronary reactivity and coronary blood flow (CBF) during incremental AP (up to 150 bpm for 3 minutes), before and 20 minutes after the intracoronary infusion of 75 ng/ml E which increased coronary sinus E levels from post- to pre-menopausal levels. The cross sectional area (CSA) and the blood flow velocity of the proximal coronary segments were measured with quantitative coronary angiography and with a doppler flow wire respectively. Measurements were obtained before, during AP and at 7 mins after AP.

Results: Before E administration, AP induced a significant decrease in coronary CSA (from 0.066 ± 0.004 to 0.053 ± 0.003 cm^2) and a significant increase in CBF (from 21.5 ± 2.4 to 27.7 ± 3.3 ml/min). Furthermore, these changes in CSA and CBF remained 7 mins after AP. After E administration, at rest the CSA and CBF did not change significantly (0.067 ± 0.002 cm^2 and 22.05 ± 3.1 ml/min, respectively) but during AP the changes in CSA and CBF were significantly attenuated compared to AP-induced changes before E (by 0.003 ± 0.001 vs 0.013 ± 0.001 cm^2; $p < 0.005$ and by 10.2 ± 1 vs 6.2 ± 1.1 ml/min, $p < 0.005$, respectively) These favorable modulations in CSA and CBF remained at 7 mins after AP.



Conclusion: Acute administration of E reduces the degree of pacing-induced ischemia by attenuating the reduction in coronary CSA and improving the increase in CBF in postmenopausal women.

P3496 Relative coronary flow velocity reserve after optimal balloon angioplasty compared to stenting

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Distal coronary flow velocity (CVRd) assessed by intracoronary Doppler guide wires (Cardiometrics, Mountain View, USA) allows to estimate the functional result of a coronary intervention. Despite adequate postinterventional luminal widening CVRd increases to different levels. Instead of using a general cut-off value for CVRd we decided to guide our intervention by the individual measurement of CVRref in an non-stenotic reference artery and to calculate relative CVR (CVRrel) as the ratio of CVRd and CVRref. This approach was used to test whether optimal balloon angioplasty and coronary stenting provide similar results.

In 45 patients (pts) with de-novo LAD stenoses, who underwent optimal balloon angioplasty (PTCA, <20% residual stenosis) followed by stent implantation CVRd and CVRref were measured before and after PTCA and after stenting. CVRd was calculated as the ratio of hyperemic and baseline flow velocity before and after ic injection of 18 μg adenosine. Minimal lumen diameter (MLD) and % stenosis were measured by quantitative coronary angiography.

Results:

	Before PTCA	After PTCA	After stent
CVRd	1.3 ± 0.4	2.7 ± 0.6*	2.9 ± 0.4*§
CVRrel	0.47 ± 0.16	0.94 ± 0.09*	0.89 ± 0.06*§
MLD [mm]	0.89 ± 0.32	2.72 ± 0.18*	3.03 ± 0.16*
% stenosis	71 ± 23	12 ± 6*	3 ± 5*

*p < 0.001 versus before PTCA, §n.s. versus after PTCA

Conclusion: Optimal PTCA provides similar results on CVRd and CVRrel compared to adjunct stent implantation. This approach can be cost-effective since unnecessary elective stenting can be avoided.

P3497 Effect of the potential confounding factors on the thrombolysis in myocardial infarction (TIMI) trial frame count

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The corrected TIMI frame count has been proposed as an objective method to assess coronary blood flow. Although the variability between two consecutive injections appear low, the potential factors that introduce variability into the TIMI frame count has not been systematically investigated. The goal of this study was to determine if nitrate use, rate of dye injection, size of catheter used, the phase of the cardiac cycle dye injected or heart rate affect the TIMI frame count.

Methods: A mechanical electrocardiographic-gated power injector was used to inject contrast dye at rates 3–4 ml/sec in left coronary arteries and 2–3 ml /sec in right coronary artery. In the first 25 pts, injection rate of dye was increased 1-ml/s without any change in the catheter used. In the second 25 pts, coronary angiogram was taken with 6 F catheter, after changing the catheter with 8 F, angiography was repeated in the same dye injection rate. In the third 25 pts, after taking angiogram, 300 microg. intracoronary nitrate was given, and the angiography was performed with the same catheter without any change in dye injection rate. In another 25 pts, after the angiogram taken in basal condition, heart rate increased 25 beat/min over the basal rate and angiography was repeated with same catheter without any change in injection rate. Finally, injection of dye was performed at the beginning of systole and also repeated at the beginning of diastole. The angulation of cinecamera was not varied between repeated studies. The TIMI frame count was measured by counting the number of cine frames (25 frames/sec) during coronary angiography required for the leading edge of contrast to reach predetermined distal landmarks.

Results: The TIMI frame count was not significantly changed by increasing the dye injection rate (28.2 ± 11.4 vs. 27.2 ± 11.5, p = 0.467) or changing the catheter size (25.1 ± 8.7 vs. 25.7 ± 12.4 p = 0.693). With the nitrate administration, the TIMI frame count was significantly increased from 26.4 ± 11.9 to 32.8 ± 13.3 (p < 0.001). The injection of dye at the beginning of diastole or increasing of heart rate significantly decreased the TIMI frame count from 30.1 ± 8.8 to 24.4 ± 7.9 (p < 0.001) and from 30.4 ± 6.1 to 25.3 ± 7.2 (p < 0.001), respectively.

Conclusions: The injection rate of dye and size of catheter have not any effect on the TIMI frame count. However, nitrate use, heart rate, and the phase of the cardiac cycle dye injected have significant effect on the TIMI frame count. Therefore, studies comparing the TIMI frame count need to consider these factors.

P3498 How much coronary collateral flow protects against myocardial ischaemia?

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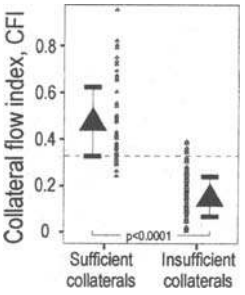
Purpose: The purpose of this study was to determine how much collateral flow is necessary to protect the ipsilateral myocardial area against ischemia during vessel occlusion.

Methods: In 201 patients (pts) undergoing percutaneous transluminal coronary angioplasty (PTCA) an index of collateral flow (CFI) was determined using intracoronary (i.c.) pressure- or Doppler-guidewires. Mean aortic (P_{ao}) and distal occlusive (P_{occl}) pressure during PTCA or distal flow velocity during (Vi_{occl}) and after ($Vi_{0\text{-}occl}$) PTCA were measured continuously. The pressure derived CFI was calculated as follows: (P_{occl}-CVP)/(P_{ao}-CVP), CVP: Central venous pressure = 5 mmHg. The ratio between $Vi_{0\text{-}occl}$ and Vi_{occl} was used for the determination of Doppler-derived CFI. The degree of collateralisation to the vessel to be dilated was also graded angiographically (Rentrop; grade 0–3).

Results: Based on the absence or the presence of ST-segment changes (< or ≥1 mm) on i.c. ECG during balloon occlusion, 50 pts were in the group with sufficient collaterals and 151 pts in the group with insufficient collaterals. There was an overlap of 15/201 data points (CFI) between the 2 groups. By defining a value of CFI ≥ 38% as sufficient collaterals, there were 5 false negative and 10 false positive test results (figure).



	Sufficient Collaterals	Insufficient Collaterals	P
n	50	151	
Age	59 ± 10	58 ± 10	NS
CFI	0.48 ± 0.18	0.17 ± 0.09	<0.0001
Rentrop (0–3)	2.0 ± 0.7	0.8 ± 0.8	<0.0001
AP	9%	91%	<0.0001

AP: Angina pectoris during PTCA, CFI: Collateral flow index

Conclusions: A collateral flow of ≥38% relative to normal flow through the patent vessel predicts protection against myocardial ischemia with 94% specifity and 89% sensitivity.

P3499 L-arginine-induced dilation in stenotic atheromatous plaque is depending to its severity and morphology

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Administration of L-arginine may stimulate the release of endothelium derived nitric oxide and improve myocardial ischemia. We sought to examine the effects of L-arginine administration on coronary stenosis vasomotion in patients with coronary artery disease (CAD).

Methods. Intracoronary infusions of normal saline, the receptor mediated nitric oxide stimulant, L-arginine (L-A) (50 and 150 μmol/min) and nitroglycerin (GTN) (250 mcg bolus) were administered in 15 patients with coronary artery disease and stable angina. Coronary stenoses were classified as smooth (smooth with regular borders) or complicated (irregular borders). The diameter of 12 smooth and 10 complicated coronary stenoses and their adjacent reference (R) segment was measured by quantitative angiography. The mean (±SEM)% change from baseline was:

	NS	L-A 50	L-A 150	GTN
Smooth Stenoses	0.9 ± 0.5	6.4 ± 1.4	7.3 ± 2.9	14.9 ± 3.4
R segment	0.7 ± 0.4	4.5 ± 1.4	10.5 ± 2.2	12.3 ± 3.5
Comlex Stenoses	1.0 ± 0.8	7.1 ± 3.2	13.7 ± 2.5*	19.4 ± 2.3
R segment	0.4 ± 0.5	6.3 ± 2.9	10.4 ± 2.4	10.4 ± 2.5

* = p < 0.01 vs smooth stenoses

There was a significant correlation between stenosis severity and L-arginine induced dilation (r = 0.56, p < 0.001).

Conclusions. In patients with CAD, complex coronary stenoses dilate significantly more than smooth stenoses after L-arginine administration. This raises the possibility of partial deficiency of the substrate for nitric oxide synthesis at the site of complicated stenoses. The provision of the substrate significantly enhances nitric oxide activity at the site of irregular and severe stenoses.

P3500 Systemic nature of endothelial dysfunction: association between coronary and peripheral regulation of resistance vessels

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Endothelium-dependent vasodilator function is altered in the presence of risk factors for coronary artery disease. Thereby, risk factors act systemically on all vascular beds, including peripheral vessels as well as coronary arteries, where atherosclerosis develops. However, it is not known whether vascular reactivity of the peripheral microcirculation correlates with regulation of coronary resistance vessels. Thus, in 22 patients, we investigated endothelium-dependent vasoreactivity of the coronary microcirculation by i.c. infusion of acetylcholine (Ach, 10^{-6} M). Coronary blood flow increase was calculated by Doppler measurements and quantitative angiography. Plethysmography was used to measure blood flow increases in the forearm after infusion of Ach (50 μg/min). Endothelium-independent blood flow increase was assessed via i.c. adenosine (2.4 mg/min) or papaverine (7 mg) in the coronary arteries, respectively, by sodium nitroprusside (8 μg/min) in the forearm.

Results: Relative Ach-induced coronary blood flow responses correlated with Ach-induced blood flow responses in the forearm circulation ($r = 0.46$; $p = 0.03$), whereas endothelium-independent coronary and peripheral blood flow responses were not associated with each other. The relation between coronary and peripheral endothelium-dependent blood flow responses persisted after normalization to endothelium-independent responses ($r = 0.52$; $p = 0.013$). No correlation was found between Ach-induced vasoreactivity of epicardial arteries and forearm Ach-induced blood flow response ($r = 0.11$; p = NS).

Conclusions: Impaired peripheral endothelial blood flow regulation is a surrogate marker of endothelial dysfunction of the coronary microcirculation.

P3501 Homocysteine impairs endothelium-dependent vasodilation of the coronary microcirculation

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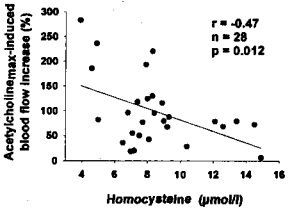
Homocysteine has been shown to play a role for progression of coronary artery disease. Endothelium-dependent vasodilator function of peripheral arteries is impaired in patients with elevated homocysteine levels. However, it is not known, whether homocysteine is associated with impaired coronary endothelial vasodilation. Thus, we investigated the role of fasting homocysteine levels on endothelium-dependent coronary blood flow increase (i.c. acetylcholine, ACH, 10^{-6} M) and endothelium-independent (7 mg papaverine or 2.4 mg/min adenosine) coronary blood flow responses. Coronary microcirculation was tested by quantitative coronary angiography and i.c. Doppler measurements in 28 patients with normal or minimally diseased coronary arteries (<30% focal stenosis).

Results: There is a significant inverse relation between ACH-induced coronary blood flow increases and plasma homocysteine levels (figure). In contrast, endothelium independent coronary blood flow responses were unaffected by homocysteine levels ($r = -0.17$; $p = 0.39$).



Conclusions: Homocysteine seems to be an important risk factor for endothelial dysfunction of the coronary microcirculation. This mechanism might contribute to progression of atherosclerosis in patients with elevated homocysteine levels.

P3502 A study with intracoronary injection of ergonovine in 365 patients: the incidence of coronary spasm in various cardiac disorders

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We performed selective intracoronary administration of ergonovine for 365 patients to clarify the incidence of coronary spasm in various cardiac disorders in Japanese patients from April 1991 to October 1997. We studied 245 patients strongly suspected of having ischemic heart disease and 120 patients with non-ischemic heart disease. Under no medication for at least 24 hours, ergonovine was injected in total doses of 40 μg into the right coronary artery and 64 μg into the left coronary artery for 4 minutes. We defined spasm as positive with ≥90% luminal narrowing. The result was as follows:

	Rest	Effort	R & E	AMI	OMI	Post PTCA	IHD suspected
No of pts	72	42	22	44	14	51	245
Spasm (+)	43 (60)	16 (38)	10 (46)	15 (34)	3 (21)	24 (47)	111 (45)

	Atypical	Val	DCM	HCM	Other	Non-IHD suspected
No of pts	63	5	5	7	40	120
Spasm (+)	3 (5)	0 (0)	0 (0)	1 (14)	2 (5)	6 (5)

	No	Male	Age	HT	Smoking	HL	DM	Organic (>75%)
Spasm (+)	117	102 (87)	64 ± 10	39 (33)	91 (78)	32 (27)	26 (22)	49 (42)
Spasm (−)	248	127 (51)	63 ± 10	98 (40)	99 (40)	32 (13)	32 (13)	47 (19)
P value		0.01	ns	ns	0.01	0.01	0.05	0.01

(AMI: acute myocardial infarction, OMI: old myocardial infarction, PTCA: percutaneous transluminal coronary angioplasty, IHD: ischemic heart disease, Val: valvular heart disease, DCM: dilated cardiomyopathy, HCM: hypertrophic cardiomyopathy, HT: hypertension, HL: hyperlipidemia, DM: diabetes mellitus, 0: indicates %)

The incidence of provoked spasm in patients with ischemic heart disease was significantly higher than that in patients with non-ischemic heart disease (45% vs 5%). Moreover patients with spasm had significantly higher incidence of habitual smoking, hyperlipidemia, diabetes mellitus and organic coronary stenosis than the patients without spasm. No serious irreversible complication occurred in the procedure.

In conclusion, intracoronary injection of ergonovine is a safe and reliable method. In Japanese patients coronary artrerial spasm occurred frequently in various cardiac disorders.

P3503 Clinical characteristics in patients with provoked coronary spasm by pharmacologic agents, acetylcholine and ergonovine

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The purpose of this study is to determine the clinical charcteristics in patients with coronary vasospasm induced by acetylcholine (ACh) or ergonovine (ER). We performed spasm provocation tests of both ACh and ER in 57 patients (48 men and 9 women, 63 ± 9 years). These patients, including 23 patients with coronary spasm induced by both ACh and ER, including 14 patients with spasm provoked by only ACh not ER and 20 patients with coronary spasm induced by only ER not ACh were examined. ACh test was performed in incremental doses of 20, 50, 80 μg into the right coronary artery (RCA) and 20, 50, 100 μg into the left coronary artery (LCA). ER was performed in total doses of 40 μg into the RCA and 64 μg into the LCA. Coronary spasm was defined as total or subtotal occlusion. The result was as follows:

	ACh & ER	ACh only	ER only
No of pts (male)	23 (19)	14 (9)	20 (20)
Age (yr)	64 ± 10	64 ± 8	62 ± 9
Smoking	16 (70%)	6 (43%)	20 (100%)*
Hypertension	10 (44%)	4 (29%)	3 (15%)
Hyperlidemia	10 (44%)	3 (21%)	6 (30%)
Diabetes mellites	4 (17%)	1 (7%)	5 (25%)
Mean No of risk factors	1.73 ± 1.03	1.27 ± 1.10	1.74 ± 0.87
T cholesterol (mg/dl)	171 ± 34	168 ± 27	169 ± 27
Triglyceride (mg/dl)	172 ± 101	87 ± 42**	122 ± 36*
HDL-cholesterol (mg/dl)	41 ± 11	44 ± 17	42 ± 9
Organic stenosis (≥75%)	5 (22%)	1 (7%)	13 (65%)*
(RCA: LCX: LAD)	1:1:4	0:0:1	10:0:3
Spasm provocated vessel	29	17	21
RCA	10	7	18
LCX	5	0	0
LAD	14	10	3
Focal vs Diffuse	17 (59%): 12 (41%)	4 (23%): 13 (77%)	20 (95%)*: 1 (5%)

(*: $p < 0.01$ vs other groups, **: $p < 0.01$ vs ACh & ER)

In conclusion, the patients with coronary spasm induced by ER not ACh had significantly higher organic stenosis than other patients. ER is more sensitive to provoke coronary spasm in the RCA than ACh.

P3504 Effects of serotonin and acetylcholine on coronary microcirculation in subjects with coronary spastic angina

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Generalized endothelial dysfunction has been speculated in coronary spastic angina (CSA), however, it remains unclarified whether endothelium-dependent vasodilatory response in coronary microvascular beds is impaired. Serotonin (SER) and acetylcholine (ACh) have been known as endothelium-dependent vasodilators, as well as potent inducers of epicardial coronary artery spasm in subjects with CSA. Thus, we investigated coronary microvascular response to SER and ACh in subjects with CSA and angiographically normal coronary artery.

Methods: Eleven subjects with CSA (group S) who were diagnosed by anginal attack with ST elevation and angiographically proved coronary artery spasm induced by SER and/or ACh, and 22 subjects with atypical chest pain without CSA (group N) were enrolled in this study. All subjects had a normal left coronary arteriogram. Doppler tipped flow wire (FloWire) was placed in the proximal left anterior descending coronary artery. Coronary flow (CoF) was calculated by average peak velocity (APV) and quantitative coronary angiography according to the formula; CoF (ml/min) = APV × (coronary cross-sectional area measured by cinedensitometry) × 0.3. Steady flow after intracoronary injection of nitroglycerin (0.2 mg) into left main coronary artery to eliminate the epicardial coronary arterial tone was defined as baseline CoF. Peak CoF responses to acetylcholine (ACh, 50 μg), papaverine (PAP, 10 mg) and SER (10 μg) from baseline were measured.

Results: Baseline CoF in group S and N was 48 ± 5 and 53 ± 6, respectively. There were no differences in peak CoF responses to PAP (group S, 379 ± 37% vs N, 401 ± 23%, N.S.), ACh (group S, 323 ± 33% vs N, 296 ± 15%, N.S.) and SER (group S, 212 ± 20% vs N, 241 ± 21%, N.S.) between group S and N.

In conclusion, coronary microvascular responses to physiological amines, SER and ACh, were normal in subjects with CSA, suggesting that endothelial function is well preserved in coronary microvascular beds.

P3505 Endogenous endothelin contributes to the maintenance of coronary vasomotor tone in humans

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Endogenous production of endothelin (ET) contributes to basal human peripheral vascular tone, but its role in the maintenance of coronary vasomotor tone is unknown. We investigated the effect of endogenous ET in the human coronary circulation. An ET_A receptor antagonist, BQ123 (40 nmol/min, 15 min), was infused into the left coronary artery in 9 patients (2 male, mean age 56.8 ± 3.0 yrs) with angiographically normal coronary arteries, undergoing investigation of atypical chest pain. Epicardial coronary diameter was measured by biplane digital cineangiography with off-line quantitative coronary angiography, and coronary flow with a Doppler flow wire in the mid-left anterior descending coronary artery (LAD). Flow-dependent (ic adenosine; 18 μg via infusion catheter) and agonist-mediated dilatation (ic substance P; 20 pmol/min for 2 min via guiding catheter) were assessed at baseline. Endothelium-independent dilatation (ic GTN; 250 μg) was assessed at the end of the protocol. BQ123 caused significant vasodilation in the mid-LAD and an increase in coronary flow (table).

	LAD cross-sectional area (mm^2)			Flow (ml/min)
	Proximal	Mid	Distal	
Baseline	7.91 ± 1.0	5.18 ± 1.0	2.16 ± 0.3	25.8 ± 3.5
BQ123	8.47 ± 1.0	6.34 ± 1.0*	2.4 ± 0.3	30.0 ± 3.6*

All values mean ± SEM. * = P < 0.01 vs baseline

There were no significant changes in ECG or aortic pressure and no correlation between vasodilation following BQ123 and parameters of baseline endothelial function. These data indicate for the first time that endogenous ET plays a role in the regulation of basal vasomotor tone in normal human epicardial and resistance coronary vessels.

P3506 Endothelin-1 and coronary vasoreactivity in unstable angina

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In patients with unstable angina (UA) an increased tissue endothelin-1 (ET-1) immunoreactivity has been demonstrated at the site of the culprit lesion (CL) thus suggesting that ET-1 may be involved in the pathogenesis of the enhanced coronary tone. We studied 8 patients with UA (Class IIIB, 6 men, mean age 58 ± 11 years) and 8 patients with stable angina (SA) (CCS II–III, 6 men, mean age 65 ± 5 years) with a single proximal lesion of a major epicardial coronary vessel. Luminal diameter of the CL and of the proximal, middle and distal normal-appearing coronary segments were measured by quantitative coronary angiography at baseline, during cold pressor test (CPT) and after intracoronary administration of nitrate (NTG). ET-1 levels were measured in blood samples obtained proximally and distally to the coronary CL before and after successful stent implantation. Baseline luminal diameter of the CL was 1.0 ± 0.45 mm in UA and 0.92 ± 0.23 mm in SA (p = 0.58). During CPT, the CL in patients with UA constricted more than that of patients with SA (0.78 ± 0.35 vs 0.84 ± 0.19 mm; percent reduction compared baseline −23 ± 8 vs −7.9 ± 10%, p = 0.005). After NTG the CL in patients with UA dilated more than that of patients with SA (1.4 ± 0.45 vs 1.1 ± 0.24 mm; percent increase compared baseline 46 ± 0.22 vs 22 ± 7.5%, p = 0.01). The uninvolved proximal, middle and distal coronary artery segments had similar changes during CPT and after NTG in both patients with UA and SA. Proximal and distal ET-1 levels before stenting were similar in both patients with UA and SA (1.29 ± 0.08 vs 1.24 ± 0.2 pg/ml, p = 0.54 and 1.27 ± 0.20 vs 1.24 ± 0.24 pg/ml, p = 0.79 respectively). After stenting, proximal and distal ET-1 levels significantly increased compared to baseline values both in patients with UA and SA; however the relative increase was higher in UA than in SA patients (1.7 ± 0.26 vs 1.39 ± 0.16 pg/ml, p = 0.015 and 1.70 ± 0.14 vs 1.5 ± 0.3 pg/ml, p = 0.05, respectively). Coronary artery stenting causes a release of ET-1 which is greater in UA than SA. Thus the enhanced potential of the CL to release ET-1 might be responsible, at least partially, for the enhanced vasoreactivity of the CL in patients with UA.

P3507 Transcoronary ablation of septum hypertrophy by selective septal branch injection of ethanol: a 4-year experience in catheter interventional treatment for hypertrophic obstructive cardiomyopathy

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Since 1995 137 transcoronary ablations of septum hypertrophy (TASH) were performed in 119 pts. with HOCM and severe symptoms (57 men, 58 ± 14 years). Serial left heart catheterization, exercise right heart catheterization, transesophageal echocardiography and electrophysiologic testing were performed before as well as 2 weeks and 7 months after intervention. Clinical information is obtained with a max. of 36 months.

Major results were significant reductions of septal thickness (from 22 ± 4 to 11 ± 3 mm), outflow obstruction (from 53 ± 39 to 11 ± 17 mmHg at rest, from 146 ± 49 to 38 ± 41 mmHg postextrasystolically) and left ventricular filling pressures (from 20 ± 6 to 14 ± 5 mmHg) despite a slightly reduced ejection fraction (from 0.70 ± 0.09 to 0.68 ± 0.10). Peak CK-activity rose to a mean value of 583 ± 376 IU after injection of 3.6 ± 2.2 ml 96% Ethanol. NYHA-functional class improved from 3.0 ± 0.4 to 1.6 ± 0.6, exercise tolerance from 73 ± 30 to 91 ± 34 watts, peak oxygen consumption from 14.8 ± 4.9 to 16.8 ± 5.7 ml/kg/min and pulmonary artery mean pressure from 43 ± 9 to 35 ± 9 mmHg. The induction of sustained ventricular arrhythmias decreased from 9.6 to 4.8% (n.s) in 41 pts. investigated. Permanent high-grade av-block were observed in 14 pts. (12%) and 3 additional pts with severe co-morbidity could not be resuscitated from different emergencies related to the potential of TASH induced AV conduction disturbances. However, there was no late cardiac death after hospital discharge. The risk of a persistent total AV block was correlated to the relief of intraventricular obstruction (r = 0.31 p = 0.001).

Conclusion: TASH leads to a pronounced clinical and hemodynamic improvement that compare favorable with the results of surgical myectomy. However, it should performed only in pts with severe symptoms refractory to drug therapy, as an alternative to surgery.

CARDIOVASCULAR DISEASE IN WOMEN

P3508 The role of aspirin and nonsteroidal anti-inflammatory drugs in the primary prevention of myocardial infarction in women

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The antiplatelet effect of aspirin has been found to reduce fatal and nonfatal vascular events in secondary prevention by approximately 15% and 30%, respectively. Data are limited in primary prevention of coronary heart disease (CHD) and even more in women. We conducted a population-based case-control study in order to evaluate the association of acute myocardial infarction (AMI) with the use of aspirin and NSAIDs among postmenopausal women.

Methods: A cohort of women 50 to 74 years old registered in the General Practice Research Database in the UK between January 1, 1991 and December 31, 1995 was identified. Women with a history of MI, other cardiovascular and cerebrovascular disease, neoplasms, coagulopathies, vasculitis, and alcohol-related diseases were excluded from the source population. 1,242 potential MI cases were identified. After the review (blind to exposure status) of medical records and all the available information concerning the acute event, 1,013 first episodes of AMI, 791 non fatal and 222 CHD deaths, were confirmed using WHO adapted criteria. 5,000 women were sampled as controls from the source population. A women was defined as current user when she was taking aspirin/NSAIDs during the month before index date, and as a past user when she stopped aspirin/NSAID ingestion more than one month before index date. Nonusers were women with no aspirin/NSAID prescription in the computerized medical database.

Results: The overall incidence of AMI was 1.6 per 1,000 person-years. The odds ratio (ORs) of AMI associated with prophylactic aspirin use (defined as more than one month of continuous use) was 0.6 (95% CI: 0.3–1.2) afer controlling by age, coronary risk factors, HRT use and comorbidity. Daily doses of 300 mg were not associated with a smaller OR than doses of 150 mg or less. The greatest risk reduction was observed among non-fatal cases of AMI (OR: 0.3; 95% CI: 0.1–0.9). Overall, NSAID use was not associated with a beneficial effect on the risk of AMI. This lack of beneficial effect was also observed after stratification by either duration or daily dose, and neither for fatal and nonfatal AMI events. None of the estimates for individual NSAIDs reached statistical significance.

In conclusion, current and continuous use of aspirin was associated with a 40% reduction on the overall risk of AMI in postmenopausal women, and this reduction was even greater when only nonfatal cases were considered. Chronic use of NSAIDs was not associated with lower risk of AMI in this population.

P3509 Impact of conventional risk factors and the angiotensin-converting enzyme in women treated with coronary stent placement

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Plasma levels of the angiotensin-converting enzyme (ACE) and the deletion (D) allele of the (I/D) polymorphism of the ACE gene are predictors of restenosis (R) after coronary stenting. Women have a lower incidence of coronary artery disease (CAD) before menopause due to the protective effect of estrogen, but post-menopausal women equal the incidence of CAD in men probably because of the cessation of the activity of these hormones and the concomitant increment of the conventional risk factors.

Methods: we analyzed the incidence of R (DS% > 50) in the 141 women treated with coronary stents in our Centers in 1997–98, and the variables associated with CAD shown in the table, including basal plasma ACE level. These variables were also compared to a matched control group of 68 women with normal coronary angiogram and left ventricular function.

	Normal (68)	Non restenosis (112)	Restenosis (29)	p
Age (years)	63 ± 10	67 ± 9	64 ± 8	ns
Hypertension	31%°*	66%°	55%*	<.0001
Diabetes	4%°*	17%°	25%*	<.01
Insulin dependent	3%*	3.5%°	10%°*	<.01
Total cholesterol	200 ± 38	202 ± 58	205 ± 42	ns
Lipoprotein (a)	28 ± 20	35 ± 31	29 ± 23	ns
Apo B	117 ± 27°	124 ± 34	132 ± 35°	<.05
Triglycerides	96 ± 62	98 ± 48	100 ± 65	ns
Fibrinogen	281 ± 59°	348 ± 90°	318 ± 107	<.05
ACE	21 ± 16°	20 ± 16*	37 ± 22°*	<.005

* and ° indicate significant difference between groups.

By multivariate analysis, basal ACE level and insulin dependent diabetes were associated with R, p = 0.006 and p = 0.03 respectively. The comparison between control group vs CAD showed a significant increment of conventional risk factors in the latter, but these were not associated with restenosis.

In conclusion, conventional risk factors in women are associated with CAD but not with R after stenting except for insulin dependent diabetes. The basal level of ACE is an additional risk factor that strongly predicts the occurrence of in-stent R in aged women.

P3510 Aetiology of heart failure in women aged <75 years in the population

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Background: The Bromley Heart Failure Study is an epidemiological study of the incidence and aetiology of heart failure (HF) in a population of 292 000 within South East London. Uniquely, all incident (new) cases aged <75 were investigated by coronary angiography.

Methods: All new HF cases were identified by in-patient monitoring and from a dedicated rapid access heart failure clinic over a period of 15 months. Cases were assessed by a panel of 3 cardiologists who assigned an aetiology on the basis of the information prior to study angiography. A final aetiology was subsequently assigned combining all clinical, non-invasive and invasive data. We examined the incidence and aetiology of HF in women.

Results: 136 cases were identified aged <75. Angiographic data were available on 99/136 cases (80% of the 124 cases surviving the initial presentation of HF). 91/136 (67%) cases were male and 45 (33%) cases female. The incidence of heart failure in the population aged 25–75 years was 0.78 cases/1000 population/year for men and 0.38 cases/1000 population/year for women. This difference in incidence was dominated by a greater incidence of HF due to CAD in men (0.51 cases/1000 population/year) compared to women (0.09 cases/1000 population/year). The incidence of HF not due to CAD (hypertension, valve disease, arrhythmia, alcohol, idiopathic, other and undetermined) was similar in men (0.26 cases/1000 population/year) and women (0.29 cases/1000 population/year). Prior to angiography no aetiology or an aetiology other than CAD was assigned in 46 cases (29 male and 17 female). Angiography revealed important CAD in 16/29 (55%) of the men compared to only 2/17 (12%) of the women (p < 0.01), both of whom were diabetic.

Conclusions: HF due to CAD is uncommon in women aged <75. If CAD is not suspected from clinical assessment then, in the absence of diabetes, subsequent angiography is very unlikely to reveal important CAD.

P3511 Insulin resistance in postmenopausal women with coronary heart disease

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Insulin resistance is associated with coronary heart disease (CHD) and its risk factors. Surrogate measures of insulin sensitivity, such as fasting plasma glucose and insulin levels, are predictors of CHD. Insulin resistance plays a coordinating role in the association of metabolic risk factors for CHD. We explored whether postmenopausal women with CHD are insulin resistant compared to women without CHD.

Methods and results Postmenopausal women (FSH > 40 IU) with angiographically documented CHD (n = 19) and healthy volunteers (n = 30), matched for age and menopausal age, underwent measurement of insulin sensitivity [S_I, intravenous glucose tolerance test (IVGTT)], plasma lipids and body fat (dual-energy X-ray absorptiometry). Compared to controls, CHD patients had a lower S_I [3.96 (−0.59, +0.64) *vs* 5.97 (−0.47, +0.49) 10^5/min/[pmol.l^{-1}], p = 0.012) and a higher IVGTT insulin area [1.92 (−0.21, +0.24) *vs* 1.36 (−0.11, +0.11)] 10^4. (pmol/l).min, p = 0.015). No group differences emerged with respect to fasting glucose and insulin levels, IVGTT glucose area, body mass index, amount of android or gynoid fat or android: gynoid fat ratio. Patients and controls also had similar total and HDL-cholesterol levels and HDL-cholesterol subfractions. Patients with CHD, had higher serum urate levels than controls [287.8 (16.7) vs 229.3 (11.6) μmol/l, p = 0.005]. In multivariate analysis, disease status emerged as a significant predictor of S_I (F ratio = 7.1, p = 0.01), independently of systolic blood pressure and serum uric acid (square multiple R = 0.16).

Conclusions This is the first demonstration that, compared to healthy postmenopausal women of similar chronological and menopausal age, women with CHD are insulin resistant. Further studies are needed to assess the role of insulin resistance in the coordination of metabolic risk factors for CHD in women. The effects of estrogens on S_I warrants further investigation.

P3512 Revascularisation rates in patients with coronary artery disease: no evidence of gender bias

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Background: The previous studies which have shown that women undergo less invasive investigation and treatment of coronary artery disease than men are limited by poor measurement of need.

Objective: To measure whether for a given need (defined by severity of anatomical disease, severity of functional impairment, and numerical ratings of procedure appropriateness) there were sex differences in invasive management of coronary artery disease.

Design: prospective study (24 months mean follow up) of unselected patients undergoing angiography during 12 months from April 1996.

Participants: 1181 women and 2837 men.

Setting: Royal Hospitals NHS trust, London.

Main outcome measures: Rate of coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG) in the presence of coronary artery disease (n = 151 and 192 procedures respectively in women) and survival.

Results: Compared with men, women were older and less likely to have a previous history of MI, exercise ECG or revascularisation ($p < 0.01$ for each comparison). Women were more functionally impaired than men on the CCS, SF-36 and SAQ scales ($p < 0.01$). Amongst patients with significant coronary artery disease there were no overall differences in revascularisation rate; women were however more likely than men to undergo PTCA (hazard ratio 1.34 (95% CI 1.11–1.64). The excess PTCA in women was confined to those deemed inappropriate. There was no difference in mortality.

Conclusion: Women with coronary artery disease were revascularised at the same rate as men and with the same survival. The higher rate of PTCA among women may reflect their greater functional impairment.

P3513 The metabolic syndrome of cardiovascular risk in middle-aged men and middle-aged, postmenopausal women

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Compared to women, men are at an increased risk of early death from coronary heart disease. We explored whether, in middle age, insulin sensitivity (S_I) and other variables that are relevant to the metabolic syndrome differ from those in women.

Methods: Men aged 53.3 (0.8) years [mean (SEM), n = 132] and age-matched postmenopausal women (n = 132, follicle-stimulating hormone > 40 IU) underwent measurement of $S44_I$ (i.v. glucose tolerance test (IVGTT)] and plasma lipids.

Results: Men had a lower S_I ($p < 0.001$), higher fasting glucose ($p < 0.001$), IVGTT glucose ($p < 0.001$) and IVGTT insulin ($p < 0.001$), serum urate levels ($p < 0.001$) and triglycerides ($p = 0.034$), and lower HDL-cholesterol ($p < 0.001$), higher body mass indices (BMI, $p < 0.001$) and blood pressures ($p < 0.001$). Sex was a predictor of S_I [sex: F-ratio 6.60 ($p = 0.011$); BMI: F-ratio = 9.28 ($p = 0.003$); $R^2 = 0.09$; ANOVA, BMI as covariate]. S_I correlated with BMI in women ($r = -0.33$, $p < 0.001$) but not in men; BMI correlated with blood pressure in men ($r = 0.21$, $p < 0.05$) but not in women; and BMI correlated with both triglycerides ($r = 0.25$, $p < 0.01$) and HDL-cholesterol ($r = -0.18$, $p < 0.05$) in men but not in women.

Conclusions: This is the first demonstration that, compared to post-menopausal women, middle-aged men are insulin resistant. The sex-dependent expression of the metabolic syndrome may be important in the increased CHD risk in men. It also emphasises the need to take sex into account in studies of metabolic risk factors for cardiovascular disease.

P3514 Secondary prevention in women with acute coronary syndrome in France: results of the PREVENIR survey

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The aim of the French nation-wide observational study (PREVENIR) was to detail the treatment prescribed at hospital discharge and 6 months later to patients with unstable angina (UA) or myocardial infarction (MI).

Methods. The survey was performed in 77 private and public cardiology centres. All patients admitted to hospital in January 1998 who survived an acute coronary syndrome were included: 1456 patients, MI: 819, UA: 637. Treatment at discharge was collected retrospectively. Data on the ongoing treatment were collected during an out-patient consultation or, by questioning the patient's GP.

Results. Data concerning 355 women alive at 6 month and not lost for follow-up was analysed. Baseline patients' characteristics are comparable with those reported in previous French epidemiological studies (MONICA, USIK, PRIMA). At discharge some treatments [fibrates: 7% (25), omega 3 fatty acid: 1.4% (5), aspirin: 88.2% (313), ACE-inhibitors: 45.4% (161), nicotine-patch: 0.6% (2)] were similar for either male or female patients, whereas the other treatments [statins: 30.4% vs. 39.6%, $p < 0.01$; beta-blockers: 66.2% vs. 73.1%, $p < 0.05$; cardiac rehabilitation: 17.4% vs. 27.2%, $p < 0.001$; oestrogen: 3.4% (12)] were less frequent in women. There were no significant changes in treatment at 6 months, except for statins (40% vs. 30.4%, $p < 0.001$). Six months after discharge, only 4.6% (5) of patients stopped statin therapy. If statin therapy was not initiated in hospital, family physicians initiated it for only 15.8% (39) of untreated patients.

Conclusion. Prescription of aspirin, and ACE-inhibitors after ACS has improved in women in France, while beta-blockers and cardiac rehabilitation are underused and measures against smoking are used sparingly. Whereas in secondary prevention clinical trial had proved a similar effect in men and women, prescription of statins was underutilized in female patients. An older age of women could be an explanation for this difference. Nevertheless, the lessons from recent clinical trials have not yet been completely applied to daily clinical practice.

P3515 Tolerance to oestrogen replacement therapy during long-term treatment: an explanation for lack of clinical benefit?

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Background: Oestrogen replacement therapy is thought to protect against vascular disease in post-menopausal (PM) women. This putative protective effect may result from oestrogen counteracting the actions of vasoconstrictor and mitogenic vascular peptides such as endothelin-(ET-1). In a double blind, randomised, placebo controlled trial, we have studied the effects of oestradiol (E2) on ET-1 induced vasoconstriction in PM women with coronary heart disease.

Methods: 19 women aged 51–77 (mean 66) years were studied on 3 occasions: pre-randomisation and 1 and 3 months after randomisation to E2 2 mg/d or placebo. On each occasion forearm blood flow (FBF) was measured using venous occlusion plethysmography before and during a brachial arterial infusion of ET-1 5 pmol/min for 60 minutes.

Results: % change from baseline in FBF during ET-1 infusion.

	Placebo	Estradiol	p value
Pre-randomisation	−19.4	−16.7	0.31
1 month	−8.6	−21.8	0.002
3 months	−25.9	−23.2	0.22

Conclusion: E2 attenuates the powerful vasoconstrictor action of ET-1 but this action of E2 does not persist over 3 months of therapy. Oestrogen replacement therapy may not have sustained vascular actions during long term treatment. This finding may help explain the disappointing results of a recent controlled trial of hormone replacement therapy in women with coronary heart disease.

P3516 Tamoxifen acutely relaxes rabbit coronary arteries by an endothelium-, nitric oxide, and oestrogen receptor-dependent mechanism

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Tamoxifen (T) belongs to a group of structurally diverse compounds (SERMS – Selective Estrogen Receptor Modulators) which act as either an estrogen agonist or antagonist depending on the target tissue and hormonal milieu. The effects of T on coronary vascular reactivity have not been investigated. We therefore investigated the effect of T on rabbit coronary arteries in vitro. Epicardial coronary arterial rings of male and female rabbits were suspended in organ baths for measurement of changes in isometric tension. In alternate rings the endothelium was denuded. T (3, 10, 30 mM) induced significant relaxation of rings precontracted with K^+ (30 mM) in a dose-dependent manner (mean ± SEM; 47 ± 8***, 63 ± 8***, 81 ± 7***% respectively; *P < 0.05, **P < 0.01, ***P < 0.001; n = 16) compared to control (3.2 ± 1.5, 4.2 ± 1.5, 5.1 ± 1.5; n = 11). Relaxation to T at lower concentrations (0.3, 1 mM) was not significant. T-induced relaxation at 3, 10, 30 mM was significantly less in rings with no endothelium (29 ± 12, 47 ± 14***, 58 ± 12***%; n = 8), in rings with endothelium incubated in L-NAME (12 ± 4***, 41 ± 9*, 55 ± 9**%; n = 11), and in rings with endothelium incubated in ICI 182,780 (26 ± 4**, 47 ± 5, 61 ± 5*%; n = 9) compared to control. There were no differences between arteries from male or female rabbits. BaCl had no effect on T-induced relaxation. T (10 mM) did not affect the calcium concentration dependent contraction curve. We conclude that T induces significant endothelium-dependent relaxation of isolated rabbit coronary arteries via a NO- and estrogen receptor-dependent mechanism. This effect may contribute to the observed decrease in cardiovascular mortality in female breast cancer patients on Tamoxifen therapy.

P3517 Impact of pregnancy in pulmonary vascular disease: maternal and fetal outcomes

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Pulmonary vascular disease (PVD) and pregnancy are associated with great risk of maternal death. Our aim, was to evaluate the clinical course of pregnant women with PVD and identify possible prognosis factors.

Methods: We followed prospectively 34 pregnancies in 30 pts with PVD who decided carry on pregnancy despite advise of therapeutic abortion. Eighteen pts had Eisenmenger's syndrome (ES), eight with PVD associated to schistomiasis (PS) and four with primary pulmonary hypertension (PH). Their clinical characteristics are depicted below:

	Age (years)	Hb mg.dl^{-1}	Ht%	ST O_2%	PAPmmhg
ES (18 pts)	25.7 ± 5.6	16.5 ± 1.6	52.1 ± 5.1	81.5 ± 7.3	103.0 ± 19.8
PS (8 pts)	26.6 ± 4.5	13.9 ± 13	42.8 ± 2.4	89.1 ± 4.3	92.7 ± 16.4
PH (4 pts)	26.2 ± 4.0	13.1 ± 1.5	41.7 ± 2.2	89.8 ± 4.1	94.8 ± 14.5

Hb – haemoglobin; Ht – haematocrit; ST O_2 – arterial oxygen saturation PAP-degree of pulmonary hypertension (PAP) assessed by echoDoppler.

Prenatal care included bed rest, oxigen therapy and subcutaneous heparin from second trimester of gestation. Drugs therapy were maintained, as indicated.

Results: Only 8 (23.5%) pregnancies had an uneventful course. The events were:heart failure (8 pts; 23.5%), hypoxemia (9 pts; 26.5%), syncope (1 pt; 2.9%), hemoptysis (2 pts; 5.9%), severe arterial hipotension (1 pt, 2.9%), genital haemorragia (3 pts, 8.8%) and genital infection (3 pts; 8.8%). There were 10 (33.3%) maternal deaths due to: sudden death (3 pts), heart failure and/or hipoxemic (6 pts), haemorragia (2 pts) and thromboembolism (3 pts). There were 21 (61.7%) newborns alive, 4 of them died before hospital discharge, 10 spontaneous abortions and 3 stillbirth. ES group was different ($p < 0.01$) from PH and PS groups (combined) in relation to Ht, Hb and St O_2, but not in relation to maternal morbidity or mortality. Regression logistic analyses showed that death probability was not associate to Ht, Hb, or PP degree, in either groups.

Conclusions - PVD is associated to ominous maternal and fetal prognosis, independent of its cause. Predictors of prognosis are still uncertain. Hence, absolute contraindication to pregnancy must be sustained in women with PVD.

P3518 Initial results and long-term clinical and angiographic implications of coronary stenting in women

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Background: Coronary stenting (ST) is increasingly used during coronary interventions. The influence of gender on balloon angioplasty results has been extensively studied. However, results of coronary ST in women are not well established.

Methods: The initial results and long-term clinical and angiographic follow-up of 158 consecutive women undergoing ST implantation were prospectively compared with those of 823 consecutive men.

Results: Women were older (66 ± 10 vs 59 ± 11 years), and had more hypertension (65% vs 42%) and diabetes (34% vs 16%) than men (both $p < 0.001$). Clinical presentation and number of diseased vessels was similar in both groups. Procedural success angiographic success without complications) was lower (90% vs 95%, $p < 0.01$) and major complications (death, myocardial infarction or surgery) were more common (9% vs 4.3%, $p < 0.05$) in women. Although hospital mortality was higher for women (RR 3, 95% CI 1.2–7.4) this difference disappeared after adjustment for adverse baseline characteristics. However, on multivariate analysis, female gender was selected as an independent predictor of procedural failure or major complications (RR 2.4, 95%CI 1.2–4.8). Clinical follow-up (mean 19 ± 19 months) was obtained in 96% of patients with procedural success. On actuarial analysis event-free survival (death, myocardial infarction or repeat revascularization) at 2 years was similar in both groups (70% men, 69% women, Log Rank p = 0.8). In addition, on systematic late angiography, restenosis rate (evaluated by QCA in 878 lesions, 93% of those eligible) was similar (29% vs 31%, NS) in both groups.

Conclusions: 1) Coronary ST in women is associated with poorer initial results. 2) Women with procedural success have a long-term outcome similar to men 3) Restenosis after ST is not influenced by gender.

P3519 Effect of postmenopausal hormone replacement on atherosclerosis in carotid and femoral arteries : the PHOREA trial

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Many observational studies have found lower cardiovascular morbidity and mortality in women that take estrogens and progestins (hormone replacement therapy, HRT) after menopause. This is commonly attributed to an antiatherogenic potential of HRT. PHOREA is the first large randomized, observer-blind trial that evaluates the effect of HRT on progression of atherosclerosis.

Methods: 321 clinically healthy postmenopausal women with pathological intima-media thickness (IMT) in at least one part of the carotid arteries were randomized to 3 treatment groups: (1) 1 mg 17-beta estradiol daily plus 0.025 mg gestodene on 12 days of every 28 day cycle, (2) gestodene on every third cycle, or (3) no hormone replacement. Using identical ultrasound technique, before and after 48 weeks of treatment images of the maximum IMT in the following arterial segments were recorded: common, internal, and bifurcation of a.carotis, common and superficial a. femoralis. Ultrasound operators and readers were blinded with respect to treatment. History, signs and symptoms, medication, and laboratory values were obtained before and after treatment. The study strictly adhered to the GCP guidelines.

Results: Randomization was successful with regard to all major influencing factors on progression of carotid atherosclerosis (e.g. age, smoking, HDL- and LDL-cholesterol, use of statins etc.). FSH as a marker of medication adherence, and LDL decreased in both HRT groups, but increased with no HRT. There was no difference in progression of IMT of carotid and femoral arteries between the 3 groups, neither in intention-to-treat (n = 264, table) nor valid case (n = 214) analysis.

Table. Change (absolute values) after 48 weeks of treatment, intention-to-treat:

	(1) e+g (m)	(2) e+g (3rd m)	(3) no HRT
FSH (mU/ml)	−19.9 ± 28.9****	−14.1 ± 27.6****	+10.6 ± 27.7
LDL (mmol/l)	−0.15 ± 0.92*	−0.24 ± 0.91**	+0.14 ± 0.67
A. carotis:			
Mean IMT (mm)	+0.03 ± 0.05	+0.03 ± 0.05	+0.02 ± 0.05
Max. IMT (mm)	+0.04 ± 0.13	+0.04 ± 0.12	+0.04 ± 0.13
A. femoralis:			
Mean IMT (mm)	+0.02 ± 0.05	+0.02 ± 0.05	+0.03 ± 0.05
Max. IMT (mm)	+0.04 ± 0.14	+0.04 ± 0.11	+0.05 ± 0.12

*p < 0.05, ** p < 0.01, ****p < 0.0001 compared to no HRT

Conclusion: This sample of postmenopausal women with early signs of atherosclerosis (increased IMT) at baseline, had a slightly accelerated progression of carotid and femoral IMT after 48 weeks, compared to published data. HRT moderately lowered LDL cholesterol, but had no substantial effect on atherosclerosis in these arteries.

P3520 Breast arterial calcification as cardiovascular risk indicator in women undergoing routine mammography for breast cancer screening

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Background: Breast Arterial Calcification (BAC) is commonly seen on screening mammograms, and its frequency increases with age, especially after menopause. Recent studies show a relation between arterial calcifications in the breast and cardiovascular disease (CVD). Whether BAC can be detected in middle-aged apparently healthy women undergoing periodical routine mammography for breast cancer screening, is unknown. This pilot study was performed to determine whether BAC, seen on screening mammograms, may detect silent CVD in women age 50–69 years.

Methods: The setting of this study was the population based breast cancer screening programme of Nijmegen and Barneveld (NL) at the beginning of 1998. In 1500 middle-aged women undergoing routine mammography, analysis for BAC was performed. Questionnaires asking for manifested CVD and CVD risk factors were handed out to the participants at the screening centre.

Results: Questionnaires were returned by 953 women (response: 63.5%). BAC was present in 131 women (13.7%). Documented CVD was significantly more present in women with BAC than in those without BAC (Odds Ratio: 1.61; 95% CI: 1.06–2.45). BAC and CVD risk factors was present in 21 women (2.2%) without documented CVD.

Conclusions: Calcifications in breast arteries seen at routine mammography may detect silent CVD in 1 out of 40 women. The widespread use of routine mammography may contribute to the prevention of CVD manifestations in women. Large prospective studies in this field are warranted.

P3521 Baseline C-reactive protein is higher in women than in men with chronic stable angina

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Background: Increased C-reactive protein (CRP) has prognostic significance in apparently healthy individuals and men with coronary artery disease (CAD). Little information is available regarding whether there are CRP differences between women and men with CAD. We compared CRP concentration in men and women with chronic stable angina.

Material and methods: We prospectively studied 821 consecutive patients (236 women) with typical exertional chest pain. Patients underwent clinical, biochemical and angiographic characterization at study entry. Serum CRP was measured with a highly sensitive assay. Follow-up ranged from 1.0 to 3.7 years. Study end points were: development of unstable angina, myocardial infarction, stroke, and cardiac death. Adjusted CRP values were obtained by multiple regression.

Results: Baseline CRP was significantly higher in women than men (3.0 mg/L [1.3–5.8] vs 2.1 mg/L [1.0–4.2], P = 0.006), even after adjustment for other risk factors. Patients with events had significantly higher CRP levels than patients without events (P = 0.035). Women had fewer cardiac events than men (P = 0.039). After adjustment for confounding variables, CRP in women still was a 16% (CI95% of the difference: 6%-25%; p = 0.002) higher than in men.

Conclusions: CRP levels are higher in women than men despite similar clinical and angiographic characteristics and after adjustment for other variables. Despite higher CRP concentration, women had fewer events than men. These findings may have important pathophysiological and clinical implications.

P3522 Is preeclampsia a risk factor for coronary artery disease in women?

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Coronary artery disease (CAD) and preeclampsia could share two risk factors known to induce endothelial dysfunction namely insulin resistance and hyperhomocysteinemia.We have earlier demonstrated that a history of preeclampsia 17 years earlier is assoaciated with elevated levels of insulin and testoterone which may contribute to the increased risk of vascular morbidity in such women.

We measured insulin sensitivity (IS) with intravenous glucose tolerance test (Minimal Model technique) in 22 pre-eclamptic patients and 16 normotensive women between 29–39 weeks of gestation and three months after delivery. During the the iv-glucose tolerance test we took blood samples for plasma homocysteine, vitamine B12 and folic acid measurements.

In pre-eclamptic women IS was 37% lower (P = 0.009) than in control women. After delivery IS increased 4- to 5- fold but IS was still 26% lower in pre-eclamptic women (P = 0.04) than in control women. During pregnancy fasting homocysteine levels were significantly elevated in pre-eclamptic women compared to control women (P = 0.0001) and were related to severity of the disease measured by the level of proteinuria. Vitamin B12 concentrations were lower in preeclamptic women, whereas levels of folic acid showed no difference between the groups. IS was in significant negative relation to plasma homocysteine levels in pre-eclamptic women (r = −0.51, P = 0.02), but not in control women. The mean 3-fold increase in glucose and 50-fold increase in insulin levels during iv-glucose tolerance test failed to affect homocysteine levels. After delivery, levels of homocysteine and vitamin B12 increased almost two-fold, but no difference was observed between the goups.

Hyperhomocysteinemia and increased insulin resistance could both induce/worsen endothelial dysfunction during preeclamptic pregnancy. Pregnancy, as an insulin resistant state, could reveal by development of preeclampsia the tendency towards insulin resistant syndromes and CAD. We suggest, that history of preeclampsia should be added to the list of risk factors in women's CAD.

P3523 Evaluation of gender differences in diagnosis and treatment of coronary artery disease from 1981 through 1997: no evidence for a Yentl syndrome

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Several studies have documented a gender bias in diagnostic procedures and in treatment of coronary artery disease (CAD). This presumed discrimination of women is known as the Yentl syndrome.

Methods: Over a 16-year period (1981 through 1997), we evaluated 1894 consecutive patients (1526 men, 368 women) with angiographically documented CAD (luminal stenosis > 60%). Extent and localisation of the coronary angiographic data and subsequent management (PTCA/CABG) were analysed. The study was divided into the early PTCA years (1981 through 1989) and current PTCA years (1990 through 1997).

Results: No differences in extent and localisation of coronary artery lesions between men and women were found [*extent:* one-vessel disease 42% and 40%, two-vessel disease 27% and 27%, three-vessel disease 26% and 24%, left main 5% and 8%, resp. (pNS); *localisation:* LAD 36% and 39%, RCA 34% and 32%, LCX 27% and 26%, resp. (pNS)]. Over time there was a significant shift from multi-vessel to single vessel disease in both men and women (p < 0.001). As to subsequent management a significant gender difference in favour of women was observed (p = 0.021), which held for both the first and the second PTCA period. Referral to PTCA (n = 353) and CABG (n = 616) in relation to the extent of disease did not show any gender bias in favour of women.

Conclusions: Based on the angiographic findings no gender differences in extent and localisation of CAD was observed. Furthermore, no substantial evidence could be found for under-referral of women to subsequent management. Therefore our study questions the presence of a Yentl syndrome in the current era especially within Europe.

P3524 Relationship between leptin serum levels and common carotid artery intima-media complex in pre-menopausal women

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Common carotid artery intima-media thickening (IMT) represents an early marker of atherosclerosis. Obese patients show an increase of intima-media complex as compared to a healthy people, but the cause of this thickening is unknown. The aim of the present study was to determine if intima-media thickening correlates with plasma levels of leptin i.e. a marker of adipose tissue accumulation.

Methods: The study was carried out in 70 women with age ranging between 18 and 45 years. Body Mass Index (BMI) was ≤25.0 in 22 women and >25.0 in 48. The following parameters were measured: IMT of the common carotid artery and fasting plasma levels of leptin, insulin, blood glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerids. All blood samples were taken during the follicular phase of the menstrual cycle. Blood concentration of leptin and insulin were measured by RIA. IMT was measured by high definition vascular echography.

Results: Leptin plasma concentrations showed a positive correlation with IMT (p < 0.005); BMI (p < 0.001), mean arterial blood pressure (MBP) (p < 0.001), insulinemia (p < 0.001), fasting glycaemia (p < 0.005), triglycerides (p < 0.005) and LDL-cholesterol (p < 0.05) and a negative correlation with HDL-cholesterol (p < 0.001). Stepwise multiple regression analysis confirmed the positive association between leptin (dependent variable) and IMT (p < 0.005), indipendent of age and MBP, insulinaemia, fasting glycaemia, lipids.

Conclusion: We can conclude that progressive adipose tissue accumulation produce high serum levels of leptin and a parallel increase of IMT, which may enhance the risk of developing atherosclerosis.

P3525 Influence of gender on the predictive accuracy of clinical practice guidelines regarding the likelihood of coronary artery disease

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Clinical evaluation of chest pain in women continues to be a diagnostic challenge. We prospectively investigate the accuracy of the Agency for Health Care Policy and Research (AHCPR) Clinical Practice Guidelines regarding the likelihood of coronary artery disease (CAD) in women.

Methods: 330 consecutive patients (P) (124 females, 206 males; 66 ± 11 yr) without prior CAD diagnostic testing were admitted because of possible unstable angina. Strict application of AHCPR Guidelines regarding the likelihood of CAD was performed in each P at admission. The P were then grouped as having high, intermediate or low likelihood of significant CAD. Confirmation of ischaemic heart disease was sought by doing coronary angiography (252 P), myocardial perfusion imaging (42 P) or stress-echo (36 P). We consider as erroneous evaluations the misclassifications observed in high and low levels of likelihood.

Results: The prevalences of positive and negative results indicating presence or absence of CAD were:

Likelihood of CAD	Males		Females	
	No CAD	CAD	No CAD	CAD
High	15	107	25	33
Intermediate	33	33	36	17
Low	15	3	12	1
Total	63	143	73	51

Thus, the rates of misclassifications in males and females were 8.7% (16/206) and 21% (26/124), respectively ($p < 0.0001$).

In conclusion, a rigid application of AHCPR criteria results in a rate of misclassifications that is much higher in females. The latter is mainly due to inaccuracy of high likelihood criteria and emphasizes the need for refinement and modification of these guidelines for women.

P3526 Heart failure in women: clinical, epidemiological and prognostic differences in relation with men. Substudy of national survey of heart failure in Argentina (CONAREC VI Study)

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Objectives: To compare the clinical and epidemiological findings in women (W) and men (M) with chronic heart failure (CFH), as well as prognostic during the hospitalization period.

Methods: Between December 1996 and October 1997, 857 patients (ptes) were included in the National Survey of Heart Failure in Argentina (CONAREC VI Study). They were admitted in 31 centers with a diagnosis of CHF (>30-day evolution) according to Framingham modified criteria. Three hundred and fifty-two of them (41%) were females.

Results: Mean age for female was 67.8 ± 15 years and 64 ± 14 for males ($p = 0.0004$). Regular workers was found less frequently in W than M (13 vs. 29% $p = 0.001$). Risk factors prevalence was different between W and M in the followings: smokers (21 and 48% $p = 0.001$); alcoholism (5 and 18% $p = 0.001$); previous infarct (18 and 28% $p = 0.001$); intermittent claudication (4.8 and 8.7% $p = 0.03$) and COPD (9 and 20% $p = 0.001$). Evolution time of CHF was shorter for W than for M (36 vs. 45 months $p = 0.04$). NYHA class previous was similar for both sexes, but it proved to be higher for W at admission (3.7 and 3.6 $p = 0.01$). During physical examination S3 sound was found in a lower proportion among female patients (22 vs. 31% $p = 0.002$), as well as hepatomegaly (38 vs. 50% $p = 0.001$). ECG registry disclosed a higher rate of atrial fibrillation among women (32 vs. 24% $p = 0.001$). Chest x-ray scan yielded a lower cardiomegaly rate among female (73 vs. 79% $p = 0.02$). Bidimensional echocardiography (2D-Echo) showed that end diastole diameter was smaller for the W group (58 vs. 63 mm $p > 0.001$) as well as atrial size (46.6 vs. 48.7 mm $p = 0.002$) with a higher shortening fraction (27.7 vs. 24.3% $p = 0.001$). Ischemic heart disease was diagnosed less frequently among W (24 vs. 38%) and was observed a higher prevalence for hypertensive heart disease (30 vs. 22% $p = 0.01$) and valve disease (24 vs. 18% $p = 0.05$).

No differences were observed between female and male in incidence of complication (pulmonary or systemic embolism, ventricular or atrial arrhytmias, infections, refractory heart failure, stroke) (15.6 and 17.2%) as well as mortality rate during hospitalization (5.6 and 4.3%).

Conclusion: Women who are admitted because descompensated CHF showed to be older and with shorter time of evolution than men. Physical findings, ECG abnormalities, chest x-ray and 2D-Echo all suggest that diastolic dysfunction is more frequent in W than M, showing a higher prevalence for hypertensive or valvular etiology than for ischemic heart disease. However, in hospital course and death rate were similar for both groups.

SMOKING AND HYPERTENSION

P3527 Smoking affects lipid and thrombogenic factors in postinfarction patients

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The aim of this study was to determine the effect of current and past smoking on the thrombo-metabolic environment, described by a complex of lipid and thrombotic parameters, in a large population of 1045 post-MI patients.

Methods: In the prospective Thrombogenic Factors and Recurrent Coronary Events (THROMBO) study, blood samples were drawn two months after an index MI to determine levels of the following parameters: fibrinogen, von Willebrand factor, factor VII and VIIa, plasminogen activator inhibitor, D-dimer, cholesterol, apolipoprotein A-1, apolipoprotein B, lipoprotein (a), triglycerides, and HDL cholesterol. Smokers were asked to refrain from smoking for 24 hours prior to blood drawing. The effect of current and past smoking on the above factors was evaluated in univariate and multivariate analyses.

Results: There were 247 current, 443 past, and 349 never smokers. Mean (sd) levels of lipid factors significantly different among three groups were respectively:

ApoB: 129 (31), 121 (26), 121 (28), $p = 0.001$;

Cholesterol: 208 (46), 193 (41), 196 (45), $p = 0.001$;

Triglyceride: 217 (107), 201 (116), 190 (107), $p = 0.019$.

Smoking within 24 hours of blood draw (64 non-compliant patients) resulted in further elevations of ApoB, cholesterol, and fibrinogen compared to smokers who refrained.

Factors in Current and Past Smokers

	Current vs. Never			Current vs. Past		
	OR	95% CI	p value	OR	95% CI	p value
ApoB	2.29	1.51–3.46	0.001	1.64	1.13–2.36	0.009
Cholesterol	2.00	1.33–3.00	0.001	1.76	1.22–2.54	0.002
Triglyceride	1.38	0.92–2.08	0.122	1.41	0.98–2.03	0.068
Fibrinogen	2.20	1.32–3.11	0.001	1.23	0.84–1.79	0.291
FVIIa	1.57	1.04–2.37	0.032	1.33	0.91–1.94	0.147

OR: odds ratios represent the risk of having a blood level in the upper fourth quartile after adjustment for significant covariates ($p < 0.05$): gender, age, race, diabetes, and beta blockers. Fibrinogen and VIIa were not different in univariate comparisons, but were higher in current compared to never smokers after adjustment.

Conclusions: Smoking promotes atherosclerosis via profound lipid altering effects. Smoking cessation favorably modifies the lipid profile but fibrinogen remains elevated. Prothrombotic and atherogenic changes occur immediately after smoking.

P3528 Quitting smoking immediately improves in vivo oxidation injury

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Isoprostanes (IP) have been identified as reliable in-vivo oxidation injury markers. Cigarette smoking, a major cardiovascular risk factor, together with elevated blood lipids has been shown to be associated with increased 8-epi-prostaglandin (PG)$F_{2\alpha}$ in plasma, serum, urine and vascular tissue. We studied healthy adults (n = 8; 5 m, 3 f; 26–47 a) as well as patients suffering from familial hypercholesterolemia (FH) with various risk factors (n = 27; 15 m, 12 f; 29–50 a) having been smoking at least a pack of cigarettes a day since more than 5 years. Plasma, serum and urinary 8-epi-$PGF_{2\alpha}$ was determined after extraction and purification using a specific immunoassay daily to weekly after quitting cigarette smoking up to 4 weeks. After a few days only, 8-epi-$PGF_{2\alpha}$ significantly drops, reaching a steady state after about 4 weeks (urine: prevalue: 504 ± 71 pg/mg creatinine; 1 week 376 ± 61; 2 weeks 337 ± 59; plasma: prevalue: 56 ± 11 pg/ml; 1 week: 37 ± 9; 2 weeks 33 ± 7). While patients without additional risk factors approach controls (urine: 299 ± 56 vs. 237 ± 37; plasma 24 ± 6 vs. 17 ± 5), values in FH remain higher (urine 357 ± 71; plasma 29 ± 6). Comparable trends are found for the serum values.

These findings indicate a significant in-vivo oxidation injury in cigarette smoking ± FH. Ex-smokers quite fastly are recovering from their enhanced in-vivo oxidation.

P3529 Smoking induces microalbuminuria in essential hypertension

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Microalbuminuria is thought to reflect endothelial dysfunction in patients with essential hypertension. This study was performed to determine the relationship between traditional cardiovascular risk factors and the occurrence of microalbuminuria in elderly, previously untreated hypertensives.

Methods: From a population survey a group of 178 previously untreated hypertensive patients (4× systolic blood pressure ≥ 160 and ≤220 mmHg and/or diastolic blood pressure ≥ 95 and ≤115 mmHg), mean age 67 (± 4) years, were screened for microalbuminuria. Patients were considered to have microalbuminuria (MA+) when microalbuminuria was between 20 and 300 mg/24 hour. Traditional cardiovascular risk factors were identified by history and bloodsampling.

Results: See table.

Mean (SD)	N	Age (years)	SBP/DBP (mmHg)	% Male	Chol (mmol/l)	DM II	BMI	% Smoke
MA–	162	67 (4)	177 (14)/94 (8)	51	6.0 (0.9)	4	28 (4)	20
MA+	16	66 (5)	183 (14)/97 (7)	69	6.0 (1.1)	2	28 (3)	80*

* = P < 0.001 Chi square; S (D) BP = Systolic (Diastolic) Blood Pressure; Chol = Total cholesterol; DM II = Diabetes Mellitus II; BMI = Body Mass Index.

Logistic regression analysis, including traditional risk factors, duration of hypertension and diabetes, identified smoking as independent variable for the presence of microalbuminuria.

Conclusion: Smoking is a major contributing risk factor for the presence of microalbuminuria in elderly mild to moderate hypertensives. Whether hypertensives with microalbuminuria benefit most of an ACE inhibitor besides cessation of smoking remains to be investigated.

P3530 Hyperhomocysteinaemia is a novel risk factor for hypertension

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Experimental studies show that hyperhomocysteinaemia causes arterial stiffness, due to degradation of elastin and hypertrophy of smooth muscle cells, and suggest that homocysteine may promote atherosclerosis through elevated blood pressure. We have assessed the relationship between homocysteine concentrations and blood pressure in 299 men with hypertension (mean age 51 ± 6 yrs, SBP > 160, DBP > 90 mmHg), without coronary heart disease (CHD), and in 715 age/sex-matched normotensive controls.

Homocysteine concentrations were measured in the fasting state and after an oral L-methionine load (100 mg/kg). Subjects were characterised for other CHD risk factors.

Homocysteine levels were higher in hypertensive patients compared to controls (fasting 12.0 ± 0.3 vs 10.7 ± 0.1 p = 0.001; post-load 36.6 ± 0.7 vs 34.3 ± 0.4 μmol/l, p = 0.001). Hypertensive patients had higher body mass index (BMI, 28.4 ± 0.2 vs 26.1 ± 0.1, p = 0.001), waist-hip girth ratio (0.98 ± 0.1 vs 0.94 ± 0.1, p = 0.001), fasting glucose (6.1 ± 0.1 vs 5.4 ± 0.1, p = 0.001), fasting triglycerides (2.1 ± 0.1 vs 1.6 ± 0.1, p = 0.001), and lower HDL cholesterol (1.24 ± 0.02 vs 1.29 ± 0.01, p = 0.001) compared to controls. Logistic regression analysis showed that the relationship between elevated homocysteine concentrations and hypertension was graded, and independent of BMI, waist-hip ratio, fasting glucose, triglycerides, and HDL cholesterol.

In summary, elevated homocysteine concentrations are associated with hypertension independently of other risk factors. Our results support the hypothesis that, in part, hyperhomocysteinaemia may promote atherosclerosis through elevated blood pressure levels.

P3531 Calcium antagonists and cardiovascular risk in patients with essential hypertension and non-insulin-dependent diabetes

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Objective: It is uncertain whether the use of calcium antagonists is associated with an increase in cardiovascular (CV) risk in hypertensive subjects with diabetes.

Methods: We conducted a prospective cohort study in 164 consecutive subjects with essential hypertension, non-insulin-dependent diabetes and no previous cardiovascular (CV) morbid events included in the PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale) registry. Subjects were studied before therapy and followed for up to 12 years (mean, 5). The use of calcium antagonists that preceded the event was considered for classification. At entry, the patients who were subsequently given calcium antagonists had a higher clinic (174/98 vs 161/92 mmHg, both p < 0.01) and 24-hour ambulatory blood pressure (150/90 vs 141/84 mmHg, both p < 0.01) than those who were not. During follow-up there were 53 major CV morbid events (6.46 per 100 person-years).

Results: The rate of total CV events (5.6 vs 6.8 events per 100 person-years, relative risk 0.88 [95% confidence interval: 0.47–1.61]) and that of cardiac events (4.0 vs 3.3 events per 100 person-years, relative risk 1.33 [95% CI: 0.62–2.89]) did not differ between users of calcium antagonists (n = 50) and non users. The use of angiotensin converting enzyme inhibitors (n = 66) was unrelated to the risk of CV events (relative risk 1.24, 95% CI: 0.71–2.16). The CV event rate was slightly lower (p = 0.040, log-rank test) among users of calcium antagonists or ACE-inhibitors, alone or combined (5.80 events per 100 person-years) than among the subjects receiving different classes of drugs, mostly diuretics and beta-blockers (10.0 events per 100 person-years). In a Cox multivariate analysis, only age (p = 0.002) and 24-hour pulse pressure (p = 0.04) were independent predictors of CV morbid events.

Conclusions: These findings do not support an association between use of calcium antagonists and increased CV morbidity in subjects with essential hypertension and type II diabetes.

P3532 Validation of three devices for home blood pressure monitoring by comparison with mercury sphygmomanometer and intraarterial pressure measurement

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Oscillometric devices for home blood pressure self-measurement are widely used among patients and clinicians. The aim of our study was to assess precision of these instruments and to compare the results with the standard auscultatory method and with blood pressure (BP) measured invasively.

Patients and Methods: Fifty-one patients (11 women and 40 men, age range 32 to 74 years) undergoing cardiac catheterization for coronary artery disease were included in the study. BP was measured using a fluid filled intraarterial catheter system with the catheter tip placed in the thoracic aorta. Simultaneousy, BP was measured with a calibrated mercury sphygmomanometer and three different types of monitors for home blood pressure self-measurement connected to a single cuff according to recommendations of the protocol of the British Hypertension Society (BHS). Three types of monitors were tested: Omron 711, Omron M4 and Omron HEM-705CP, using two devices of each type in all subjects studied.

Results: Similar correlations were observed between auscultatory and oscillometric measurements and intraarterial BP levels with correlation coefficients ranging between 0.95 and 0.96 for systolic BP (p < 0.001) and between 0.84 and 0.90 for diastolic BP (p < 0.001). Correlations were comparable in all devices tested. The difference between the oscillometric and intraarterial systolic blood pressure ranged from 1.1 ± 9.4 mmHg in Omron 711 to 2.9 ± 9.7 mmHg in Omron M4. Diastolic BP was overestimated by 6.5 ± 6.5 mmHg in Omron 705-CP to 8.3 ± 6.8 mmHg by Omron 711. Differences between the devices did not achieve statistical significance and overestimation of diastolic BP by auscultatory measurement was comparable to the oscillometric method. Comparing auscultatory and oscillometric results using BHS criteria, Omron 711 and M4 were graded A and Omron HEM-705CP was graded B for both systolic and diastolic BP.

Conclusions: BP assessed by the oscillometric method is highly correlated with intraarterial measurements. Systolic BP measured by the two methods is almost identical. In contrast, the oscillometric method tends to overestimate diastolic BP by 6 to 8 mmHg. However, this overestimation is similar to that observed by using the auscultatory method and probably is due to different site of blood pressure measurements (aorta vs. brachial artery). Compared to the auscultatory method, all the tested devices fulfilled requirements of BHS protocol and can be recommended for clinical use.

P3533 Altered circadian rhythm of heart rate variability in normotensive subjects with a family history of hypertension

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Objective: To test whether normotensive subjects with hypertensive parents (H+) have an altered autonomic nervous system activity as compared to normotensive subjects with normotensive parents (H−).

Design and methods: Family history of hypertension was defined when at least one of the parents showed essential hypertension which appeared before the age of 55 years; secondary hypertension was excluded. Thirtyeight H+ (mean age 26+5 years) subjects and 33 sex and age matched H− subjects underwent a 24-h ECG monitoring in order to evaluate the following heart rate variability parameters over the 24 hour, daytime (10.00–16.00, D) and nighttime (00.00–06.00, N) hours: mean RR, SDRR, rMSSD.

Results: All D parameters were similar in the 2 groups, while those evaluated over the 24-h and N were significantly lower in H+ (table).

	H−	H+	p
RR-24 (ms)	834 ± 86	773 ± 90	0.005
SDRR-24 (ms)	180 ± 33	154 ± 40	0.004
RMSSD-24 (ms)	51 ± 14	44 ± 16	0.07
RR-N (ms)	1014 ± 113	911 ± 153	0.005
SDRR-N (ms)	142 ± 41	119 ± 37	0.015
RMSSD-N (ms)	67 ± 23	55 ± 25	0.043

Conclusions: H+ have a different circadian rhythm of HRV parameters from H− which seems to be due to a reduction of cardiac vagal activity during the night.

P3534 Major differences in casual blood pressure in two epidemiologic studies due to minor differences in methodology

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Purpose: Standardisation of minor differences in the methodology of blood pressure measurements between epidemiological studies is hard to overcome. The effect of blood sampling before, respectively after the measurement of casual blood pressure was examined.

Methods: The material comprised of two age-cohorts of 60–62 years old individuals from the same epidemiological center: the first examined in 1993–94 (born 1932, n = 593); the second in 1996–97 (born 1936, n = 695). The two cohorts were chosen on the same criteria and had similar rates of participation. In both studies blood pressure was measured with 2 methods: 1) casual BP by a standard mercury sphygmomanometer with the subject in the sitting position after 5 min. of rest (average of 2 readings); 2) 24-h ABP with the TAKEDA TM-2421 device (both auscultatory and oscillometric readings; only the oscillometric results are presented). The same apparatuses were used in the 2 studies; calibration was performed regularly. One very experienced observer performed all measurements of casual blood pressure at the same time of the day (07:30–11:30 a.m.). Fasting blood samples were taken before the measurements of casual blood pressure in the 1932-cohort, respectively after the measurements of casual blood pressure in the 1936-cohort.

Results: see table.

Results

Cohort	Women		Men	
	1932 (n = 291)	1936 (n = 370)	1932 (n = 302)	1936 (n = 325)
1. Casual BP	133.0/82.3	137.7*/87.8*	136.6/84.3	137.0/90.8*
2. 24-h ABP	126.9/72.5	126.2/71.9	130.7/78.0	129.6/78.2

Results given as systolic/diastolic BP in mmHg. *P < 0.01 for differences between comparable measurements in the two cohorts.

Differences of 5.5–6.5 mmHg and of 0.4–4.7 mmHg were found for the measurements of casual diastolic, respectively systolic blood pressure in the two studies; standard deviations were alike.

Conclusions: The significant differences in casual blood pressure in the two studies could only be explained by differences in the methodology, i.e. the taking of blood samples before, respectively after the measurement of blood pressure. No significant differences were found between ambulatory readings.

Results of casual blood pressure between epidemiological studies should be compared with caution, even when only minor differences in the methodology exist.

P3535 Lack of an association between dopamine D3 receptor gene polymorphism (SER-9-GLY) and essential hypertension

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Recent studies suggest a potential role of the dopamine D3 receptor in the development of hypertension, because disruption of D3 receptor gene in mice causes hypertension. The human dopamine D3 receptor gene contains a polymorphism resulting in a serine to glycine substitution in the extracellular N-terminus of the receptor protein altering dopamine binding.

In order to determine the possible role of the D3 receptor gene in susceptibility to essential hypertension, we determined the frequency of this intragenic polymorphism in a sample of 123 hypertensive patients and 136 normotensive controls. Hypertensive subjects were defined of the individual's blood pressure before starting medications (153 ± 14/89 ± 12 mmHg) and absence of secondary forms of hypertension determined through extensive clinical workup. Control subjects were normotensive anonymous blood donors (123 ± 13/80 ± 6 mmHg) with no anti-hypertensive medications. In a subgroup, with normal or mildly elevated blood pressure (but never treated.for that), we assessed 24-h ambulatory blood pressure (Spacelab 90207), plasma AII and aldosterone concentrations (RIA), 24-h urinary sodium excretion, and LV structure (2D guided M-mode echo).

No significant differences in allele (0.72/0.28 vs. 0.67/0.33) or genotype frequencies (0.54/0.37/0.09 vs. 0.46/0.41/0.13) between a group of hypertensive patients and normotensive controls were found (p = 0.18 and p = 0.5, respectively). A subgroup analysis revealed no significant association between either angiotensin II, aldosterone, and sodium secretion.

Thus, this polymorphism has no major effect on the susceptibility to essential hypertension in our sample of hypertensive patients and is not associated with either angiotensinII, aldosterone, and sodium secretion.

CARDIOVASCULAR DISEASE IN OLDER PERSONS

P3536 Heart failure in the elderly in hospital cardiology units: data from the Italian network on congestive heart failure

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Background: Congestive heart failure (CHF) represents a major public health problem with an age-related increasing prevalence. Despite the high incidence of mortality and morbidity in elderly CHF pts, limited epidemiological data are available for development of appropriate prevention and treatment modalities.

Methods: 3327 outpatients consecutively enrolled in the registry of the Italian Network on CHF by 133 cardiological centers were studied. Data were collected using an ad-hoc software. Univariate and multivariate analysis were performed to compare pts <70 and ≥70 yrs-old and to evaluate associations between clinical variables and 1-year mortality.

Results: The 1033 (31%) elderly pts (64.7% M) did not differ from 2294 younger pts with respect to CT ratio, renal dysfunction and history of ventricular tachycardia but were significantly more likely to be female, in NYHA III-IV, to have preserved left ventricular systolic function (EF>40%), an ischemic or valvular etiology and atrial fibrillation/flutter. At baseline visit, elderly pts significantly received ACE-inhibitors, oral anticoagulants and betablockers less frequently than younger ones. One year mortality was significantly higher in pts ≥70 years (22 vs 13.7% p < 0.001). Multivariate analysis, adjusted for main clinical-epidemiological variables showed that age, as a continous variable, is an independent predictor of mortality (RR 1.03; 95%CI 1.021–1.039), with 1-year mortality 3% increase by year of age. At least 1 hospital admission in the year preceding the entry visit (RR 2.11; 95%CI 1.54–2.9), systolic blood pressure (RR 0.98; 95% CI 0.97–0.99) and NYHA class III-IV (RR 1.6; 95%CI 1.22–2.1) were independent predictors of 1-year mortality in elderly pts.

Conclusions: The present study confirms that elderly patients with CHF: 1) have more severe clinical manifestations of CHF; 2) are less likely to receive ACE-inhibitors, betablockers and anticoagulants; 3) have more frequently preserved systolic function; 4) have a worse prognosis. Consequently, there is a need to develop more effective and targeted preventive and management strategies for this increasingly common health problem.

P3537 The impact of coronary stent implantation in reducing event rates and restenosis in elderly population

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Percutaneous interventions in elderly patients (pts) is associated with frequent procedural complications and low success rates. Elderly pts are more prone to acute ischemic complications of balloon angioplasty (PTCA). It's reported that coronary stenting improves clinical outcomes and reduces complications of PTCA in younger pts. This study was designed to evaluate the impact of stents in reducing event rates in elderly population. A total of 226 consecutive pts undergoing native coronary artery stenting were enrolled. We performed a prospective analysis of elderly pts (age>65 yrs; n = 44) and compared to younger pts (age < 65 yrs; n = 182) according to risk factors, lesion morphology, primary procedural success, clinical and angiographical stent restenosis rates (follow up = 5.7 ± 1 months). Results are illustrated in table.

Comparison of the groups

	Elder pts	Young pts	P
Age (years)	70 ± 4	50 ± 14	0.0001
Diabetes Mellitus	17(38%)	22(12%)	0.03
Smoking	19(44%)	100(55%)	ns
LAD Lesion	33(79%)	111(61%)	ns
Minimal luminal diameter (preprocedure)	0.81 ± 0.4	0.59 ± 0.4100	0.001
Acute gain (mm)	2.11 ± 0.4	2.35 ± 0.4	ns
Late loss (mm)	1.05 ± 0.9	1.2 ± 0.9	ns
Acute major complications	2 (5%)	11 (6%)	ns
Follow-up: Angina	6 (13%)	22 (12%)	ns
AMI	0	1 (0.5%)	ns
PTCA	7 (16%)	54 (30%)	ns
CABG	7 (16%)	32 (14%)	ns
Death	0	0	ns
Angiographic restenosis	14 (33%)	79 (44%)	ns

Despite a higher risk profile, clinical and angiographical success of coronary stenting in elderly was similar to younger pts. Although not statistically significant, restenosis rates were lower in elderly pts (33% vs 44%). It can be concluded that stents can be implanted safely and successfully in older ages. Age itself should not preclude pts from undergoing coronary stenting.

P3538 Profound reductions in exposure to major risk factors to coronary heart disease (CHD) in 70 year old Danes, surveyed 1967, 1984 and 1991

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Since 1964 monitoring of levels of risk factors for CHD in random samples of the population in Copenhagen County have been carried out at regular intervals in cross-sectional and in longitudinal designs.

Methods: Standardised methods based on WHO recommendations have been applied since 1964. We report risk factor levels in 3 cohorts, born in 1897, 1914 and 1921; surveyed at age 70.

Results:

Year of survey	1967		1984		1991	
Gender (n)	men (230)	women (209)	men (412)	women (209)	men (201)	women (201)
Smokers (%)	75.6	39.3	51.9	36.7	46.5	29.4
Hypertension (%) ≥160 or ≥95 mmHg	33.0	32.3	15.1	18.8	22.4	19.5
High cholesterol (%) >6.2 mmol/l	98.4	98.1	52.4	72.2	38.7	63.5
BMI ≥ 30 (%)	10.2	22.5	12.2	16.4	13.4	19.9
Syst. blood pressure (mmHg) mean and SEM	146.4/1.7	146.5/1.9	138.0/1.0	140.8/1.0	143.5/1.4	140.8/1.4
S-cholesterol (mmol/l) mean and SEM	8.0/0.10	9.1/0.13	6.2/0.06	7.0/0.06	5.9/0.07	6.7/0.08
BMI (kg/m^2) mean and SEM	25.6/0.23	26.6/0.34	25.2/0.18	25.5/0.25	26.3/0.26	26.5/0.34

Significant reductions in exposure to major CHD risk factors were observed 1967 to 1984. From 1984 to 1991 BMI increased in both genders, systolic blood pressure and the proportion of hypertensives increased in men. The proportion of smokers, and high cholesterol, decreased significantly in both genders. S-cholesterol continued to decrease.

In conclusion: In both genders a significant and continuous reduction in s-cholesterol and smoking prevalence was observed. The prevalence of high blood pressure was almost halved from 1967 to 1984 but no further improvement was observed the following 7 years, whilst BMI increased in both genders. The observed reduction in major risk factors coincided with a 30% decrease in the incidence of myocardial infarction from 1982 to 1991 in people aged 70–74 years of both genders in the same population (Dan-MONICA heart register).

P3539 Dobutamine stress echocardiography after uncomplicated myocardial infarction in the elderly

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Background: The elderly are at higher risk for adverse events after myocardial infarction (MI). Thus, risk stratification is mandatory but physical limitations often preclude conventional risk assessment.

Aim: The aim of this study was to assess the prognostic value of Dobutamine Stress Echocardiography (DSE) after an uncomplicated MI in the elderly.

Methods: Fifty seven consecutive patients aged ≥70 years (males 37; age 75 ± 4) underwent DSE within ten days after uncomplicated MI. DSE was carried out following the standard method. Five myocardial responses were identified: 1) negative; 2) sustained improvement of contractility; 3) initial improvement followed by worsening; 4) worsening in the infarcted zone; 5) worsening at a distance.

Results: DSE was well tolerated without any severe complication. Mean follow-up was 14 ± 8 months. There were 26 events: non cardiac death 4, cardiac death 6, AMI 1, heart failure 1, unstable angina 10 and revascularization 4. Clinical and echocardiographic variables were considered, including those previously related to adverse prognosis. Multivariate stepwise regression showed that worsening of contractility in the infarcted zone was the only independent predictor of impaired outcome ($p < 0.001$, relative risk 2.80; 95% confidence interval 1.68 to 4.66).

Conclusion: Ischemia in the infarcted zone detected as worsening in contractility during DSE after uncomplicated MI predicts a poor outcome in the elderly.

P3540 Management of heart failure and atrial fibrillation in older people in the community

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Both heart failure and atrial fibrillation (AF) are common in older people. Improving recognition and care of patients with heart failure has a major impact on morbidity, mortality and heath-care costs. Treatment with angiotensin converting enzyme (ACE) inhibitors can improve survival and quality of life even in those with mild systolic left ventricular (LV) dysfunction. Anti-coagulants are effective in stroke prevention in AF with aspirin being an alternative for those unsuitable for formal anti-coagulation.

Methods: A random sample of 500 subjects was drawn by 2 stage random sampling from 5002 subjects aged 70 years and over living at home. Subjects attended a hospital clinic for clinical assessment. AF was diagnosed by electrocardiography and systolic LV function was assessed qualitatively on echocardiogram as normal, mild, moderate or severe dysfunction.

Results: 452 of the 500 subjects (90%) participated in the study. In total, 351 (78%) received an echocardiographic assessment The population prevalence amongst older people of systolic LV dysfunction was 8% and AF 7%. 32% of those with AF had impaired systolic LV dysfunction compared to 10% of those in sinus rhythm. Those with LV dysfunction were more likely to be prescribed diuretics (50% vs 31%, $p < 0.05$), aspirin (48% vs 26%, $p < 0.001$) and ACE inhibitors (30% vs 9%, $p < 0.0001$). Of those in AF, 34% were taking aspirin, 24% warfarin and 41% were on neither aspirin nor warfarin.

In conclusion, heart failure is under-recognised and under-treated in older people in the community. The majority of those with systolic LV dysfunction are not on ACE inhibitors and a significant proportion of those in AF are not on any treatment for stroke prevention, be it warfarin or aspirin.

P3541 How age does and should influence the management of myocardial infarction

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Background: Around 75% of patients with acute myocardial infarction (AMI) are aged >70, but they are often treated less vigorously than younger patients. In part this may be because clinicians have misconceptions about their likely prognosis, and give age undue weight in clinical decisions. We have examined how age does and should influence management and risk stratification in AMI.

Methods: Prospective cohort study of the management and outcome of 1225 consecutive patients with AMI.

Results: Older patients were slower to arrive in hospital and less likely to receive thrombolysis or discharge beta-blockers: odds ratios (95% CI) for patients aged >70 years compared to those <60 were 0.63 (0.45–0.88) for thrombolysis and 0.25 (0.16–0.37) for beta-blockers, adjusted for sex, diabetes, previous AMI, Q waves, and left ventricular failure. Left ventricular failure (LVF) was the strongest independent predictor of death within *a* year of infarction (adjusted hazard ratio 4.76 (3.53–6.43)). Its influence was such that patients aged >70 without LVF had significantly better survival at 1 year than patients <60 with LVF. 70.8% (62.2–78.2%) of this older group who survived to hospital discharge were still alive three years later.

Conclusion: Elderly patients with AMI were treated less vigorously than younger patients. Prognosis however was heavily influenced by the development of LVF such that many older patients had a better outlook than younger patients with adverse clinical factors. In planning risk based management, consideration of age independently of clinical status is inappropriate.

P3542 Secondary prevention in elderly patients with acute coronary syndrome in France: results of the PREVENIR survey

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The aim of the French nation-wide observational study (PREVENIR) was to detail the treatment prescribed at hospital discharge and 6 months later to patients with unstable angina (UA) or myocardial infarction (MI).

Methods. The survey was performed in 77 private and public cardiology centres. All patients admitted to hospital in January 1998 who survived an acute coronary syndrome were included: 1456 patients, MI: 819, UA: 637. Treatment at discharge was collected retrospectively. Data on the ongoing treatment were collected during an out-patient consultation or, by questioning the patient's GP.

Results. Data concerning 715 elderly patients (≥65 years) alive at 6 month and not lost for follow-up were analysed. Baseline characteristics are comparable with those reported in previous French epidemiological studies. (USIK, PRIMA). At discharge some treatments [fibrates: 6.9% (49), omega 3 fatty acid: 1.3% (9), ACE-inhibitors: 43.2% (309), nicotine patches: 0.6% (4)] were similar for patients either under or over 65 years, whereas the other treatments (statins: 28.3% vs. 47.8%, $p < 0.001$; aspirin: 88.1% vs. 93.2%, $p < 0.001$; beta-blockers: 65.2% vs. 78.1%, $p < 0.001$; cardiac rehabilitation: 18.7% vs. 31.9%, $p < 0.001$) were less frequent. There were no significant changes in treatment 6 months later, except for statins (35.5% vs. 28.3%, $p < 0.001$). Only 6% of patients (12) with statin at hospital discharge had stopped the medication at 6 month follow-up. Family physicians will initiate statin therapy for only 12.5% (64) of untreated patients.

Conclusion. Rehabilitation and measures to prevent smoking are used sparingly. Statins and beta-blockers are underused compared with younger patients. Whereas, in secondary prevention, statin clinical trials have demonstrated a similar beneficial effect in patients under or over 65 years, prescription remains at a modest level indicating that the lessons for recent clinical trials have not yet been completely applied to daily clinical practice. Our population, however, comprised 12% of patients of more than 85 years, in whom the beneficial effect of statins is not documented to date.

P3543 Exercise conditioning prevents the age-dependent increase in coronary microcirculatory resistance, while arterial hypertension accelerates epicardial artery narrowing

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Exercise conditioning is supposed to decrease cardiovascular morbidity, while arterial hypertension represents a risk factor for ischemic heart disease. A different susceptibility of coronary circulation to ageing may, at least partially, explain these observations.

Aim of this study was to compare the relation of coronary vasodilator capacity and conduit vessel remodeling with age in 16 healthy sedentary normotensives (NL), 16 highly trained athletes (A) and 16 hypertensive subjects (HT) of comparable age (50 ± 15, 53 ± 18, 58 ± 9 years). By means of TEE-Doppler, coronary flow velocity (CFV) in left anterior descending artery was monitored at baseline and during i.v. dipyridamole infusion (Dip: 0.84 mg/kg/9 min), and left main artery (LMA) diameter was measured in zoomed 2-D diastolic images. Coronary flow reserve (CFR) was calculated as ratio of maximal CFV during dipyridamole and basal CFV, and minimum coronary resistance (MCR) as ratio of mean BP to maximal CFV during dipyridamole.

Results: CFR and MCR were 3.23 ± 0.65 and 0.96 ± 0.23 mmHg*s/cm, respectively, in NL. Compared to NL, not significantly different values were found in A (CFR: 3.60 ± 0.70, MCR: 1.04 ± 0.17 mmHg*s/cm), while HT showed lower CFR (2.31 ± 0.32, $p < 0.01$) and higher MCR (1.21 ± 0.3 mmHg*s/cm, $p < 0.05$). Age was directly related to MCR ($r = +0.63$, $p < 0.01$) in NL and inversely related to CFR in A ($r = -0.56$, $p < 0.02$): such a different pattern was depending in NL on relations of age with dipyridamole BP (direct: $r = 0.61$, $p < 0.01$) and – close to statistical significance – dipyridamole CFV ($r = -0.40$, $p = 0.1$), while in A basal CFV tended to increase with age, paralleling systolic BP and rate-pressure product. No age-dependent changes in LMA area were found in either group. By contrast with NL and A, HT showed a significant inverse correlation of age with LMA area ($r = -0.44$, $p < 0.01$), but not with MCR or CFR.

Conclusions: chronic exercise training counteracts the "physiological" increase of coronary microcirculatory resistance with age, while arterial hypertension seems to accelerate epicardial artery narrowing.

P3544 Stress echocardiography in octogenarians: safety, tolerability and better visualization of the myocardial segments using native harmonics

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Introduction: With the gradual displacement of the generational pyramide in the different cultures towards an advanced age, coupled to the fact that this age group has a greater probability of coronary artery disease (CAD). A safe and reproducible exam that can evaluate this entity is of great importance.

Methods: Group 1: 241 pts, range 70–95 yr, Group 2: 788 pts with age less 70 yr. These groups were compared for safety, tolerability and myocardial segment visualization. All patients underwent Dobutamine Stress Echocardiography (DSE). The standard protocol of 3 minute stages of 5, 10, 20, 30, 40 and 50 mcg/kg/min of DBT was used until at least 90% target heart rate (THR) was reached if at 30 mcg/kg/min less than 70% of THR was achieved atropine in boluses of 0.25 mg was used up to a maximum of 2.0 mg.) or Exercise Stress Echocardiography (ESE) until achievment of target heart rate (THR) for age or changes in regional contractility. An Acuson Sequoia C256 (Mountain View, CA) with native harmonics and a H3.5 MHz frequency transducer was used.

Results: Group 1: Was composed of 52.7% women, the mean age of: 75.5 ± 4.8 yr, weight: 65 ± 11.4 kg. ESE was done in 10.5%. The indications were: CAD = 57%, typical angina: 17.2%, atypical chest pain: 4.8%, nonvascular surgery 13.4%, valvular disease:2.7%. THR was achieved in 89.9% with DSE and 95.5% in ESE. 99.5% of the segments were visualized in both groups. The adverse effects between the groups were: None: 90.2% vs 94.3%, Supraventrycular arrythmia:0.5% vs 0.1%, ventricular arrythmia 1.5% vs 0.1%, Bradicardia 0 vs 0.3%, Angina 5.4% vs 4%, Hypotension: 1.5% vs 0.3%, Headeache 1% vs 0.6%, Nausea:0% vs 0.3%. There were no deaths during the examination. A total of 3.836 segmentos were visualized of 3.856 segments possible.

Conclusion: DSE + ESE in octogenarians is a safe and tolerable exam. Adverses effects are comparable to a population of less age. Native harmonic adds the feasibility of visualizing 99.5% of segments allowing a better interpretation of this test modality.

ADVANCES IN PRIMARY AND SECONDARY PREVENTION

P3545 Healthy offspring of men with premature myocardial infarction have significantly elevated factor VII and factor XII plasma levels

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A family history of premature myocardial infarction (PMI) consists an independent cardiovascular risk factor (F) while elevated FVII and FXII plasma levels are associated with increased cardiovascular morbidity and mortality. Aim of the study was to determine FVII and FXII plasma levels in healthy offspring of men with PMI (<55 yrs) and to compare these findings with those of healthy offspring without a family history of cardiovascular disease (CVD).

Methods: Sixty eight (32 M, 36 F) mean age (MA) 18.2 ± 2.75 yrs and body mass index (BMI) 22.5 ± 3.3, kg/m^2 healthy offspring of men with PMI (group A) and 32 (15 M, 17 F) MA 18.45 ± 2.46 yrs and BMI 21.8 ± 3.6 kg/m^2 healthy offspring without family history of CVD, diabetes mellitus or hypertension were studied. Fasting FVII and FXII plasma levels were determined in the whole population (ELISA method).

Results:

	FVII %	FXII %
Group A	163.6 ± 36.9	82 ± 21
Group B	106.2 ± 31.9	72 ± 17
	p < 0.0001	p < 0.01

Conclusions: Our results suggest that fasting FVII and FXII plasma levels are significantly increased in healthy offspring of men with PMI compared to those of healthy offspring without a family history of CVD. This finding may be another mechanism which enhances the cardiovascular risk.

P3546 The effect of weight loss with or without exercise training on large artery compliance in healthy obese men

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Objective: To investigate the effect of weight loss with or without exercise training on compliance of large arteries in healthy obese men.

Methods: Thirty-seven healthy, obese men were studied. Seventeen were randomized to a very low calorie diet (D) for 6 weeks, 20 to a very low calorie diet and an additional exercise program (DE). Subjects were examined before and 12 weeks after start of the study. Systolic (SBP), diastolic (DBP) and mean arterial pressures (MAP) and heart rate (HR) were semi-automatically measured. Cross sectional compliance (CC) and distensibility coefficient (DC) at operating pressures and under isobaric conditions (isoCC and isoDC) were measured with a wall track system at the common carotid artery (CCA) and the brachial artery (BA). Changes between start and end of the study period were analyzed with the Wilcoxon signed ranks test. Differences between interventions (D and DE) were analyzed using the Mann-Whitney test. Results are given as mean ± SEM.

Results: Weight loss averaged 15 ± 1 kg (P < 0.001). Body Mass Index was 32.3 ± 0.4 kg/m^2 before start of the study and decreased (P < 0.001) with 4.7 ± 0.3 kg/m^2. SBP (129 ± 2 mmHg), DBP (81 ± 1 mmHg) and MAP (99 ± 1 mmHg) decreased (P < 0.001) during the study with 9 ± 2 mmHg, 6 ± 1 mmHg and 7 ± 2 mmHg, respectively. HR did not change significantly. DC and CC were 26.2 ± 0.1 10^{-3}.kPa^{-1} and 1.29 ± 0.07 mm^2.kPa^{-1} for the CCA and 5.1 ± 0.5 10^{-3}.kPa^{-1} and 0.12 ± 0.01 mm^2.kPa^{-1} for the BA. No changes between groups were noted for the above mentioned parameters.

Changes (Δ) during the study period are shown in table.

	ΔDC	ΔCC	ΔisoDC	ΔisoCC
BA (n = 34)	1.0 ± 0.8	0.05 ± 0.04*	0.1 ± 1.0	0.04 ± 0.04
CCA (n = 33)	4.7 ± 1.7*	0.18 ± 0.08*	2.2 ± 1.7	0.10 ± 0.09

Δ(iso)DC: 10^{-3}.kPa−1; Δ(iso)CC: mm^2.kPa−1; * = P < 0.05

Conclusion: significant weight loss, with or without exercise, in otherwise healthy obese men decreases blood pressure and increases compliance of the CCA and BA at operating pressures but not at isobaric levels. The increase in compliance at operating pressures is therefore most likely a passive process due to the decrease in mean arterial pressure and is not an indicator of structural changes in the arterial wall in this 12 week period.

P3547 Do we miss the opportunity for effective secondary prevention?

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The guidelines on the efficacy of secondary prevention after coronary revascularization, based on clinical trials are unequivocal. Many studies have analyzed the cost-effectiveness and the appropriateness of revascularization procedures or drug therapies, but preventive actions appear less attractive.

We studied 700 random patients after revascularization in four public hospitals in the Canary Islands, the Spanish community with the highest coronary heart disease mortality. Revascularization procedures were coronary artery bypass graft in 22%, and non-surgical in 69% (stents 47%, PTCA 20%, atherectomies 2%), 9% underwent multiple procedures. Demographic features and risk factors prevalence were similar in both surgical and non-surgical groups. We found statistically significant differences regarding current smoking (10 vs. 90, p < 0.006) and the number of angiographic studies performed (309 vs. 1344, p < 0.002). In spite of revascularization, 74% of the patients received 3 or more cardiovascular drugs; surgical patients were treated with fewer betablockers (p < 0.003), but more cholesterol-lowering agents than non-surgical patients (p < 0.006).

In conclusion: Revascularized patients have still a great potential of modifiable risk factors. Patients undergoing percutaneous revascularization are more likely to continue smoking and have further angiographic studies. Though non-surgical patients received more cardiovascular drugs on average, especially betablockers, cholesterol-lowering agents were among the least used. A greater effort is needed to enhance patients benefits and rationalize the use of our resources, following the guidelines of clinical trials and avoiding the underuse of simple preventive actions.

P3548 Secondary prevention of patients with acute coronary syndrome in France: results of the PREVENIR survey

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The aim of the French nation-wide observational study (PREVENIR) was to detail the treatment prescribed at hospital discharge and 6 months later to patients with unstable angina (UA) or myocardial infarction (MI).

Methods. The survey was performed in 77 private and public cardiology centres. All patients admitted to hospital in January 1998 who survived an acute coronary syndrome (ACS) were included: 1456 patients, MI: 819, UA: 637. Treatment at discharge was collected retrospectively. Data on the ongoing treatment were collected during an out-patient consultation or, by questioning the patient's GP.

Results. Baseline characteristics of patients with coronary artery disease are comparable with those reported in previous French epidemiological studies (MONICA, USIK, PRIMA). Treatment at hospital discharge included statins: 35.6% (519), fibrates: 6.7% (97), omega 3 fatty acid: 2.7% (40), aspirin: 89.8% (1307), beta-blockers: 68.3% (995), ACE-inhibitors: 41.5% (605), nicotine patches: 0.7% (11), cardiac rehabilitation: 23.8% (347). Data concerning 1290 patients alive at 6 month and not lost for follow-up were analysed. Few patients stopped the medication prescribed at discharge: statins: 4.4% (23), fibrates: 16.5% (16), omega 3 fatty acid: 15% (6), aspirin: 3.8% (49), beta-blockers: 6.1% (61), ACE-inhibitors: 9.4% (57). There were no significant changes in treatment 6 months later, except for a higher prescription of statins (45.7% vs. 35.6%, p > 0.001). When statin therapy was not initiated at hospital, subsequent prescription by the GP or referring cardiologist was uncommon [14.2% (137)].

Conclusion. Prescription of aspirin, beta-blockers and ACE-inhibitors after ACS has improved in France, while cardiac rehabilitation and measures to prevent smoking are used sparingly. The prescription of statins is improving, although it remains at a modest level, indicating that the lessons from recent clinical trials have not yet been completely applied to daily clinical practice.

P3549 A cardiac prevention programme can benefit all patients at first presentation with coronary artery disease in the population

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Background: Traditional cardiac rehabilitation programmes have not included patients with stable or unstable angina unless revascularised, and are usually restricted to patients managed within hospital. This excludes over 50% of patients at first presentation of their coronary artery disease (CAD), despite such patients having mortality benefits from secondary prevention measures. We provided a comprehensive cardiac prevention programme for all patients whose first presentation of CAD was angina or unstable angina in addition to those presenting with myocardial infarction.

Methods: All patients listed with 80/159 (50%) of GPs in Bromley Health Authority (total population 292 000) presenting with CAD were eligible for the new nurse led programme and the other half of patients received usual care. A rapid access chest pain clinic to which GPs referred all suspected new cases of CAD, combined with daily hospital admission monitoring, ensured complete and prompt case identification. Patients were recruited at the time of first diagnosis and visited on the ward and at home within 2 working days. A 3 month programme of lifestyle and risk factor modification including pharmacological treatment of hypertension and hypercholesterolaemia was undertaken. Family screening was offered to first degree relatives. The objective was to achieve defined lifestyle, risk factor and therapeutic targets.

Results: 162 patients (83% of 196 possible cases) were recruited over 15 months with 65% completing the programme. Targets for achieving non-smoking status, blood pressure < 140/90, and total cholesterol < 5.2 mmol/l were achieved in 90%, 73% and 75% respectively and the proportion of patients on aspirin, beta blockers and lipid lowering therapy was 93%, 57% and 62% on discharge to general practice.

Conclusion: A comprehensive prevention programme should be offered to all patients presenting with CAD. A high recruitment rate can be achieved from patients who have not undergone infarction or revascularisation and those normally managed in primary care. Lifestyle and risk factor targets can be achieved with such a programme.

P3550 Long-term course of cardiovascular risk factors following cardiac in-patient rehabilitation

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Short-term positive effects on cardiovascular risk factors by altering lifestyle and/or drug therapy have been demonstrated, however, not in the long-term course. In a large cohort we therefore investigated the long-term persistency of risk factor improvements achieved by cardiac inpatient rehabilitation at discharge.

Method: Between January and June 1997 2,441 consecutive CHD patients (22% women, 65 ± 10 years, 78% men, 60 ± 10 years) were enrolled in the study after acute cardiac event (primary diagnosis 38% CABG, 56% MI, 6% PTCA). Standardized questionnaires were completed by the patients and their physicians at admission (A) to and discharge (D) from inpatient rehabilitation as well as after 3, 6 and 12 months.

Results: The percentages of patients with pathologic values of conventionally defined risk factors were:

	A	D	3 mo	6 mo	12 mo	p-value*
BP (>140/90 mmHg)	24	8	19	22	20	0.001
Smoking	39	5	-	10	10	0.001
BMI (>30 kg/m^2)	18	15	17	21	24	0.001
Glucose (>140 mg/dl)	14	11	19	20	24	0.001
Total cholesterol (>200 mg/dl)	59	30	48	51	45	0.001
LDL cholesterol (>100 mg/dl)	87	67	79	78	80	0.006
Triglycerides (>200 mg/dl)	22	15	27	28	29	0.001

• Statistical comparison A vs D and D vs 12 months (mo)

Conclusion: The success of cardiac inpatient rehabilitation in modifying cardiovascular risk factors is not maintained in the long term. Since the patients BMI as well as glucose and triglyceride levels relapsed beyond baseline levels, closer cooperation with the outpatient medical care provider is required.

P3551 Long-term (25 years) efficacy of comprehensive post myocardial infarction rehabilitation program

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Aim: To assess the effectiveness of a public health approach in rehabilitation and comprehensive secondary prevention after myocardial infarction on 25 years follow-up.

Method: Random allocation of 129 male patients < 65 years, dicharged after acute myocardial infarction during 1973–1975 to either regular care (group C) or a comprehensive program (group I) to reduce risk factors (hypertension, diabetes mellitus, smoking, cholesterol, obesity, alcohol consumption) and regular physical activity, supervised for the first 3 month.

Results: The intervention group (I) comprised 65 p, mean age 52 ± 8 years and the control group (C) 64 p, mean age 53 ± 8 years. The efficacy of intervention was evaluated at 1 year of follow-up: 35% weight reduction, 16.7% blood pressure drop, 22.2% serum cholesterol drop, 40.5% smoking changes, 45.5% alcohol consumption changes, 23.1% improvement in physical work capacity and 6.2% worsened physical work capacity. All cause mortality was 4.9% group I at 1 year vs 7.1% in group C – NS. At 3 year follow-up all cause mortality was 11.9% in group I and 15% in group C – NS. At 25 years all cause mortality was 56.9% in group I and 75% in group C – p = 0.03. Return to work was, at 1 year of follow-up 70.6% in group I and 58.7% in group C – p = 0.02, at 3 years 75.5% in group I and 65.5% in group C – p = 0.04. At 25 years 2 patients in group I were still full-time active.

All cause mortality and return to work

Parameters		Follow-up		
		1 year	3 years	25 years
Mortallty (%)	Group C	7.1	15.0	75.0
	Group I	4.9	11.9	56.9
p		NS	NS	0.03
Return to work (%)	Group C	58.7	65.5	–
	Group I	70.6	75.1	2 pts.
p		0.02	0.04	–

Conclusions: A comprehensive post myocardial infarction rehabilitation program has immediate effect (after 1 year) on risk factor reduction and quality of life (measured by return to work) and on long-term i.e. 25 years reduces all cause mortality by 18.1%.

P3552 Prevention practices in patients with atrial fibrillation and neurological events: evidence for underutilization of anticoagulation

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Background: The purpose of the study was to investigate the primary and secondary prevention practices in patients (pts.) with neurological events (TIA, PRIND and stroke) and atrial fibrillation (AF).

Methods: Between 1/97 and 1/98 all pts. admitted to our hospital with acute neurologic events were prospectively registered and the pts. were stratified according to heart rhythm. Antithrombotic medication on admission and at discharge was recorded.

Results: Of 388 pts. with neurologic events 5 pts. were excluded from the analysis because of subarachnoid hemorrhage as well as 13 pts. because of insufficient ECG data. Of the remaining 369 pts. 82 were in afib (22.2%). The mean age of these pts. was 80.4 ± 7.5 years, 70.7% were female. 15.9% suffered from a TIA, 4.9% from a PRIND and in 79.2% stroke was present. Only 2 pts. had intracranial hemorrhage on admission. In 50 pts. (60.9%) afib was previously known. Of these pts. only 6 (12%) received oral anticoagulation at the time of admission, 26 (52%) were on aspirin or ticlopidine and 18 pts. (36%) received no antithrombotic treatment at all. Of 63 surviving pts. with AF 32 pts. (55.6%) had no absolute or relative contraindications against oral anticoagulation. Of these pts. 14 (40%) were on anticoagulants at discharge, 20 (57.1%) received aspirin or ticlopidine and 1 pt. (2.9%) had no antithrombotic treatment.

Conclusions: In the majority of AF pts. with neurologic events the rhythm disorder had been known before the event, however oral anticoagulation had not been prescribed in 78% of these pts. Only 40% of pts. with AF and no contraindications against anticoagulation were on oral anticoagulants for secondary prevention at discharge. To translate the benefit of oral anticoagulation in preventing stroke in pts. with AF from trials to daily clinical practice, much consequenter adherence to clinical guidelines is needed.

P3553 Adherence to recommendations for prevention in patients with stable angina pectoris: observations from the ACTION (A Coronary disease Trial Investigating Outcome with Nifedipine GITS) study

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Adherence to current recommendations of the European societies for prevention in patients with established coronary disease was evaluated based on screening data from the ongoing double-blind **ACTION** trial.

Methods: Patients with proven coronary disease and stable angina requiring anti-anginal treatment were recruited in Canada, Israel, Australia, New-Zealand and 15 Western European countries. Patients with heart failure or other conditions that limit life expectancy were excluded, as were patients on a Calcium-blocker that could not be stopped.

Results: Entry characteristics of 78% of randomised patients were:

Total number of patients in data base	5,891 (100%)
Median age in years (range)	63 (35–89)
Male/Caucasian	80%/98%
History of MI or revascularisation	70%
History of claudication, TIA or stroke	12%
Insulin/non-insulin dependent diabetes	2%/12%
Hypertension/hyperlipidaemia treated with drugs	39%/70%
On a beta-blocker/on two or more anti-anginal drugs	80%/52%
Risk factor: current smoker	18%
Risk factor: blood pressure > 140/90 mmHg	36%
Risk factor: cholesterol > 5.0 mmol/l	66%
One/two/three risk factors	46%/30%/4%

18% are still smoking. Despite frequent use of drugs, 36% have a blood pressure > 140/90 mmHg, 66% has a cholesterol > 5.0 mmol/l and 34% have two or three risk factors. There were no differences between patients with (70%) and without a history of MI or revascularisation.

Conclusion: Intensified risk factor management is required to achieve the risk factor goals recommended. This conclusion applies to all countries participating in the ACTION study.

P3554 Lipid treatment goals in patients with atherosclerotic disease

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Purpose: Our primary study objective was to evaluate the application of the "5-4-3-2-1" guideline in secondary prevention (total cholesterol [TC] < 5.0 mmol/l, total/HDL-cholesterol ratio < 4, LDL-cholesterol [LDL-C] < 3.0 mmol/l, triglycerides [TG] < 2.0 mmol/l and HDL-cholesterol [HDL-C] > 1.0 mmol/l), recommended in Norway from 1995. After the new European guidelines were presented, with treatment goals of TC < 5.0 mmol/l and LDL-C < 3.0 mmol/l, we added a secondary study objective before opening the database, in intention to explore this optional treatment goal. In addition, we wanted to discuss a treatment criterion of TG < 1.5 mmol/l ("1.5"), since elevated TG are connected with an atherogenic lipoprotein phenotype.

Methods: In 1997/98 in general practice 2134 patients with established atherosclerotic disease on a lipid lowering therapy were monitored. Their mean age was 63 years.

Results: The "5-4-3-2-1" guideline was met in 19.2%, the "3-1.5" goal in 22.5% and the "5-3" guideline in 36.2% of the patients. Our data showed a good conformity between the "5-4-3-2-1" rule and the "3-1.5" rule, also in diabetic patients. Of the patients who achieved the "5-3" guideline approximately 50% still had unfavourable values of HDL-C and TG, while only 15% in those who fulfilled the "3-1.5" criteria had HDL-C ≤1.0 mmol/l.

Conclusions: A treatment goal of LDL-C < 3.0 mmol/l and fasting TG < 1.5 mmol/l seems justified in secondary prevention and can replace the "5-4-3-2-1" guideline. This simple goal of "3-1.5" should also be preferable to the official European guidelines.

P3555 The benefit of clopidogrel over aspirin is amplified in high-risk subgroups with a prior history of ischaemic events

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CAPRIE showed the superiority of clopidogrel (C) over aspirin (A) in reducing the combined risk of ischaemic stroke (IS), myocardial infarction (MI) or vascular death in patients with recent IS, recent MI or symptomatic peripheral arterial disease (PAD). We performed a multivariate analysis to: 1) define the role of pre-existing symptomatic vascular disease in predicting further atherothrombotic events; 2) test whether such disease defines a high-risk patient cohort; 3) assess the efficacy of C versus A in patients with previous vascular disease.

Methods: A multivariate model was constructed that included all medical variables recorded at patient inclusion. Analysis of established risk factors and the presence of pre-existing vascular disease (previous MI, stable or unstable angina, TIA, RIND, stroke, claudication or amputation) was performed for all CAPRIE patients. Absolute and relative risk reductions (ARRs and RRRs) for C vs A were calculated for the 2 cohorts of patients shown below.

Results: For the combined endpoint IS, MI, hospitalization for angina/ claudication/peripheral ischaemia/TIA/myocardial ischaemia, patients with previous IS, previous MI or previous claudication had risk ratios of 1.23 (p = 0.031), 1.25 (p < 0.001), and 1.44 (p < 0.001), respectively. For the same outcome cluster the following data were obtained in the 2 patient cohorts (see table).

Cohort	Drug	3-year Event Rate	ARR	RRR (p-value)
1. Previous acute events (IS or MI)	C (n = 2249)	32.6%	3.9%	12.4% (0.034)
	A (n = 2247)	36.5%		
Previous vascular disease	C (n = 4421)	30.5%	2.6%	9.3% (0.033)
	A (n = 4433)	33.1%		

Results were consistent for the endpoint IS, MI, or vascular death (ARR = 3.4%, RRR = 14.9% [p = 0.045] for Cohort 1; ARR = 2.8%, RRR = 11.5% [p = 0.05] for Cohort 2).

Conclusions: CAPRIE patients with a prior history of ischaemic events had high event rates, and different disease manifestations represent risk factors for recurrent vascular events. The absolute benefit of C over A is amplified in such high-risk patients.

P3556 Low-dose red wine reduce the risk of upper gastrointestinal bleeding of patients on low-dose aspirin regimens: a prospective case-control study

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Low-dose aspirin (<350 mg) and low-dose red wine (<20 gr of alcohol/day) are commonly recommended for patients with ischemic heart disease. Low-dose aspirin increases the risk of upper gastrointestinal (GI) bleeding. Red wine may induce acute gastritis and peptic ulcer bleeding. Objective: to study the influence of red wine on the risk of upper gastrointestinal bleeding in patients who receive low-dose aspirin.

Methods: We prospectively studied 1122 consecutive patients (69% males) with upper gastrointestinal bleeding induced by peptic lesions and 2231 age- and sex-matched controls (1109 hospitalized and 1122 non-hospitalized controls). Data were collected by structured and direct interview with patients/controls and family members during hospitalization or family practitioner outpatient clinics.

Results: Low-dose alcohol was consumed by 11.2% of cases and 14.7% of controls. >97% of the alcohol consumed was red wine. Stepwise conditional logistic regression analysis (Table) identified low-dose aspirin use, moderate-dose red wine and high-dose red wine daily consume as independent risk factor for bleeding, whereas low-dose red wine use was found as protective factor. This protective effect was also observed in patients on low-dose aspirin regimens (OR: 0.52; 95%CI: 0.2–0.9).

Variable	Cases	Controls	OR (95% CI)	p value
Upper GI bleeding history	23.5%	4.1%	5.8 (4.2–8.1)	<0.0001
Ulcer history	35.7%	11.7%	3.4 (2.6–4.3)	<0.0001
NSAID use	46.3%	9.9%	13.1 (10.6–16)	<0.0001
Low-dose aspirin	13.2%	9.9%	2.8 (2.1–3.6)	<0.0001
Low-dose alcohol: ≤20 gr/day	11.2%	14.7%	0.68 (0.5–0.8)	0.0058
Moderate-dose alcohol: 20–50 gr/day	7.9%	6%	1.6 (1.1–2.2)	0.0087
High-dose alcohol: >50 gr/day	5.1%	3.3%	2.4 (1.6–3.6)	<0.0001

Conclusion: Low-dose red wine use is an independent protective factor for peptic lesion-induced upper GI bleeding and reduces the increased risk associated with low-dose aspirin regimens. Moderate or high doses of red wine are independent risk factors for upper GI bleeding.

NUTRITION AND LIPIDS

P3557 Nutrition and frequency of coronary heart disease in Kabardino-Balkarian republic

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The peculiarities of nutrition and the incidence of CHD have first been investigated at the Kabardino-Balkarian State University in the South of Russia. The research involved 1057 males aged 40–59. They were of different nationalities – Russians, Kabardians, Balkarians; They lived in towns and rural areas of the republic and they had the same economic and social conditions of living. But they all had different food traditions. The epidemiological studies have been performed in according with the international standard methods of investigation. There were significant differences in the incidence of CHD and risk factors which depend on the way of nourishment of Russians, Kabardians and Balkarians in the towns and villages of the Republic. It has been determined that the national nourishment traditions are more stable in the rural areas of Kabardino-Balkaria. The people who leave villages for towns are constantly loosing something in their nourishment traditions. The incidence of CHD (17.4%), arterial hypertension (37%), excessive body mass (33%), hypertriglyceridemia (17%), hypercholesterolemia (14%) are mostly observed among the Russian town-dwellers. The incidence of CHD (5.4%), arterial hypertension (16.2%), excessive body mass (23%), hypertriglyceridemia (9%), hypercholesterolemia (8%) are observed least among the Kabardians who live in rural regions ($p < 0.01$). The food of the first group contains more animal protein, sugar and animal fat. The food of the Kabardians who live in the rural districts of the Republic contain more vegetable proteins, polyunsaturated fatty acids, complex carbohydrates. Such food is nearer to the diet which is recommended by the International Health Organisation for prevention of atherosclerosis. Multiple regression analysis confirmed the connection of CHD and risk factors with the peculiarities of nutrition. The negative connection was found between the incidence of CHD and polyunsaturated fatty acids level ($p < 0.01$). The strongest connection is observed between the caloric value and the body mass index ($p < 0.01$; $R = 0.7$). The increase of systolic and diastolic blood pressure, the level of triglyceridemia of blood directly depend on the content of alcohol and sugar ($p < 0.01$) and indirectly depend on the content of polyunsaturated fatty acids in the diet ($p < 0.01$). It has been statistically proved that the peculiarities of nourishment affect the incidence of CHD and risk factors. This fact is to be taken into consideration in the organisation of primary prevention of cardiovascular and other noncommunicable diseases among the population of the Republic.

P3558 The long-term results of weight reduction in obese coronary patients with different educational programmes and different calorie-restricted low fat diets

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The long-term success of weight reduction in obese coronary patients is still unsatisfactory. Therefore, we studied prospectively the influence of two different calorie-restricted low fat diets and two different educational programs on long-term weight loss in 529 obese (BMI = 30.7 kg/m^2) coronary patients (P).

During an inpatient cardiac rehabilitation (CR, 26+ −4 days) P were randomised either to a low fat diet with 1200 kcal (R) or 1800 kcal (M). Additionally each group was subdivided into two different educational programs: one hour session by a physician at the beginning and end of CR (S) or a 10 hour-group-session with psychologists, dietitians and physicians (I). 181 P were in RS, 80 in RI, 194 in MS and 74 in MI. After discharge P continued to weigh themselves for 6 months and returned the results with a questionnaire. 66% of all P responded after 6 months; the intensively educated P showed a better compliance with 73% returns vs 63% of the short-trained P.

The weight loss at the end of CR with 1200 kcal (RI = 4.1 kg; RS = 3.9 kg) was significantly greater ($p < 0.01$) then with 1800 kcal (MI = 3.1 kg; MS = 3.2 kg). However, no difference was found in reduction of body fat mass (BIA). The total weight loss at 6 months after CR amounted to: RI = 5.1 kg, RS = 5.2 kg, MI = 4.5 kg, MS = 4.1 kg. Thus, there was no significant long-term difference between the 1200 kcal and 1800 kcal group. Intensity and duration of educational sessions did not show a short or long-term effect on weight loss.

Obese coronary patients lost successfully and permanently weight with a low fat diet of 1800 kcal and a short educational program. A lower calorie-restricted diet and more intensive education did not induce greater weight loss.

P3559 Plasma homocysteine levels in a cohort of apparently healthy subjects in Northern Italy: relation to age, sex and nutritional status

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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. Genetic disorders and vitamin deficiencies can lead to a moderate increase in tHCy levels. The definition of normal fasting tHCy is still a matter of debate. The aims of our study were the following: 1) to measure fasting tHCy (tHCy) and determine the correlation with age, body mass index (BMI), sex and levels of folate, vitamin B12 (vit.B12) pyridoxal-5'-phosphate (PLP) in a cohort of apparently healthy subjects in Northern Italy (Bologna); 2) to define reference values for tHCy for the population in the same geographic area.

Methods: Apparently healthy subjects (n = 147; 82 men 65 women, age range: 14–94 y) were selected from the general population in the area of Bologna, Italy. High performance liquid chromatography assays were used to measure plasma levels of the following: 1)tHCy, according to Araki and Sako method (1987) with modifications; 2)PLP according to the method of Sassi et al (1997).Folate and vit.B12 serum levels were measured by automated chemiluminescence assay (Chiron Diagnostics, East Walpole, MA, USA).

Results: The geometric mean (GM) of plasma tHCy levels for the entire group was 9.00 μmol/L. Significant positive correlation was found between tHCy and age (Spearman's r; rs: 0.37; $p < 0.0001$) and tHCy and BMI (rs: 0.22; p:0.041). Significant negative correlation was found between tHCy and folate, and tHCy and Vit.B12 (rs: −0.47, $p < 0.0001$; rs: −0.40; $p < 0.0001$, respectively). No significant correlation was observed between tHCy and PLP. Mean tHCy levels were significantly lower in women than men (GM:8.00 and 9.89 μmol/L, respectively, $p < 0.0023$), but no difference was observed in folate, PLP and Vit.B12 levels in men and women. A significant negative correlation was found between age and folate, age and vit.B12 (rs: −0.16, $p = 0.05$ and rs: −0.37; $p < 0.0001$; respectively), age and PLP (rs: −0.56; $p < 0.0001$). In a stepwise multivariate regression analysis, age and folate levels explained 13% and 7.3% of the tHCy variance, while no significant effect was due to BMI, vit.B12, PLP. We calculated reference values on the basis of sex and age. The 90th percentiles of tHCy for men and women <45 y were 16.38 and 10.33 μmol/L, respectively. The 90th percentiles for men and women > 45 y were: 20.28 and 14.62 μmol/L, respectively.

Conclusions: 1) tHCy levels are influenced by age, BMI, sex and vitamin status 2) reference values for tHCy levels should be expressed according to age and sex.

P3560 Alcohol drinking and cardiovascular disease mortality in Japanese men

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Moderate drinking is associated with lower CVD death risk in Western populations. The association of alcohol drinking with risk of all cause and CVD death in Japanese men were investigated by analyzing a representative dataset of a 14-year prospective study (NIPPON DATA).

In 1980 a national cardiovascular survey was done in randomly selected subjects and it included information on drinking habit of participants. In 1994, a follow-up survey to ascertain vital status was conducted with a follow-up rate of 91.3%. In this study data of 4044 men aged 30–74 years were analyzed. Age and smoking adjusted relative risk (RR) of death from all causes and CVD death for different drinking categories were calculated by Cox proportional hazard model. Subjects with history CVD were excluded while calculating RR from CVD death.

The age adjusted rates per 100,000 person-year and age and smoking adjusted RR with 95% CI of all causes and CVD death are shown in the table. Occasional drinker had lower death rate and RR of all cause and CVD deaths in comparison to those of non-drinker.

	Non	Ex-drinker	Occas. drinker	Daily drinker
All Death				
No. exposed	784	216	1097	1947
No. death	139	67	103	240
Mortality	1174.9	1365.5	830.8	942.3
RR (95% CI)	1	1.18 (0.88 to 1.58)	0.71 (0.55 to 0.91)	0.84 (0.68 to 1.04)
CVD				
No. exposed	736	177	1033	1868
No. death	46	18	21	70
Mortality	495.5	464.2	145.3	327.8
RR (95% CI)	1	1.16 (0.67 to 2.00)	0.45 (0.27 to 0.76)	0.72 (0.49 to 1.05)

In this cohort of Japanese men occasional alcohol drinking was associated with lower 14-year mortality risk.

P3561 Moderate alcohol consumption is associated with reduced risk for coronary heart disease among women with type 2 diabetes mellitus

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Moderate alcohol consumption has been associated with reduced risk for coronary heart disease (CHD) among general populations. To assess whether moderate alcohol intake is also associated with reduction in CHD among women with Type 2 diabetes mellitus, a population with high baseline risk for CHD, we studied diabetic participants in the Nurses' Health Study, a large prospective cohort study. During 20,370 person years of follow-up among 5103 women reporting a diagnosis of diabetes mellitus at age 30 years or older without a history of prior CHD, we documented 295 CHD events (194 cases of non-fatal myocardial infarction and 101 cases of fatal CHD). As compared with women reporting no alcohol consumption, the age-adjusted relative risk for non-fatal or fatal CHD among women reporting average daily alcohol intake 0.1–5 grams (less than half a typical alcoholic drink) was 0.74 (95% confidence interval [CI], 0.56–0.98), and, among those reporting 5 grams or more daily, was 0.48 (95% CI, 0.32–0.72) (p,trend < 0.0001). After adjusting for body mass index, smoking, family history of MI, and other potential confounders, corresponding relative risks for CHD were 0.72 (95% CI, 0.54–0.96) and 0.45 (95% CI, 0.29–0.68), respectively (p, trend 0.0003). While potential risks of alcohol consumption must be addressed in the setting of diabetes, these data suggest that moderate alcohol consumption is associated with reduced CHD risk in this population and should not routinely be discouraged.

P3562 Relation between the levels of folate in whole blood, homocysteine in serum, and risk for first acute myocardial infarction

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High level of total homocysteine (tHcy) in plasma is a risk factor for coronary artery disease (CAD). The mechanism underlying the association between tHcy levels and CAD is not known although associations between tHcy, smoking, and other known risk factors including lipoproteins have been observed. While it is known that the intracellular metabolism of the vitamin, folate, is a major determinant for the level of tHcy in plasma, most studies of tHcy levels in CAD include measurements of folate in serum only.

We studied the levels of folate in whole blood and the serum concentration of tHcy, total cholesterol, high density lipoprotein cholesterol (HDLC), and apolipoprotein AI (Apo AI), in 107 patients who were hospitalized with their first acute myocardial infarction (MI) and in 103 controls. The mean level of whole blood folate was lower and that of serum tHcy was higher in cases than in controls. An inverse correlation was observed between the levels of whole blood folate and tHcy. Before adjustment for cigarette smoking logistic regression analysis revealed a significant association between the concentration of whole blood folate or tHcy and risk of first MI. The protective effect of folate remained after adjustment for tHcy concentration, but the effect of tHcy level on risk was not significant after adjustment for folate. Correlations were seen between the levels of whole blood folate and HDLC or Apo AI as well as between tHcy and HDLC or Apo AI. The number of cigarette smokers was significantly higher among MI cases. The level of tHcy was higher and that of whole blood folate was lower in smokers. After adjustment for smoking the risk for MI associated with whole blood folate or tHcy levels was non-significant. The results indicate that cigarette smoking may affect folate status and tHcy level adversely. Low folate or hyperhomocysteinemia may contribute to the risk of MI in smokers. There is evidence for interactive effects of folate, tHcy, and Apo AI in a process associated with the development of CAD.

P3563 Low serum folate levels are associated with an excess risk of acute coronary events: the Kuopio Ischaemic Heart Disease risk factor study (KIHD)

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A number of studies have noted higher levels of plasma total homocysteine concentration (tHcy) in cardiovascular disease patients, suggesting that elevated tHcy is a risk factor for atherosclerosis. Plasma tHcy levels may be elevated due to deficiences of enzyme activity in homocysteine metabolism or deficiencies of folic acid, vitamin B6 or B12, of which folic acid is considered the most important.

The purpose of this study was to test the hypothesis that low serum folate levels are associated with an increased risk of acute coronary events in men free of coronary heart disease. We investigated this association in a population based sample of 734 men aged 46–64 years as part of the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD).

The mean serum folate concentration was 10.4 nmol/l.We compared men in the highest third of serum folate concentration to those with lower serum folates. In a Cox model including age, examination years, body-mass index, and serum triglycerides, men with higher serum folate had 82.5% reduced (95% CI 25.1 to 95.9, p = 0.019) risk of acute coronary events compared with others. After adjusting for age, examination years and three nutritional factors, men with the higher serum folates had 81.0% reduced (95% CI 17.4 to 95.6, p = 0.027) risk of acute coronary events compared with other men. During the average follow-up of 4 1/3 years, two (0.8%) men with higher serum folates and 23 (4.7%) men with lower folates developed an acute coronary event.

This prospective cohort study in middle-aged men from Eastern Finland indicates that moderate-to-high levels of serum folate are associated with greatly reduced risk of acute coronary events. Although folic acid could lower the risk of coronary disease through reducing plasma homocysteine levels, homocysteine may also be only a marker for folate and vitamin B6 status rather than a causal risk factor. Intervention studies are required to test the effect of folic acid supplementation in the prevention of coronary disease.

P3564 Differentiation of the incidence of risk factors in the variable types of genetic dyslipidaemias

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Dyslipidemia is a main risk factor for coronary artery disease (CAD). The coexistence of other risk factors aggravate the prognosis. The purpose of the present study was to investigate the incidence of other risk factors in the different types of genetic dyslipidemias.

Method: We studied 831 patients (pts), without treatment. 351 pts with heterozygous familial hypercholesterolemia (hFH), 343 with familial combined hyperlipidemia (FCH) and 137 with familial hypertriglyceridemia (HTGL), mean age: 44.57 ± 10.74, 45.98 ± 8.93, 44.93 ± 9.72 years respectively, P = NS. Lipid plasma levels, thrombogenic factors [fibrinogen (FB) and Lp(a)], and somatometric factors [body mass index (BMI) and waist to hip ratio (W/H)] were measured in all pts. We also evaluated the incidence of arterial hypertension, diabetes mellitus, smoking and CAD.

Results: Somatometric and thrombogenic factors are shown in the table.

	hFH (1) (n = 351)	FCH (2) (n = 343)	HTGL (2) (n = 137)	P
Lp (a) (mg/dl)	41.2 ± 39.74	32.38 ± 36.56	24.89 ± 26.67	1 vs. 2: <0.0001 1 vs. 3: <0.0001 2 vs. 3: = 0.007
FB (mg/dl)	290.13 ± 56.07	293.43 ± 56.53	299.97 ± 65.14	NS
BMI (kg/m^2)	25.47 ± 3.76	27.48 ± 3.29	27.91 ± 3.45	1 vs. 2: <0.0001 1 vs. 3: <0.0001 2 vs. 3: NS
W/H	0.82 ± 0.09	0.88 ± 0.08	0.93 ± 0.07	1 vs. 2: <0.0001 1 vs. 3: <0.0001 2 vs. 3: <0.0001

The incidence of hypertension in the variable genetic types was 13.1% (46/351) in hFH, 37% (127/343) in FCH and 16.8% (23/137) in HTGL, (between groups, P < 0.0001). Respectively, diabetes mellitus was 2% (7/351) in hFH, 11.7% (40/343) in FCH and 24.8% (34/137) in HTGL, (between groups, P < 0.0001). The incidence of smoking was 31.6% (111/351) in hFH, 40.2% (138/343) in FCH and 51.1% (70/137) in HTGL (between groups, P < 0.0001). The incidence of CAD was 21.4% (75/351) in hFH, 16.3% (56/343) in FCH and 10.9% (15/137) in HTGL, (between groups, P < 0.0001),

Conclusion: hFH pts had higher incidence of CAD, but more favorable somatometric factors and lower incidence of arterial hypertension and diabetes mellitus. FCH pts had the highest incidence of arterial hypertension and the HTGL pts had the most unfavorable somatometric factors.

P3565 Medical history of hypercholesterolaemia adversely affects the outcome of pre-hospital cardiopulmonary resuscitation: the "SHAHAL" experience in Israel

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Purpose: to evaluate the impact selected risk factors for cardiac death may have on the success rate in a large cohort of subscribers to 'SHAHAL' who were resuscitated from out-of-hospital cardiac arrest.

Methods: In this medical facility currently serving 50,000 subscribers, data were prospectively gathered from its establishment in 1987 to December, 1998. The information retrieved from the patient's medical record included a medical history of hypertension, diabetes, hypercholesterolemia (>220 mg/dL), smoking, angina, previous myocardial infarction, and congestive heart failure. The reporting of pertinent time intervals was taken from a form designed for precise listing of the sequences of events and actions taken from the moment of collapse.

Results: A total of 998 patients aged 74 ± 12 years (mean ± 1 SD) were included. Death was announced at the scene for 659 (66%) victims, while 339 (34%) patients were taken to hospital. Of these, 140 (14% of the total cohort) survived and were discharged from hospital.

A comparison of various selected parameters between survivors and non-survivors of resuscitation revealed that survivors were younger, had a higher rate of pulseless ventricular tachycardia/ventricular fibrillation, more were among the arrests witnessed by the 'SHAHAL' team, and that more had a shorter time lag to initiation of cardiopulmonary resuscitation than non-survivors. None of the studied risk factors predicted outcome of cardiopulmonary resuscitation with the exception of hypercholesterolemia, which carried a significantly worse prognosis for cardiopulmonary resuscitation ($p = 0.009$).

In conclusion, history of hypercholesterolemia appears to be an important risk factor which adversely affects the outcome of cardiopulmonary resuscitation.

P3566 Long-term stability of lipoprotein(a) levels in healthy young subjects with parental myocardial infarction: a five-year follow-up

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Background: The "tracking" phenomenon of cardiovascular risk factors (i.e. blood pressure or cholesterol levels) is well understood. Less is known about the stability over time of lipoprotein(a) [Lp(a)], another independent risk factor for cardiovascular disease. Aim of this study was to evaluate, in healthy young subjects with parental myocardial infarction (PMI), the correlation between Lp(a) levels at baseline and five years later.

Method: In twenty-three healthy young subjects with PMI (6 M, 17 F) serum Lp(a) levels were measured at baseline (mean age 15 ± 6 years) as well as after a 56 ± 9 months follow-up (range 46 to 77 months). Lp(a) concentration was determined by a nephelometric assay. Because Lp(a) levels show no normal distribution, values were Log transformed.

Results: There was an high correlation between the Log Lp(a) concentrations at baseline and five years later ($r = 0.918$, $p < 0.001$). All the 12 subjects with Lp(a) levels < 25 mg/dl at baseline had Lp(a) levels < 25 mg/dl at five-year follow-up; moreover, all the 11 subjects with Lp(a) levels > 25 mg/dl at baseline had Lp(a) levels > 25 mg/dl five years later ($p < 0.00001$; diagnostic accuracy: 100%).

Conclusions: In healthy young subjects with PMI, baseline Lp(a) levels were strong predictive of Lp(a) values determined five years later. Therefore, Lp(a) levels are stable over time.

P3567 Gender-related differences in serum levels of lipoprotein(a) in healthy young subjects with a history of parental myocardial infarction

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Background: The Bogalusa Heart Study demonstrated that lipoprotein(a) [Lp(a)] levels are significantly related to a family history of parental myocardial infarction (HPMI) in white children, without gender-associated differences. Aim of the present study was to determine if Lp(a) serum levels would be different among men and women with HPMI.

Methods: Serum concentrations of Lp(a) and other lipids were measured in 173 healthy young subjects with HPMI (Cases; 81 M, 92 F; mean age 18 ± 6 years; 22% current smokers) and in 173 healthy young subjects without HPMI (Controls) matched for age, gender and smoking status. Because Lp(a) and triglycerides did not show a normal distribution, log transformation was used.

Results: Among men, Cases had higher apo B levels than Controls (94 ± 30 vs. 83 ± 21 mg/dl, $p = 0.006$) while total cholesterol, HDL cholesterol, LDL cholesterol, Log Lp(a), apo A1 and Log triglycerides did not differ between the two groups. Among women, Cases showed not only higher apo B levels (89 ± 25 vs. 81 ± 22 mg/dl, $p = 0.003$) but also higher Log Lp(a) values (1.25 ± 0.44 vs. 1.08 ± 0.48, $p = 0.018$) than Controls.

Conclusions: HPMI is associated with increased Lp(a) levels among women only. These results suggest that in healthy young subjects with HPMI measurement of Lp(a) should be performed only in women.

P3568 Serum lipoprotein(a) in healthy young subjects with family history of myocardial infarction is predicted by parental lipoprotein(a) level

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Background: High serum concentrations of lipoprotein(a) [Lp(a)] are an independent predictor of premature myocardial infarction (MI). In addition, is now recognized that children of patients with MI (C) deserve aggressive screening. In order to provide the best treatment for primary prevention of MI, aggressive measures should be taken to identify C at major risk.

Methods: We evaluated the serum concentrations of Lp(a) in 36 patients (33 M, 3 F; mean age 48 ± 6 years), at least 6 weeks after an acute MI, and the lipid profile in their 85 healthy C.

Results: Serum Lp(a) was raised (>30 mg/dl) in 13 patients, who had 33 C (C+) admitted to the study (15 M, 18 F; age 19 ± 5 years) and resulted normal in 23 patients, who had 52 C (C−) enrolled in the study (24 M, 28 F; mean age 19 ± 5 years. Total cholesterol, HDL cholesterol, LDL cholesterol, Log triglycerides, apo A1 and Apo B did not differ between C+ and C−. In contrast, C+ showed significantly higher Log Lp(a) levels (1.45 ± 0.46 vs 0.91 ± 0.36, $p < 0.001$) and had more frequently raised Lp(a) levels than C− (17/52 vs 3/33, $p < 0.001$; RR 17.3, 95% CI 4.5–67).

Conclusions: These findings may have clinical implications: high Lp(a) levels in patients with MI seem to be a good predictor for high Lp(a) levels in their C, who may deserve more aggressive preventive measures.

GENERAL ASPECTS OF MYOCARDIAL PERFUSION SCINTIGRAPHY

P3569 The ROBUST study: a randomised comparison of three tracers for myocardial perfusion scintigraphy

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Background and Methods: There are no large studies available to guide the selection of thallium (Tl), MIBI, or tetrofosmin (Tf) for myocardial perfusion imaging. We have randomised 2540 patients to receive one of the three during routine imaging. A one day stress/rest protocol was used for MIBI and Tf. Tomograms were scored visually in 17 segments and defects were quantified from a polar plot. Quality and artefact scores were assigned (0 to 3), and ratios of heart (H), liver (L), sub-diaphragmatic (S) and lung activity were measured.

Results: The groups were similar in terms of risk factors for coronary artery disease and proportion of abnormal studies. Mean quality scores were Tl 2.13, MIBI 2.29, Tf 2.30 ($P < 0.001$). For attenuation artefact MIBI = Tf<Tl ($P < 0.05$) and for low count artefact Tf<MIBI<Tl ($P < 0.001$). For H/S, Tl>MIBI = Tf, for H/L Tl>Tf>MIBI, and for H/Lung Tf>Tl = MIBI (max $P < 0.02$). Stress defects in the abnormal scans were more severe for Tl than for the other tracers (mean summed score out of 68: Tl 51.8, MIBI 54.7, Tf 55.3, $P < 0.01$), but mean rest scores were similar (Tl 60.2, MIBI 59.1, Tf 58.5, P = NS). In the subset of patients without prior infarction who underwent coronary angiography within 3 months of perfusion imaging, accuracy of each tracer for detecting angiographic disease was the same (sensitivity 90% Tl, 100% MIBI, 95% Tf, specificity 86% for all three).

Conclusion: We conclude that there are technical differences between the tracers. They all perform well in clinical terms, but overall image quality score is superior using technetium.

P3570 A prospective multi-centre comparison of Tc-99m-sestamibi and Tc-99m-tetrofosmin for the assessment of mild to moderate coronary artery disease by dipyridamole SPECT imaging

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The extraction fraction of Tc-99m tetrofosmin (TETRO) is lower than that of Tc-99m sestamibi (MIBI) and its myocardial uptake may plateau at lower blood flow levels. Whether these biokinetic differences affect the relative ability of these two tracers to detect mild to moderate coronary artery disease (CAD) and reversible ischaemia is unknown. Accordingly, dipyridamole SPECT imaging with both agents was performed in 81 patients with recent (<2 months) coronary arteriographie eveidence of 50–90% stenosis in one or two vessels and 7 patients with <5% likelihood of CAD. Patients with left mainstem or 3 vessel disease and previous myocardial infarction were excluded. The MIBI and TETRO studies were carried out in random order, within a week of each other and reported by a blinded panel using a 17 segment LV model, with the aid of quantitative anaylses.

Results:

	MIBI	TETRO	P value
Sensitivity	63% (51/81)	58% (47/81)	0.09
Specificity	57% (4/7)	57%	ns
Segments with reversible segments	363	285	<0.0001
Defect extent (% LV involved)	15.8 ± 12.3%	12 ± 11.9%	<0.03
Defect severity (Ischaemic/normal wall ratio)	0.60 ± 0.15	0.73 ± 0.14	0.01

Therefore MIBI may be superior to TETRO for the assessment of mild to moderate CAD by dipyridamole SPECT imaging. These findings may have important diagnostic and prognostic implications.

P3571 Does the presence of diabetes mellitus change the predictability of significant coronary artery stenoses by 99m-Tc-MIBI myocardial perfusion imaging?

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Patients with diabetes mellitus are prone to diffuse and multivessel coronary disease. Therefore the sensitivity and specifity for detection of coronary artery disease (CAD) by 99m-Tc-MIBI myocardial perfusion imaging (MIBI-SPECT) could be altered in diabetics.

Methods: 1000 consecutive patients (pat.) with suspected CAD underwent MIBI-SPECT and coronary angiography for detection of significant coronary artery stenoses (>70% lumen diameter stenosis). Patients were analyzed as a cohort and regarding the prevalence of diabetes.

Results:

	All	Diabetics	Non-Diabetics	
Number of patients (n)	1000	116	884	
Coronary stenoses > 70% (%)	53	*68*	*51*	*p < 0.001*
Women (%)	27	31	27	
Criterion of ischemia: *any perfusion defects*				
Sensitivity (%)	94.9	94.9	94.9	p > 0.05
Specificity (%)	57.2	56.8	57.2	p > 0.05
Positive pred. value (%)	71.7	*82.4*	*70.1*	*p < 0.02*
Negative pred. value (%)	90.8	84.0	91.4	p > 0.05
Criterion of ischemia: *stress/rest mismatch*				
Sensitivity (%)	74.3	70.9	74.9	p > 0.05
Specificity (%)	83.1	86.5	82.8	p > 0.05
Positive pred. value (%)	83.0	91.8	82.1	p > 0.05
Negative pred. value (%)	74.0	*58.2*	*75.7*	*p < 0.001*

Conclusion: The differences in positive and negative predictive values are due to the higher prevalence of significant CAD in diabetics. The potential of MIBI-SPECT to predict the presence of significant coronary artery stenoses (sensitivity and specificity) is not deminished in patients with diabetes mellitus.

P3572 Cardiac normality in myocardial perfusion imaging: patients with normal coronary angiography are better than healthy volunteers with a low likelihood of coronary artery disease

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The optimal reference standard in noninvasive stress testing has been disputed for years. Mainly two criteria have been used: patients with a normal coronary angiography (CAG) and subjects with a low likelihood for coronary artery disease (CAD). Especially the criterion based on a normal CAG has been criticized, since the subjects referred to CAG typically usually have some symptoms in spite of a normal CAG, indicating that they may not be representative for the normal population and may represent a "too sick" part of this population. Thereby the criterion for cardiac normality should be too broad. The purpose of the present study was to compare two different criteria of cardiac normality: normal CAG versus low CAD likelihood.

Methods: An artificial neural network was trained on myocardial SPECT studies from 87 patients with angiographically documented CAD and on studies from two different normal groups: 48 patients with no signs of CAD based on CAG or 128 volunteers without any symptoms and a likelihood for CAD less than 5%. The performance of the network trained on either a patient group with a normal CAG or volunteers with a CAD likelihood of less than 5% was then tested on scintigrams from 68 patients referred for CAG without prior myocardial infarction or bypass surgery. CAG was used as gold standard in this group and a diameter reduction of >50% was regarded as significant.

Results: The ROC-area for the network was 94% using patients with a normal CAG versus 74% using subjects with a low likelihood of CAD. $P < 0.01$.

Conclusion: Our results indicate that when the criterion for significant CAD is based on an abnormal CAG a criterion for cardiac normality based on a normal CAG should be preferred, even though theoretical considerations may favorite subjects a low likelihood of CAD. The explanation may be related to the fact that the images of myocardial perfusion and of coronary arteries contain different information.

P3573 Usefulness of exercise tomographic Tc-99m-tetrofosmin imaging for detection of restenosis after coronary stent implantation

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Background: After coronary stent implantation restenosis rate during the first 6 months still remains between at 20% and 30%. Exercise myocardial perfusion scintigraphy may be a valid alternative to invasive strategies for a close follow-up of such patients. The purpose of the study was to assess prospectively the accuracy of exercise ^{99m}Tc-tetrofosmin SPECT for detecting restenosis in patients after coronary stent implantation.

Methods: In 52 patients (mean age 58 ± 12 years) an exercise ^{99m}Tc-tetrofosmin SPECT scintigraphy was performed prospectively to evaluate 57 vascular territories with stents. The average interval between the stent implantation and the scintigraphic study was 111.9 ± 57.3 days while that from the scintigraphic study to coronary angiography 47.9 ± 14.9 days. A reversible exercise-induced perfusion defect within the segments matched to individual stented vessel was used as the criterion of stent restenosis.

Results: With SPECT scintigraphy, 14/18 vascular territories with 50% angiographic restenosis showed exercise-induced reversible perfusion abnormalities (sensitivity = 78%), while 35/39 territories without restenosis did not (specificity = 90%). Predictive accuracy was 86%. In 24 patients who underwent stenting for complete revascularization sensitivity and specificity for stent restenosis were 9/10 (90%) and 16/18 (89%), while in the remaining 28 patients with partial revascularization 5/8 (63%) and 19/21 (90%), respectively.

Conclusions: Exercise ^{99m}Tc-tetrofosmin SPECT imaging can accurately predict restenosis in patients after coronary stent implantation. This method is most sensitive for evaluating patients who undergo stenting for complete revascularization.

NON-INVASIVE IMAGING OF CORONARY ARTERIES AND CORONARY FLOW

P3574 Correlation of three-dimensional magnetic resonance coronary angiography with selective coronary angiography: impact of the novel motion adapted gating technique

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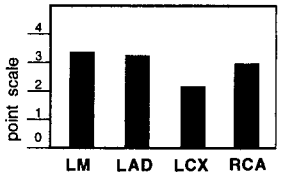
Reliable noninvasive assessment of coronary artery stenoses and occlusions with MRI in patients with known or suspected coronary artery disease would be an advantage. So far, inconsistent breathholding impairs image quality. The impact of the novel respiratory motion compensation (Motion Adapted Gating, MAG) for visualization of coronary arteries (CA) was verified in this study by correlation with selective coronary angiography (SCA) findings.

Methods: 20 subjects (10 patients/10 healthy volunteers), age 52 ± 20 yrs. were investigated. All patients had MRI and CA within 2 weeks. A Philips Gyroscan ACS-NT (Philips Medical Systems, Best, The Netherlands) operating at 1.5 T, equipped with the PowerTrak 6000 gradient system providing 23 mT/m within 0.2 ms, was used. A newly developed MRI protocol consists of a 3D TFE ECG triggered and respiratory motion gated sequence. Repiratory motion was obtained from 3 pencil navigator beams interleaved with one R-R interval. The real-time gating algorithm utilizes the concept of k-space weighing in combination with an automatic analysis of the respiratory motion.

The three main CA and left main (LM) were evaluated. The results of the patient group were compared to SCA. Qualitative analysis of volunteer and patient data was performed by two blinded investigators.

Results: All 80 CA were adequately visualized. Visibility was graded on a four point scale (1 = insufficient, 2 = sufficient, 3 = good, 4 = excellent) (see figure).



Evaluation of coronary artery stenoses (luminal narrowing > 50%) is best in the LM and the proximal part of LAD, LCX and RCA (5/5 stenoses were correctly detected) still of good quality in the middle part (4/5 stenoses were correctly detected) but of less diagnostic accuracy in the distal portion.

Conclusion: MRI with MAG demonstrates to be a promising new technique for noninvasive imaging of CA with high patient comfort (breathholding is not nescessary). Adequate image quality for LM and proximal and middle segments of the main CA was achieved. Stenoses were in 90% correctly assesed. The clinical impact has to be verified.

P3575 Magnetic resonance coronary angiography with targeted volume scans (VCATS): preliminary clinical results

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Background: Magnetic resonance coronary angiography (MRCA) with breathhold two-dimensional and respiratory gated three-dimensional (3D) techniques has yielded unsatisfactory results. We developed a new strategy which we refer to as Volume Coronary Angiography using Targeted Scans (VCATS), which uses a small targeted volume to cover one coronary segment in a single breathhold. We report the preliminary clinical results for the detection of stenoses of >50% luminal diameter reduction.

Methods: 34 patients referred for elective coronary angiography (CAG) were examined with several targeted volume scans along the major coronary branches, using a 3D segmented

gradient echo sequence (resolution 1.9 × 1.25 × 1.5 mm)optimal orientations along the coronary arteries were obtained from a single breath-hold 3D localizer scan covering the entire heart. CAG served as the goldstandard for the determination of the diagnostic value of MRCA. Proximal, mid and distal segments of the right coronary artery (RCA), left main (LM) and proximal and mid segments of the left anterior descending (LAD) and left circumflex (LCX) coronary artery were evaluated by a radiologist and a cardiologist blinded for the results of the CAG.

Results: The imaging protocol was completed within 30 minutes. Adequate visualization was obtained in 187 (69%) of the major coronary segments. Overall diagnostic accuracy was 92% with a sensitivity and specificity of 68% and 92%, respectively. Data for the segments in the 3 coronary branches are listed in the table.

	Visualized	Sensitivity	Specificity	PV+	PV−	Acc
LM + LAD	91 (89%)	77%	97%	83%	92%	91%
RCA	68 (67%)	64%	94%	75%	91%	88%
LCX	31 (46%)	50%	100%	100%	93%	94%
Overall	187 (69%)	68%	97%	81%	94%	92%

Conclusion: VCATS adequately visualizes the major coronary arteries in the majority of the patients. The observed accuracy for the detection of significant coronary lesions is encouraging, but should increase before reliable use in a clinical setting is possible.

P3576 Evaluation of coronary bypass grafts by navigator echo magnetic resonance angiography

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The development of nonivasive procedures to assess coronary artery bypass grafts (CABGs) is an emergent medical need. The purpose of this study was to validate respiratory gated (navigator echo) magnetic resonance angiography (MRA) in detecting occlusion/patency of CABGs.

Methods: 20 patients with previous history of CABG surgery and recurrent episodes of chest pain were enrolled. Two patients could not be studied (claustrophobia, erratic breathing). Thus, 18 patients with 51 CABGS were examined using a non-velocity-compensated electrocardiographically-triggered and respiratory-gated (navigator echo) three-dimensional gradient echo fat-suppressed sequence: 21 arterial grafts (6 sequential) and 30 saphenous vein grafts (5 sequential). All patients had undergone contrast conventional angiography (CCA) 3–15 days before MRA. The MR data set was analyzed by two independent readers blinded to the CCA results (occlusion of 12 of 51 grafts).

Results: at MRA, 2 CABGs of the posterior descending artery, patent at CCA, could not be visualized because of imaging slab malpositioning. Interobserver concordance was 96% (47/49). After consensus MR reading, MRA and CCA provided identical answers in 47 out of 49 (96%) (of the examined grafts. Eleven out of 12 occluded grafts and 36 out of 37 patent grafts were correctly identified with MR. As far as occlusion is concerned, the sensitivity of MR angiography was 91%, the specificity 97%.

In conclusion, this experience establishes that a 30 minutes outpatient MRA examination without contrast agent administration is highly reliable in determining occlusion/patency of arterial and venous, single and sequential CABGs.

P3577 Magnetic resonance coronary angiography in patients with ST-T changes during exercise

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Purpose: A False positive exercise test represents a serious diagnostic problem and the mechanism by which this results has not been clarified. It is difficult to discriminate between effort angina pectoris (AP) and microvascular angina pectoris (MVA). We evaluated coronary circulation in patients with exercise-induced ST depression using magnetic resonance coronary angiography (MRCA).

Methods: Twenty healthy subjects (N group) and 25 patients showing ST depression greater than 1 mm during a treadmill exercise test were studied. Of these, 18 patients showed significant stenosis (AP group) and 7 did not (MVA group), as evidenced by coronary angiography. MRCA was performed with a Signa Horizon (1.5 Tesla, G.E.). Cross sections of left and right coronary arteries were obtained, and a flow velocity measurement was obtained using segmented k-space fast gradient-echo phase contrast. The washout rate (%WR) was also calculated by 123I-beta-methyliodophenyl pentadecanoic acid myocardial scintigraphy.

Results: Coronary blood flow pattern displayed two peaks, with the diastolic peak velocity being greater than that of systolic in normal subjects. Diastolic peak velocity was not significantly different for the N and the MVA group (24.6 ± 3.4, 21.3 ± 4.8 cm/sec), but was significantly lower in the AP group (17.4 ± 5.5 cm/sec; $p < 0.01$). However, diastolic/systolic velocity ratio was significantly lower ($p < 0.05$) in the MVA group (1.50 ± 1.10), as compared with the N group (1.68 ± 0.19). The%WR were significantly higher in the MVA group, compared to N group (16.4 ± 7.3, 10.0 ± 6.4%, $p < 0.05$).

Conclusion: The patients, who showed ST depression during an exercise test but did not show any significant stenosis in coronary angiography, showed abnormal blood flow velocity of the coronary arteries, suggesting that dysfunction in myocardial microvascular perfusion might be the cause of abnormal ST changes in these patients.

P3578 Non-invasive coronary angiography by contrast-enhanced electron-beam computed tomography in patients after acute myocardial infarction

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Electron-beam computed tomography (EBCT) is a cross-sectional imaging method which, after intravenous injection of contrast agent, permits non-invasive visualization of the coronary artery lumen. So far, the accuracy of EBCT coronary angiography has been evaluated only in patient groups with a relatively low prevalence of significant stenoses. We therefore investigated the value of EBCT to detect high-grade coronary artery stenoses and occlusions in patients after acute myocardial infarction (AMI).

Methods: 35 patients (28 male, 7 female, mean age: 53 years) were studied 4–70 days after AMI. 40 to 50 axial cross-sections of the coronary arteries were acquired triggered to the ECG in breathhold (3 mm slice thickness, 1 mm overlap, 140–160 ml of contrast agent i.v.). Both the original images as well as thresholded 3-D surface reconstructions of the heart and coronary arteries were evaluated as to the presence of high-grade coronary artery stenoses and occlusions in the proximal and mid sections of the coronary arteries. Results were compared to invasive coronary angiography in a blinded fashion.

Results: A total of 140 coronary arteries had to be assessed (left main, LAD, LCX and RCA in 35 patients). 29 coronary arteries (21%) could not be evaluated due to inadequate image quality caused by motion, severe calcifications, or low contrast-to-noise ratio. In the remaining 111 arteries, sensitivity of EBCT to detect high-grade stenoses and occlusion was 94% (31/33), specificity was 91% (71/78), the negative and positive predictive values were 97% and 82%, respectively.

In conclusion, electron beam CT confirmed its high accuracy for the detection of coronary artery stenoses and occlusions in a patient group with high prevalence of significant coronary artery lesions.

P3579 Assessment of blood flow and flow reserve in coronary grafts using breath-hold phase-contrast magnetic resonance angiography in patients with bypass stenosis

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Direct visualization of coronary bypass graft patency can be obtained non-invasively by MRI. But detection of graft stenosis is not reliably. The purpose of this study was to evaluate the feasibility of MR flow velocity and flow reserve measurements in coronary grafts in order to detect graft stenosis.

Methods. In 17 patients (mean age 65 ± 12 years) 47 coronary grafts (34 vein grafts and 13 internal mammary grafts) underwent conventional angiography and MRI at rest and during intravenous adenosine induced hyperemia. MR imaging was performed on a 1.5 T clinical imager with Torso phased array coil. The phase contrast pulse sequence (FASTCARD PC) was employed in breath-hold with 10 to 25 temporal phases with 4 view per segment, flip angle 20 deg., acquisition matrix 256 × 128, and one excitation. Field of view, TE, TR were 40 × 30 cm, 3.5 ms, 12 ms.

Results. Phase-contrast MR angiography detects coronary graft patency with high sensitivity (93%) and specificity (93%). MR angiography identified only 4 out of 8 graft stenoses. In patients without graft stenosis, mean hyperemic average peak velocity (APV) (11.0 ± 5.3 cm/s) differed from resting APV (6.1 ± 3.1 cm/s). In patients with graft stenosis, the mean APV was 5.6 ± 3.9 cm/s in the basal state and 5.6 ± 3.3 cm/s after pharmacological stress. The coronary flow reserve was higher in patients without graft stenosis than in patients with graft stenosis (2.1 versus 1.0).

Conclusion. Phase-contrast MR imaging is a noninvasive technique which can provide assessment of coronary graft blood flow velocity and vasodilator flow reserve and seems to be able to differenciate abnormal from normal coronary bypass graft.

P3580 Non-invasive haemodynamic assessment of coronary grafts using magnetic resonance imaging

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Magnetic resonance (MR) imaging provides techniques for the noninvasive hemodynamic assessment of coronary grafts. We studied changes of flow and flow velocity using adenosin in normal and diseased coronary grafts.

Methods: In 27 patients 32 coronary grafts (10 internal mammary grafts to LAD, 7 vein grafts to LAD, 15 vein grafts to RCA and CX) were investigated. Using MR phase change technique (Siemens 1.5 T; TR 110 ms, BH) measurements of mean velocity, peak velocity and mean flow were performed. The measurements were repeated during adenosin infusion and ratios for each parameter were calculated in order to obtain flow and velocity reserves (CFR). Based on cardiac catheterization performed within 24 hours results were analyzed for normal grafts (n = 27) and compared with the values for grafts with high grade stenosis (>75%; n = 5).

Results: In normal coronary grafts adenosin infusion significantly increased peak and mean velocity and the mean flow:

n = 27	basal	adenosin	p-value
Mean flow	1.15 ± 0.9	2.92 ± 1.4	0.0001
Mean velocity	5.49 ± 4.4	12.1 ± 9.6	0.0001
Peak velocity	7.12 ± 3.2	11.06 ± 4.3	0.0012

CFR based on mean flow measurement was significantly different between normal and diseased grafts (3.59 ± 2.60 vs. 0.75 ± 0.50; $p < 0.0001$) as it was analyzing the mean velocity (3.09 ± 2.12 vs. 0.75 ± 0.50; $p < 0.0001$). CFR based on peak velocity was not significantly different between both groups (1.46 ± 0.55 vs. 0.79 ± 0.35; n.s.).

Conclusion: Normal grafts are characterized by a significant increase of flow parameters during adenosin infusion which is demonstrated noninvasively by MR phase change technique. High grade graft stenosis can be detected by reduced MR mean flow and mean velocity reserve.

P3581 Magnetic resonance flow mapping versus intracoronary Doppler guide wire in the assessment of coronary peak velocity

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Purpose: Doppler Guide Wire (DGW) measurements during catheterization allow quantifying Averaged Peak Flow Velocity (APFV) in coronary arteries as an indicator for the physiologic significance of coronary artery stenosis. With magnetic resonance (MR) flow mapping it is possible to quantify this flow velocity in a noninvasive manner. We compared these two techniques to assess the APFV in patients known with ischemic heart disease.

Methods: The study included 10 patients all referred for elective diagnostic coronary angiography for evaluation of chest pain. During catheterization the APFV was measured with a Doppler Guide Wire distal from the stenosis and in a healthy reference artery. Within the same week all individuals underwent a MRI. From series of anatomic images the LAD and RCA were visualized. Perpendicular to the vessel MR phase contrast velocity mapping was performed within a breath-hold at the same location as the DGW measurement. A Region of Interest (ROI) was drawn around the vessel and nearby located myocardial tissue, to analyze the flow data and correct for myocardial motion.

Results: Flow measurements were acquired from 21 segments in the RCA and LAD, % stenosis varied from 0–99%. The mean $APFV_{MRI}$ was 21 cm/s (range 8–45 cm/s) and mean $APFV_{DGW}$ was 23 cm/s (range 7–73 cm/s). Bland-Altman analysis showed a mean difference between the two techniques of 2 ± 10 cm/s. There was no significant effect in this comparison depending on the location of the segments.

Conclusion: In patients with coronary artery stenosis noninvasive MR flow velocity quantification provides equivalent data to those acquired with DGW measurements. Assessment of the peak velocity gives an impression of the physiologic significance of coronary artery stenosis.

P3582 Approximation to diastolic coronary flow velocity from illegible recording by transthoracic pulsed Doppler echocardiography

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Background: Although recent ultrasound instrument with high-sensitive Doppler enables to visualize epicardial coronary artery, coronary flow velocity is not always recorded completely during a whole diastole by transthoracic pulsed Doppler echocardiography (TPDE). We hypothesized that the deceleration curve of diastolic coronary flow velocity is linear, and that approximate diastolic peak and mean velocity may be measured from the linear deceleration line.

Subjects and method; First, we analyzed thirty complete diastolic envelopes of proximal left anterior descending coronary artery (LAD) flow in 20 patients by TPDE and measured diastolic peak and mean velocity (DPV, DMV) in each envelope. The linear deceleration line (DcL) was derived from two velocities at mid- or late diastolic phase in the envelope. The approximate diastolic peak velocity (ADPV) was measured at the time of aortic valve closing in DcL and approximate diastolic mean velocity (ADMV) was calculated from (diastolic TVI)/(diastolic time). We estimated the relationship between DPV and ADPV and between DMV and ADMV. Secondary, we measured coronary flow reserve (CFR) by Doppler guide wire method (DGW) and by TPDE in 6 other patients.

Results; ADPV agreed well with DPV ($r = 0.99$, $p < 0.001$, mean difference = 2.2 ± 4.5 cm/s), and ADMV also agreed with DMV ($r = 0.99$, $p < 0.001$, mean difference = 1.1 ± 3.9 cm/s). There was a significant correlation between CFR by TPDE (ADMV) and CFR by DGW ($y = 0.90x + 0.25$, $r = 0.84$, $p < 0.001$).

Conclusion; The diastolic coronary flow velocities estimated from illegible envelope by transthoracic Doppler echocardiography could be substituted for true velocities to calculate CFR.

IMAGING OF MYOCARDIAL METABOLISM AND INNERVATION: PET, MRI AND ECHO

P3583 Increased myocardial glucose-uptake after percutaneous myocardial laser revascularisation in patients with end-stage coronary artery disease

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Background: Percutaneous myocardial laser revascularisation (PMR) in patients with refractory angina pectoris due to end-stage coronary artery disease not amenable to angioplasty or bypass surgery leads to improvement of clinical symptoms and increased exercise capacity. Pathophysiological mechanisms are not yet clear.

Methods: 11 patients (P) underwent positron emission tomography (PET) with 18-Flour-Desoxyglucose (FDG) and thallium-scintigraphy before and three months after PMR. FDG- and thallium-uptake in the PMR-target region (TR) were quantitated and compared with the non-treated non-ischemic septum (S).

Results: At baseline FDG-uptake in the TR (19.22 ± 12.2 mmol/100 g/min) was slightly lower than in the S (26.6 ± 13.4 mmol/100 g/min) ($p < 0.08$). 3 months after PMR relative FDG-uptake in the TR increased from 72.2 ± 24.7% to 79.9 ± 20.4% ($p < 0.05$). In P who showed improvement of symptoms (>1 CCS-class) and increased exercise capacity ($n = 7$), relative FDG-uptake in the TR increased from 70.9 ± 25.8% at baseline to 82.4 ± 19.9% after 3 months ($p < 0.05$). In patients without improvement of symptoms and exercise capacity ($n = 4$), relative FDG-uptake did not change (74.6 ± 23.0% to 75.5 ± 21.0% ($p = 0.45$). Thallium-scintigraphy failed to show an increase of relative tracer-uptake in the TR compared to the S in all P (stress: 69.9 ± 16.0% to 68.5 ± 21.0%, rest: 82.8 ± 13.9% to 80.6 ± 16.0%), both, in P who improved clinically after PMR, and in P who did not improve.

Conclusion: Increased FDG-uptake three months after PMR suggests improved perfusion of the myocardium despite unchanged thallium-scintigraphy. However, the amount of perfusion changes seems to be too small to account for the clinical benefit observed after PMR. Therefore, other mechanism may be involved in the pathophysiological process after PMR.

P3584 Left ventricular hypertrophy and insulin resistance

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Secondary cardiac hypertrophy is a major cause of cardiovascular morbidity and mortality, and is characterised by a reduced myocardial glucose uptake (MGU) in response to insulin (insulin resistance). This study investigated whether myocardial insulin resistance is also present in primary (genetic) cardiac hypertrophy i.e. in hypertrophic cardiomyopathy (HCM) and the cardiomyopathy of Friedreich's ataxia (FRDA).

Methods: Absolute MGU was measured using ^{18}F-fluorodeoxy-glucose (FDG) and positron emission tomography during euglycaemic hyperinsulinaemic clamp in patients with HCM ($n = 6$) and FRDA ($n = 5$). Asymmetric left ventricular hypertrophy was present in all cases [diastolic septal thickness 1.8 ± 0.3 cm (HCM), 1.4 ± 0.3 cm (FRDA)]. All FRDA subjects were homozygous for the GAA expansion in the frataxin gene without diabetes. Comparison was made with 6 normal control (con) subjects.

Results: Fasting blood glucose ($mmol.l^{-1}$) was 4.46 ± 0.27 (con), 4.51 ± 0.28 (FRDA), 4.48 ± 0.26 (HCM). The whole-body glucose uptake (M, $\mu mol\ kg^{-1}.min^{-1}$) was 39.3 ± 12.7 (con), 33.4 ± 12.7 (HCM) and 18.0 ± 4.7 (FRDA, $p < 0.05$ vs con and HCM). MGU ($\mu mol.ml^{-1}.g^{-1}$) was 0.64 ± 0.04 in con, 0.67 ± 0.10 in HCM and 0.48 ± 0.09 in FRDA ($P < 0.05$ vs con).

Conclusions: The primary myocardial hypertrophy of HCM is not insulin resistant whereas in FRDA myocardial glucose uptake by the hypertrophied heart and whole-body glucose uptake are both reduced. Therefore, cardiac hypertrophy per se is not necessarily associated with myocardial insulin resistance.

P3585 Binding potential of [*amido*-^{11}C]GB67, a new radioligand for assessing myocardial α_1-adrenoceptors *in vivo*

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Dysfunction of the sympathetic nervous system underlies a number of myocardial disorders. Positron emission tomography (PET) offers a way of assessing receptor function non-invasively in humans but there are no PET radioligands for α-adrenoceptors (AR). We have labelled GB67, a structural and pharmacological analogue of the α_1-adrenoceptor antagonist prazosin, by [^{11}C]methylation of *N*-desmethyl-GB67 (GB99). Studies in rats demonstrated that [^{11}C]GB67 binds to myocardial α_1-AR. Here we assess the binding potential of GB67 and its precursor, GB99.

Methods: [^{11}C]GB67 (0.4 nmol/kg) was injected intravenously into rats together with varying amounts of either unlabelled GB67 or GB99. Rats were sacrificed at 20 minutes after injection and the heart was removed. The uptake index (UI) was expressed as radioactivity per gram of wet tissue divided by the radioactivity injected per gram body weight.

Results: UI decreased as the dose of GB67 or GB99 was increased. The data were fitted to competitive binding model to provide estimates of the maximum number of binding sites (B_{max}) and half saturation doses (IC) for GB67 and GB99 in different myocardial regions. Assuming a tissue protein content of 10%, the values of B_{max} (~13 pmol/g tissue) were similar to those (50–170 fmol/mg protein) reported for myocardial α_1-AR assessed *in vitro*.

	B_{max} (pmol/g)	IC_{GB67} (nmol/kg)	IC_{GB99} (nmol/kg)
R. ventricle	13.1 ± 1.7	1.58 ± 0.29	4.89 ± 0.85
L. ventricle	12.2 ± 1.6	1.46 ± 0.27	4.61 ± 0.80
Septum	13.5 ± 1.6	1.62 ± 0.27	5.04 ± 0.80

Conclusion: [^{11}C]GB67 may be used *in vivo* to quantitate myocardial α_1-ARs. The precursor GB99 has high affinity to α_1-ARs. For PET studies, GB99 should be absent or at a low level that can be included in data analysis.

P3586 Iron in the heart: a cardiac magnetic resonance imaging study

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Introduction: Although serum ferritin is considered as a valuable index of iron tissue deposition, biopsy is the only way to detect iron in individual organs. The aim of this study was to apply MRI in the assessment of myocardial iron deposition and compare the results with cardiac biopsy data and serum ferritin levels.

Patients and Methods: Twenty patients, aged 22 ± 8 yrs., were studied. ECG-gated spin echo images were obtained from all patients using a 0.5 T superconducting system. Heart T2 relaxation time was calculated using TR = HR and TE = 17 msec in 7 symmetrically repeatable echoes (17–119 msec). Biopsy was performed in all patients within 5 days of the MRI scan. Serum ferritin levels were calculated from the average values of the last 5 years.

Results: All study patients were in heart failure (NYHA II–III). According to biopsy, heart iron deposition was graded as mild (+) or severe (++). Low heart T2 relaxation time was considered as indicative of significant iron deposition. Ferritin > 2500 ng/ml was considered as suggestive of iron overload. Agreement between MRI, ferritin, and biopsy is tabulated:

	Ferritin < 2500 ng/ml	Ferritin > 2500 ng/ml	BIOPSY (+)	BIOPSY (++)
High T2	3	0	2	1
Low T2	0	17	1	16

Heart T2 relaxation time correlated with serum ferritin ($r = -0.88$, $p < 0.001$) and cardiac biopsy results (Spearman's test, Rho = −0.47, $p < 0.04$). Ferritin also correlated with biopsy results (Rho = 0.50, $p < 0.03$)

Conclusion: According to our results, heart T2 relaxation time measured noninvasively by MRI appears in agreement with ferritin levels and cardiac biopsy data. Although there is strong agreement between biopsy and MRI in high heart iron overload, further studies are needed in milder cases.

P3587 Evaluation of myocardial energy metabolism with P-31 spectroscopy in patients with dilated cardiomyopathy

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In patients with heart failure due to dilated cardiomyopathy (DCM) cardiac energy metabolism is impaired as indicated by a reduced myocardial phosphocreatinin-to-ATP (PCr/ATP) ratio, which can be measured non-invasively by 31-P-Spectroscopy (MRS). The aim of the study was to evaluate the changes of the PCr/ATP ratio in patients with DCM treated with recombinant human growth hormone (r-HGH) and to show a correlation to data from the heart muscle biopsies.

Methods: We investigated 20 patients with DCM and an ejection fraction < 35% and a NYHA class III. All patients were treated with r-HGH (2 I.E./day, Novo Nordisk) for 3 month or placebo. 31-P-MRS and a heart muscle biopsy were performed at the beginning and after 3 month. In the 2-D chemical shift imaging of the anterior wall of the left ventricle PCr, alpha-, beta- and gamma-ATP were measured. For the controll group we investigated 10 healthy volunteers.

Results: The PCr/ATP ratio in the healthy volunteers was 1.8 ± 0.15. In the patients group before treatment, the PCr/ATP ratio was reduced at 1.6 ± 0.25. At the reevaluation after the r-HGH treatment 11 patients showed a significantly increase of the PCr/ATP ratio to 2.3 ± 0.45. In 9 patients no PCr/ATP increase were observed. There was no increase in the NYHA class or the ejection fraction in all patients due to optimal medical treatment.

Conclusions: Evaluation of the myocardial energy metabolism in human end stage heart failure is faisible non-invasively by 31-P-MRS. The PCr/ATP ratio is significantly diminshed in patients with DCM before treatment with r-HGH. Further studies have to shown, wether the increase of the PCr/ATP ratio after the r-HGH treatment will a good predictor for a possible increase of myocardial contractility. A final assessment will be possible after the correlation of the PCr/ATP-values evaluated with 31-P-MRS and heart muscle biopsies after the unblinding of the study in April 1999.

P3588 Ultrasonic integrated backscatter identifies preclinical myocardial dysfunction in patients with normal ejection fraction and anthracyclines treatment

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Based on changes of acoustic properties during the myocardial contraction, cyclic variation of ultrasonic integrated backscatter (CVIB) is a sensitive marker of regional myocardial contractile performance. Aim of the study was to investigate by CVIB the presence of preclinical myocardial toxicity in patients (pts) with normal ejection fraction (EF) treated with anthracyclines.

Methods: Thirteen pts (Group 1, mean age: 54; M = 3, F = 10; breast cancer = 10 pts, non-Hodgkin lynphoma = 3 pts), referred for routine echo evaluation during or shortly after a polichemiotherapic treatment including anthracyclines (3 to 8 cycles, mean: 5.9), were considered for the study. All pts had normal (>50%) EF and all were free of cardiac symptoms. As a control group, 13 consecutive pts (Group 2, mean age: 52; M = 5, F = 8) were considered; in all the presence of major cardiac abnormalities and of any regional or global myocardial dysfunction was excluded. High-quality ultrasonic 2D-IB images (HP Sonos 2500) in parasternal left ventricular (LV) long- and short axis (Lax, Sax) views were digitally stored for each patient through >2 R-R intervals. CVIB was separately analyzed by the same blinded operator within regions of interest (ROI, 31 × 31 or 42 × 42 pixels) in the LV interventricular septum (IVS) and posterior wall (PW). Absolute (peak to peak intensity [PPI], Db) and relative values (PPI/average intensity [AI] × 100) of CVIB were calculated and compared.

Results: EF (56.2 ± 3.9 vs 55.5 ± 6.3%; p = ns) and all basic clinical variables were comparable in the two groups. Group 1 vs Group 2,

	IVS Lax	IVS Sax	PW Lax	PW Sax
PPI (Db)				
Group 1	3.1 ± 1.1**	2.9 ± 1.2**	3.5 ± 1.5**	4.3 ± 1.7**
Group 2	5.7 ± 2.2	4.5 ± 0.9	7.2 ± 2.3	7.7 ± 2.7
PPI/AI (%)				
Group 1	26.5 ± 9.1*	26.3 ± 10.9*	32.8 ± 16.0*	44.6 ± 23.1*
Group 2	45.1 ± 16.6	37.2 ± 11.7	63.6 ± 19.7	64.9 ± 19.1

**: $p < 0.001$; *: $p < 0.03$.

Conclusions: In asymptomatic pts treated with polichemiotherapic regimens including anthracyclines the CVIB is abnormally low in spite of a preserved LV function. The reduced CVIB could represent a preclinical marker of cardiotoxicity.

P3589 Bold-magnetic resonance imaging of the ischaemic myocardium: first clinical results

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Purpose: The correlation of the apparent transversal relaxation time T2* with the oxygenation state of hemoglobin (BOLD effect) was investigated recently. In the last decade, the BOLD contrast has been exploited in neuro-functional MRI to localize areas of neuronal activity. BOLD magnetic resonance imaging has also been applied to myocardium of healthy volunteers and modulations of the deoxyhemoglobin concentration were detected. In this study, global and regional changes in myocardial oxygenation were evaluated for the first time in patients with coronary artery disease (CAD) by means of magnetic resonance. Moreover, T2* exams were performed before and after coronary revascularization.

Methods: A segmented gradient echo pulse sequence was implemented on a 1.5 T whole body scanner (SIEMENS Vision) to assess myocardial oxygenation. T2*-measurements were done at rest and under stress conditions with dipyridamole (DIP 0.84 mg/kg). 25 patients with CAD were examined. Patients underwent x-ray angiography, stress-echocardiography and MR-exam within 4 days. In 5 patients T2*-measurements were performed before and after coronary revascularization procedures like coronary angioplasty (PTA) or bypass (CABG).

Results: In the MR T2* examination expected ischemic myocardium was detected in 14 cases (10 × LAD, 2 × RCA and 2 × LCX). In these regions, T2* values were significantly reduced when compared to the remaining myocardium ($p < 0.01$). Areas with lower T2* values correlated well with echocardiographic findings of dyskinetic myocardium. In 11 patients (5 × LAD, 4 × RCA and 2 × LCX) ischemic myocardium was not detected due to severe susceptibility artifacts occurring at the infero-lateral border of the heart.

5 patients were reinvestigated after coronary revascularization. Regions with reduced T2* values were clearly delineated before and after PTA. When observing the obtained T2* maps, differences between regions of expected ischemia and regions of normal myocardium were less pronounced than they were prior to PTA. Expected ischemic areas with lower T2* values were not detected after CABG due to susceptibility artifacts.

Conclusion: Our preliminary results show for the first time, that DIP-induced regional changes of myocardial oxygenation in patients with CAD (mainly with a stenosis of the LAD) could be assessed with T2*-exams. T2*-exams may therefore become a promising tool for noninvasive diagnostic and therapy evaluation in patients with CAD.

P3590 Relation of coronary artery stenosis severity to a myocardial perfusion reserve index derived from first-pass contrast enhanced magnetic resonance imaging

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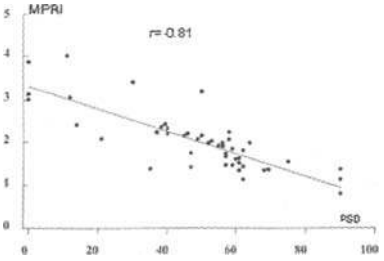
MRI could be a useful non-invasive tool to assess coronary disease. We evaluated an MRI technique using a quantitative tracer kinetic model to derive a myocardial perfusion reserve index (MPRI) in human volunteers and patients with coronary artery disease.

Methods: 20 patients with angiographically proven coronary heart disease and 5 normal healthy male volunteers, underwent both resting and stress (adenosine 140 mcg/kg/min) first-pass contrast enhanced MRI examinations,using an inversion/recovery turbo-FLASH sequence (TI 300 ms, TR 4.7 ms, TE 2 ms). We computed the unidirectional transfer constant Ki for the myocardial uptake of contrast, a perfusion marker, in each coronary arterial territory. The ratio of Ki for the rest and stress scans was used to estimate the MPRI. A validated QCA package (CAAS 2) was used to measure coronary percent stenosis diameter(PSD).

Results: MPRI was 4.21 ± 1.16 (mean ± SD) in normals and significantly reduced in patients (2.02 ± 0.70, $p < 0.001$). For regions supplied by individual vessels, there was a good negative non-linear correlation of MPRI with PSD of coronary lesions ($r = -0.81$, $p < 0.02$). Importantly, MPRI was significantly different between non-flow limiting lesions (<40%) and "intermediate" lesions (40–59%) (2.80 ± 0.77 and 1.93 ± 0.38 respectively, $p < 0.02$). However even regions supplied by vessels with <40% diameter stenosis had a significantly lower MPRI than normals ($p < 0.01$).



MPRI vs Coronary PSD.

Conclusion: A myocardial perfusion reserve index derived from first-pass MRI studies can distinguish between normal subjects and patients with coronary artery disease. Furthermore, it provides useful functional information on coronary lesions, particularly where the physiological significance cannot be predicted accurately from the angiogram.

P3591 Magnetic resonance perfusion imaging: improvement of myocardial perfusion reserve after PTCA

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Myocardial perfusion reserve (MPR) can be determined with cardiovascular MR. Aim of this study was to assess MPR before and after PTCA with a cut off value of 1.5 that was previously defined in a different study.

30 patients with angiographically significant coronary artery stenosis (≥75%) were examined with a 1.5 Tesla MR tomograph (Philips ACS NT) before and 24 h after PTCA. One short axis image per heart beat was acquired for 70 beats at the base of the papillary muscle with a turbo gradient echo technique (spatial resolution 1.7 × 1.9 × 8 mm, acquisition time 360 ms). A gadolinium DPTA bolus was injected in the superior caval vein (0.025 mmol/kg body weight) before and after dipyridamole infusion (0.56 mg/kg body weight). The signal intensity curves of the left ventricle and 6 myocardial segments were obtained and the upslope was determined using a previously validated linear fit. A correction for the left ventricular upslope (input function) was performed. MPR was calculated as the relative change of the upslope after dipyridamole infusion in comparison to that at rest.

Before PTCA MPR was significantly reduced in segments supplied by a stenotic coronary artery (S+) in comparison to the remaining segments (S−) (1.19 ± 0.24 vs. 2.18 ± 0.43; $p < 0.001$). Sensitivity and specificity for the detection of S+ using the previously defined cut off value of 1.5 were 92% and 87% before and 75% respectively 86% after PTCA. After successful PTCA ($n = 27$) MPR in S+ increased significantly in comparison to pre-PTCA values (1.96 ± 0.56 vs. 1.13 ± 0.25; $p < 0.001$) and did no longer differ from S− (2.11 ± 0.51). If PTCA was unsuccessful or not performed ($n = 3$) MPR remained <1.5 in 12 of 15 S+.

MR perfusion imaging allows a noninvasive assessment of the success of a revascularisation. This technique may be used for the follow up of patients with coronary artery disease and the detection of restenosis.

P3592 Demonstration of impaired myocardial perfusion reserve in patients with syndrome X using magnetic resonance imaging

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Background: Patients with syndrome X may have abnormalites at the microvascular level and impaired vasodilatory response. We therefore investigated subjects with syndrome X using magnetic resonance imaging (MRI) and a quantitative tracer kinetic model, which may be used to estimate myocardial perfusion reserve index (MPRI).

Methods: Five healthy controls and five patients with Syndrome X (classical symptoms of angina, a positive exercise test or reversible ischaemia with stress myocardial scintigraphy and a normal coronary angiogram), underwent both resting and stress (adenosine 140 mg/kg/min) first-pass contrast enhanced MRI examinations,using an inversion/recovery turbo-FLASH sequence (TI 300 ms,TR 4.7 ms, TE 2 ms). Using a modified Kety equation, the unidirectional transfer constant Ki for the myocardial uptake of contrast, a perfusion marker, was calculated for myocardium globally. The ratio of Ki for the rest and stress scans was used derive the MPRI.

Results: (mean ± SD) Global resting Ki (ml/g//min) in patients was not significantly different from that in normals (74.62 ± 30.49 vs 54.24 ± 13.27, $p = 0.21$). However, global MPRI with adenosine was significantly reduced in patients compared with normal subjects (2.21 ± 0.60 vs 4.21 ± 1.16, $p < 0.01$), and the reduction was homogeneously distributed across all vascular beds

Conclusion: Our preliminary data is one of the first demonstrations that global MPRI estimated with MRI is significantly reduced in patients with syndrome X compared with controls, supporting the concept that syndrome X is associated with an impaired microcirculatory vasodilator response. MRI may provide a very useful non-invasive tool to support the diagnosis of syndrome X in patients with angina and normal arteries and the ability to perform longitudinal studies will allow investigation of its mechanisms.

P3593 Myocardial perfusion quantification using dynamic magnetic resonance imaging in patients after angioplasty and brachytherapy

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Introduction: Dynamic magnetic resonance imaging (MRI) after injection of a bolus of Gd-DTPA allows the absolute determination of K1, the blood to myocardium constant transfer that is linearly related to the myocardium perfusion at rest. The objective of this study is to measure K1 in normal myocardium and persistent SPECT thallium defect area in patients with stable coronary artery disease.

Methods: 16 patients were studied 6 months after coronary PTCA followed by intracoronary brachytherapy (9 to 18 Gray). A coronary angiography, a rest and stress SPECT 201Tl imaging and a cine MRI coupled with a perfusion study were completed within 28 hours. For the MRI perfusion study, 2 short axis view of the heart were obtained at rest using a Picker Edge 1.5 T MR system with a magnetization prepared FAST sequence after injection of a bolus of Gd-DTPA (Magnevist, Schering AG, Deutschland) in a brachial vein (0.035 mmol/kg). After signal intensity calibration based on external references, blood and myocardium concentration time-curves of 4 sectors (anterior, septal, inferior and lateral) were fitted with a one compartment model for the myocardial perfusion indices: the blood to myocardium transfer constant (K1 in ml/min/g) and the Gd-DTPA distribution volume (Vd in%). From the 3D data set of 201Tl images, 2 short axis slices were reconstructed at the level of the MRI slices for the determination of the status of the 4 sector (normal versus infarct).

Results: All the 16 patients were asymptomatic without ischemia and angiographical sign of restenosis or other coronary obstruction at the time of the study. 7 patients (11 over 128 sectors) had a persistent defect on 201Tl imaging reflecting a previous myocardium infarct. Difference between normal and infarcted myocardium was observed in the wash-in but not the wash-out of the time transit curves. K1 in infarct sectors (0.33 ± 0.11 ml/min/g) was statistically decreased by comparison with normal sectors (0.50 ± 0.09 ml/min/g, $p < 0.0001$). No difference in Vd was observed between normal myocardium and infarct (16.8 ± 3% and 17.3 ± 4.8%, $p = 0.44$).

Conclusion: Quantification of myocardial perfusion using MRI in patients with stable coronary artery disease can differentiate between normal myocardium and infarct. This represents the rational for further studies on the use of MRI derived perfusion index K1 for the assessment of myocardium viability.

P3594 Analysis of the first-pass myocardial perfusion in patients with acute or subacute infarction using ultrafast magnetic resonance imaging

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The aim of the study was to compare perfusion parameters in infarcted and non-infarcted myocardium after successful revascularization using ultrafast magnetic resonance imaging (MRI).

Methods: 19 patients (55 +− 10 years) with acute or subacute myocardial infarction and angiographic TIMI flow 0 were includud into the study. Successful revascularization with TIMI flow 3 was obtained by PTCA or Stenting within 7.5 ± 6.8 hours in 16 patients. MRI was perfomed within 5.8 ± 1.7 days (Siemens Magnetom Vision 1.5 T, Single Slice, TurboFLASH, breathhold, ECG-gated, Gd-DTPA). The left myocardium was devided clockwise into 16 segments. In each segment following parameters were determined: 1. Normalized Signal intensity (NSI) = SI − Baseline SI; 2. Time to Peak; 3. Slope, 4. Mean transit time (MTT) and 5. Area under the curve (Area).

Results: In all cases central dark zones at the perfusion beds of the infarct-related artery were obvious with significantly different NSI, Time to Peak and Slope (see table). When all segments of the myocardium are compared, the best differentiation between infarct-related and non-infarct-related segments was shown by NSI (κ = 0.83) and Area (κ = 0.98).

	Infarcted	Non-Infarcted	P-Value
NSI	22.5 ± 13.4	41.2 ± 16.4	<0.0001
Time to Peak [sec]	25.4 ± 10.76	19.9 ± 11.31	0.0012
Slope [NSI × 10^{-3}/sec]	0.99 ± 0.69	2.59 ± 1.71	<0.0001

Conclusion: Infarcted myocardium can be distinguished exactly from non-infarcted myocardium. In the infarcted-related segments the perfusion is represented by the diminished SI, the prolonged Time to Peak and the reduced Slope, supporting the concept of the retarded wash-in of the infarcted region. In the differentiation of infarcted-related and non-infarcted-related myocardium NSI and Area are the most robust parameters.

P3595 Variability of regional myocardial blood flow measured by positron emission tomography in 153 normal volunteers

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Significant variability of myocardial perfusion has previously been demonstrated in animal studies using invasive techniques. Knowledge of the range and regional distribution of normal myocardial blood flow (MBF) in humans is crucial to understanding the contribution of MBF in diseased states. We therefore examined resting segmental MBF in 153 healthy volunteers.

Methods and Results. MBF (ml/min/g) was quantitated by means of positron emission tomography with oxygen-15-labeled water in 117 men (M) and 36 women (F), aged 21 to 86 years. MBF was corrected for rate-pressure product (RPP) by the formula, basal MBF × (mean RPP/individual RPP). T = total population, σ = coefficient of variance.

MBF		Septal	Anterior	Lateral	Inferior Wall
Range	T, uncorrected	0.47–1.79	0.58–2.56	0.56–2.00	0.42–1.56
	σ	0.23	0.30	0.26	0.23
	T, corrected	0.47–1.76	0.52–2.06	0.46–2.26	0.42–1.64
	σ	0.23	0.27	0.25	0.25
	M, corrected	0.47–1.80	0.58–2.56	0.56–1.66	0.43–1.55
	σ	0.22	0.24	0.20	0.26
	F, corrected	0.67–1.60	0.68–2.49	0.69–2.00	0.68–1.51
	σ	0.21	0.25	0.26	0.20
Mean ± SD	M, corrected	0.91 ± 0.19	0.96 ± 0.25	0.95 ± 0.19	0.86 ± 0.19
	F, corrected	1.14 ± 0.23	1.30 ± 0.35	1.13 ± 0.31	1.06 ± 0.20
p, M vs F		<0.0001	<0.0001	<0.0001	

Conclusion. MBF at rest, both uncorrected and corrected for workload, shows considerable variability within each myocardial segment, confirming the pattern previously observed in animals. The significantly higher MBF in women appears to be unrelated to workload.

P3596 Definition of normal and abnormal human myocardial perfusion at rest by venous contrast echocardiography

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Intermittent harmonic imaging (IHI) combined with digital image processing (DIP) allows for myocardial opacification by venous myocardial contrast echocardiography (VMCE) in humans. How normal and abnormal myocardial perfusion translate into myocardial opacification, however, has not yet been defined.

Therefore, VMCE (IHI, venous infusion of 8 g of Levovist) was performed in 8 patients with a normal TC 99 m sestamibi SPECT (TCSS) scan and normal coronary arteries (group 1). Videointensity (VI) in each of the 10 segments of the 4- and 2- chamber views was quantified after DIP and normalized to the value of the segment with maximal VI. The normalized VI's (mean ± 1 SD) in the 4- chamber view were 0.85 ± 0.06 (basal septum), 0.92 ± 0.07 (mid septum), 0.91 ± 0.07 (apex), 0.92 ± 0.07 (mid lateral) and 0.90 ± 0.08 (basal lateral); in the 2- chamber view, the values were 0.89 ± 0.08 (basal inferior), 0.96 ± 0.09 (mid inferior), 0.84 ± 0.06 (apex), 0.90 ± 0.08 (mid anterior) and 0.79 ± 0.06 (basal anterior). In a second step, VMCE and TCSS were compared in 50 patients with known coronary disease by separate observers. On TCSS (10 segments in the horizontal and vertical long axis), 60/500 segments were visually scored as abnormal. For VMCE, segmental VI's were measured after DIP and normalized as in group 1 patients. Different cut-off values were used to define a segment as ab-normal. Receiver operating characteristic curve analyses identified cut-off values of 3SD beyond the normalized mean VI of the corresponding group 1 segment as optimal contrast echocardiographic criterion for abnormal myocardial perfusion as defined by TCSS (sensitivity 90%, specificity 87%, diagnostic accuracy 89%).

Thus, beyond subjective visual assessment, quantitative criteria for accurate differentiation between normal and abnormal myocardial perfusion at rest can be defined for VMCE.

NON-INVASIVE IMAGING TO SCREEN FOR CORONARY ARTERY DISEASE

P3597 Screening with electron beam computed tomography to predict hard coronary events: choosing the appropriate age range

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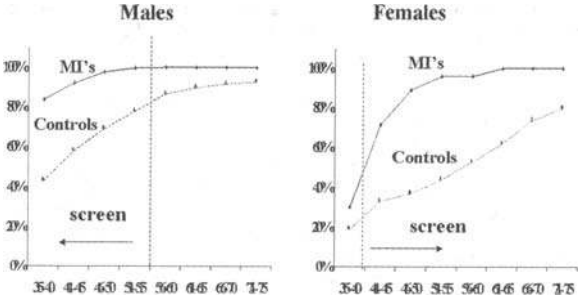
A controversy exists regarding the predictive value of coronary artery calcification (CAC) discovered on a screening electron beam-CT (EBCT). However, selection of patients (pts) for screening in an inappropriate age range may affect the prognostic significance of CAC.

Method: We studied 2 groups of pts: A) 10,937 asymptomatic pts screened with EBCT, B) 208 consecutive pts (71% men, age 35–75) submitted to EBCT within 6 weeks of suffering an acute myocardial infarction (MI). The age adjusted prevalence of CAC in pts from both groups was plotted separately for men and women (figure). We aimed to identify age ranges where the prevalence of CAC was significantly different in MI pts compared to asymptomatic pts. In these age groups EBCT screening would be most appropriate.

Results: In men >55 y/o the prevalence of CAC in MI pts and controls was very similar (100% vs 90%) and the sensitivity and specificity of CAC for prediction of MI were 100% and 10%. In men ≪55 y/o the prevalence of CAC in MI pts and controls was significantly different (97% vs 56%; P < 0.001) and the sensitivity and specificity of CAC for events were 97% and 44% respectively. In women, the age threshold that identified the best sensitivity and specificity of CAC for events was age >40 (92% and 47% respectively).



Conclusions: In men, EBCT screening of asymptomatic individuals can be conducted as early as 35 y/o, but it should not be done in pts >55 y/o because the specificity of the test becomes poor. For women, screening should begin at >40 y/o and can be continued as late as 75 y/o. These findings carry important implications for the design of future randomized trials intended to study the import of CAC discovered on a screening EBCT.

P3598 Coronary calcification in subjects under age fifty with sudden coronary death as the first manifestation of heart disease

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Sudden coronary death (SCD) under age 50 is a rare but prominent cause of death in adults at the peak of their productive lives. The detection of preclinical coronary atherosclerotic disease has been suggested as a method to predict SCD. However, subjects under age 50 may have little atherosclerosis and still sustain SCD.

Methods: Coronary arteries obtained at autopsy of 28 victims of SCD under age 50 with no prior clinical manifestation of cardiac disease or myocardial scar formation and of 16 age- and gender-matched "healthy" trauma victims were examined. Sections of the complete major coronary arteries were cut in 3- to 5-mm intervals to yield a total of 1,357 histologic sections and analysed using digitised planimetry.

Results: The fraction of sections in categories of cross-sectional area stenosis < 25%, 25–<50%, 50–<75%, and ≥ 75% was 9%, 27%, 37%, and 27%, respectively, in SCD cases and 48%, 37%, 13%, and 2%, respectively, in controls ($p < 0.001$). Plaque area per histologic section was 5.1 ± 2.1 mm^2 in SCD cases and 2.0 ± 0.9 mm^2 in controls ($p < 0.001$). Calcified plaque area per histologic section was 0.18 ± 0.19 mm^2 in SCD cases and 0.02 ± 0.05 mm^2 in controls ($p < 0.001$), providing for separation of the groups with a sensitivity and specificity of 100% and 81%, respectively. On a patient-by-patient basis, calcified plaque area was linearly related to total plaque area. Plaque rupture in SCD cases was associated with a significantly greater presence and amount of calcification compared with apparently stable plaques (univariate analysis).

Conclusions: In young victims of SCD, plaque area was significantly greater than in age-matched controls. Only a small fraction of plaque area was calcified, but calcification was frequently present in plaque rupture. Calcified plaque area was related to total plaque area and provided for good separation between SCD cases and controls.

P3599 Myocardial flow reserve is related with increased carotid intima-medial thickness in healthy men

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Reduced myocardial blood flow reserve (MFR) is associated with cardiovascular risk factors in asymptomatic subjects, and has therefore been suggested to represent a marker of increased subclinical atherosclerosis. To test this hypothesis, we examined the relationship between MFR and carotid artery intima-media thickness (IMT), an established marker of subclinical atherosclerosis, in young men free from coronary heart disease.

Methods: Basal and dipyridamole stimulated myocardial blood flow was measured using positron emission tomography (PET) in 55 healthy men aged 36 ± 4 years. MFR was calculated as the ratio of stimulated flow to basal flow. The mean carotid artery IMT was measured using high resolution ultrasound.

Results: MFR decreased across the quartiles of increasing IMT ($p = 0.006$ for trend), and was 5.2 ± 1.9 in the lowest quartile for IMT and 3.7 ± 1.2 in the highest ($p = 0.04$, I vs IV quartile). The association between MFR and IMT remained significant (p 0.01) in multivariate regression model including age, rate-pressure product, left ventricular mass, oxidized LDL, total cholesterol, HDL-cholesterol and triglycerides as covariates. Oxidized LDL (measured as baseline LDL diene conjugation) was the best single bivariate correlate for both IMT and MFR, correlating inversely with MFR ($r = -0.35$, $p = 0.01$) and directly with IMT ($r = 0.51$, $p < 0.001$).

In conclusion, the data support the concept that reduced MFR assessed by dipyridamole PET reflects subclinical atherosclerosis in asymptomatic subjects, and suggest an adverse effect of increased lipoprotein oxidation on early structural and functional atherosclerotic vascular changes.

P3600 Carotid intima-media thickness is increased in healthy young subjects with a family history of hypertension

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Background: We have previously demonstrated that carotid intima-media thickness (IMT) is increased in young subjects with a family history of parental myocardial infarction. However, to our knowledge, the influence of parental hypertension (PH) on carotid IMT in healthy young subjects has not yet been reported. This study examined whether, in young subjects, family history of PH is associated with increased carotid IMT.

Methods: Twenty-four healthy subjects with a family history of PH (Cases; 9 M, 15 F; mean age 23 ± 5 years; 33% current smokers) and 24 healthy subjects, age- and sex-matched, without family history of PH (Controls; 25% current smokers) underwent carotid ultrasonography to measure the sum of carotid IMT (i.e. the sum of common carotid IMT plus carotid bifurcation IMT, recorded for the right and the left-hand sides of the neck). None had family history of parental myocardial infarction.

Results: The sum of carotid IMT resulted significantly higher in Cases than in Controls (1.90 ± 0.35 mm vs 1.68 ± 0.22 mm, $p = 0.012$). A significant relationship was found between the sum of carotid IMT and age ($r = 0.30$, $p = 0.04$), family history of PH ($r = 0.36$, $p = 0.01$) and smoking status ($r = 0.42$, $p = 0.003$). Carotid IMT was not related to blood pressure, total cholesterol, HDL cholesterol, triglycerides, Lp(a), apo A1 and apo B. Multivariate analysis demonstrated that family history of PH and smoking status were independent predictors of carotid IMT.

Conclusions: Family history of PH appears to be a risk factor for increased carotid IMT in healthy young individuals, independent of the effects of age, blood pressure, smoking status and lipid profile.

IMAGING IN THE DETECTION OF MYOCARDIAL ISCHAEMIA: ECHO, NUCLEAR AND MRI

P3601 Comparative study of dobutamine echocardiography and dipyridamole/Tl-201 scintigraphy for detection of coronary artery disease in patiens with left ventricular hypertrophy

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The recognition of coexistent CAD in pts with left ventricular hypertrophy (LVH) may be difficult by noninvasive testing. Several studies have shown false-positive results using exercise perfusion scintigraphy while dobutamine stress echocardiography (DSE) has been found to have a better diagnostic potential.

The aim of this study was to compare the ability of DSE and TL-201/dipyridamole SPECT to detect CAD in pts with LVH.

Methods: We performed DSE and TL-201/dipyridamole SPECT in 60 pts with LVH (IVS ≥ 13 mm) who entered the hospital because of chest pain and had known or suspected CAD. All pts were referred for coronary angiography independently of tests results. CAD was defined as ≥50% diameter narrowing in at least one major coronary vessel. Tests were judged to have positive or negative results for myocardial ischemia. Ischemia,in DSE, was defined by stress-induced wall motion abnormalities ranging in severity from dyskinesis and akinesis to grades of hypokinesis.

Results: Documented CAD was found in 46 pts (76.6%). The sensitivity of DSE and TL-201-SPECT was 95.23% and 87.5% respectively ($p > 0.05$).The specificity of DSE was 100% compared with 45.45% of TL-201-SPECT ($p = 0.000$) and their respective accuracies were 96.66% and 63.1% ($p = 0.000$).

In conclusion: This study demonstrates that DSE is a safe and accurate diagnostic method and significantly superior to TL-201/dipyridamole-SPECT for the detection of CAD in pts with LVH.

P3602 Dobutamine stress magnetic resonance is superior to dobutamine stress echocardiography for the detection of wall motion abnormalities: a subgroup analysis for territories and image quality

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We have shown previously, that high dose dobutamine magnetic resonance imaging (DSMR) is superior to dobutamine stress echocardiography (DSE) for the detection of stress induced wall motion abnormalities. In this analysis we examined, if these differences can be explained by image quality and related to specific coronary territories.

In 208 consecutive patients DSE (GE VingMed System5) and DSMR (Philips Gyroscan NT, 1.5 T, turbo-gradient-echo technique) were performed before coronary angiography using a standard dobutamine/atropine stress scheme and analysed using a 16 segment model. Significant coronary artery disease was defined as a diameter stenosis of ≥50%. Image quality was graded according to the visibility of the endocardium.

51% echocardiographic examinations and 82% MR examinations ($p < 0.01$) yielded good or very good image quality. In these patients DSMR showed only a tendentially higher diagnostic accuracy, than DSE (85% vs. 89%). In contrast, in patients with suboptimal echocardiographic image quality DSMR was significantly more accurate (59% vs. 85%, $p < 0.01$). Sensitivity with DSMR was superior compared with DSE for all territories ($p < 0.05$, see table).

	Proximal		Medial		Distal	
	DSE	DSMR	DSE	DSMR	DSE	DSMR
LAD	78%	97%	71%	91%	71%	80%
LCX	65%	92%	-	-	62%	84%
RCA	73%	88%	75%	83%	71%	79%

Especially in patients with suboptimal echocardiographic image quality dobutamine stress magnetic resonance imaging is superior to dobutamine stress echocardiography. The largest difference in diagnostic accuracy between the two techniques can be found for the detection of proximal stenoses of the circumflex artery, which is a known limitation of stress echocardiography.

P3603 Identification of myocardial perfusion defects with myocardial contrast echo and MIBI SPECT during dobutamine stress echocardiography

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MIBI SPECT is an accepted non invasive imaging technique to assess myocardial perfusion. NC100100 (Nycomed) is a new fluorocarbon contrast agent able to opacify the left ventricular myocardium. Aim of this study was to compare MIBI SPECT to NC100100 enhanced echocardiograms with the use of harmonic (H) imaging during dobutamine stress echocardiography (DSE).

Methods: We evaluated 20 patients (pt) (17 males, 3 females, mean age 63 ± 15) with a recent (within six months) positive coronary angiogram. DSE was performed using a standard protocol and NC100100 was given at the dose of 0.03 ml/kg at rest and peak stress. The images were also stored in a digital format. At peak stress MIBI was also injected and peak nuclear images were acquired 1 hour after the end of stress. Rest MIBI SPECT scan was performed 24 h later. Scans were reviewed blindly.

Results: 19 pt had positive DSE + MCE and only 15 had positive MIBI SPECT ($p < 0.001$). If we then consider the ability of the techniques to unmask wall motion and/or perfusion abnormalities in single coronary artery territories then 10 of 12 pts with >50% LAD stenosis were correctly diagnosed with DSE + MCE while 9 were diagnosed with SPECT ($p = 0.08$). All 15 with >50% on RCA or Cx stenosis were diagnosed with DSE + MCE but only 8 had positive SPECT ($p < 0.001$).

Conclusions: While DSE with MCE provides similar diagnostic information to SPECT in patients with LAD disease, it shows a greater diagnostic accuracy in the RCA/Cx territory.

P3604 Dobutamine stress magnetic resonance imaging: a reliable alternative to stress echocardiography in patients with insufficient image quality?

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Approximately 15% of patients admitted to stress-echo have an inadequate acoustic window due to obesity, lung emphysema or sequelae of cardiac surgery. Therefore we studied the potential of dobutamine stress magnetic resonance imaging (MRI) to diagnose coronary artery disease (CAD) as an alternative method for the assessment of ischemia induced wall motion abnormalities in a subset of 30 patients with inadequate image quality by stress echocardiography (>2 segments inadequate for wall motion analysis).

Methods: To evaluate the diagnostic reliability of dobutamine MRI for the detection of CAD MR wall motion analysis was compared to coronary angiography and scintigraphic findings. Each patient underwent MRI at rest and during incremental dobutamine infusion (10, 20, 30 and 40 μg/kg/min + 1 mg atropine) and Tl-201 myocardial scintigraphy at rest and after high dose dipyridamole infusion (0.75 mg/kg over 10 min). MR short axis tomograms and reconstructed Tl-201 short axis tomograms were divided into 8 segments. For evaluation of the MR studies each segment was graded as normal, hypokinetic, akinetic or dyskinetic. Dobutamine-MRI was considered positive if segmental wall motion deteriorated by at least one grade after dobutamine infusion. For comparison with coronary angiography each MR and Tl-201 segment was assigned to a specific coronary artery territory.

Results: MR image quality was adequate in 29 (96.7%) of 30 MRI studies. In one patient respiratory motion precluded evaluation. The average time of examination and wall motion analysis was 62 minutes.

	Sensitivity	Specificity	Diagnostic accuracy
Dobutamine-mri	79%	80%	79%
Dipyridamole-Tl-201	89%	70%	83%

Conclusion: Dobutamine-MRI for the detection of CAD was less sensitive but more specific than Tl-201-scintigraphy with a similar diagnostic accuracy. Therefore dobutamine-MRI using a state of the art fast imaging sequence offers a reliable, clinically safe and feasible alternative to stress-echocardiography in patients with inadequate stress-echo-studies due to an insufficient acoustic window.

P3605 Myocardial perfusion imaging using the effect of stimulated acoustic emissions from SHU 563A, a novel ultrasound contrast agent, reliably identifies perfusion defects during coronary occlusion and after reperfusion

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Myocardial perfusion imaging with contrast echo currently involves harmonic triggered, gray scale B-mode [HBM] imaging and requires extensive post-processing to show perfusion in color. We investigated whether the microbubble response to high ultrasound amplitude – the phenomenon of stimulated acoustic emission [SAE]- could be recorded with harmonic triggered power Doppler [HPD] in color to identify perfusion defects. SHU 563A is an air-filled microsphere with a biodegradable cyanacrylate polymer shell, shown in in vitro studies to respond uniquely to high amplitude ultrasound.

Methods: To assess the in vivo potential of this approach, we studied 10 dogs in whom acute myocardial infarction was created by 2–3 hour ligations of either LAD (7) or Cx (3) branches followed by 1 hour reperfusion. After transvenous administration of SHU 563A, imaging was performed with HBM and HPD for SAE recordings. Post-mortem TTC staining was used to verify infarction. HBM images, HPD images and TTC data were analyzed by independent observers.

Results: During coronary occlusion, HBM and HPD showed perfusion defects in all 10 dogs in both short-axis and long-axis views. Correlation between HBM and HPD in assessing hypoperfused bed size was $r = 0.99$, $p < 0.001$. After reperfusion, HPD showed good correlation between perfusion defect size and residual infarct size by TTC ($r = 0.82$, $p < 0.01$).

Conclusion: HPD with SHU 563A identifies perfusion defects during coronary occcclusion as reliably as HBM. After reperfusion, HPD precisely portrays the site and size of residual infarct on line, in color. This approach has excellent potential for clinical application.

P3606 Detection of coronary stenosis in humans using stress contrast echocardiography with pulse inversion harmonic imaging: a comparison with Tc-99m-MIBI SPECT

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Harmonic Imaging (HI) which is currently, the most sensitive method for myocardial perfusion imaging using microbubbles, suffer from inferior resolution and poor contrast at low mechanical indices (MI). Pulse Inversion Harmonic Imaging(PIHI) is a new method for imaging nonlinear echoes from microbubbles in which, the phase of alternate transmitted ultrasound pulses is inverted and the subsequent echoes summed to produce a more efficient detection of nonlinear echoes than simple HI. However, the accuracy of MCE with this novel imaging technology in the detection of significant coronary artery disease(CAD) has not been fully investigated. We assessed the ability of PIHI with IV PESDA to produce myocardial contrast echocardiography (MCE) perfusion defects in patients who were suspected to have CAD.

Methods: MCE with PIHI and Tc-99m-MIBI SPECT were performed at the same day during rest and after 0.56 mg or 0.84 mg/kg dipyridamole infusion in 18 patients. MCE and MIBI SPECT were visually assessed for the perfusion defect according to the coronary territory. Coronary angiography was also performed in all patients to determine the degree of stenosis.

Results: Using coronary angiography as the standard, MCE had a sensitivity of 74% and a specificity of 94% for the detection of significant CAD (>70% stenosis) while MIBI SPECT showed a sensitivity of 74% and a specificity of 97%. The overall concordance rate between MCE and MIBI SPECT for the detection of perfusion defect according to coronary territory was 91%.

Conclusion: Stress contrast echocardiography with PIHI is comparable to Tc-99m-MIBI SPECT in accurately identifying significant coronary stenosis and myocardial perfusion abnormalities.

P3607 Value of biphasic response for detecting residual ischaemia after acute myocardial infarction: comparison between exercise and dobutamine echocardiography

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Detection of contractile reserve (CR) and residual ischemia is clinically important after acute myocardial infarction (AMI). We sought to assess the accuracy of biphasic response (initial improvement followed by worsening) during semi-supine bicycle exercise echocardiography (EE) and dobutamine echocardiography (DE) for detecting residual stenosis and predicting functional recovery (FR) early after AMI.

Methods: 54 consecutive patients (pts) with AMI underwent EE and DE 6 ± 2 days after AMI. Beta-blockers were interrupted for at least 24 h. To assess FR, echocardiography at rest was repeated 1 month later. Regional wall thickening was semi-quantitatively assessed using a 16-segment model. All pts had at least 2 dyssynergic segments at baseline. Ischemia was defined as worsening or extension of baseline dyssynergy with (biphasic response) or without initial improvement in ≥2 contiguous segments. All pts underwent quantitative coronary angiography 13 ± 9 days after AMI. A ≥50% diameter stenosis of the infarct-related vessel (IRV) was considered significant.

Results: Initial improvement of wall thickening was observed in 45 pts (83%) during EE and 47 pts (87%) during DE. In these pts with CR, a biphasic response was found in 29 pts with EE and 30 pts with DE. Among the pts without initial improvement, 2 had worsening in adjacent region during EE and 3 during DE. Functional recovery at 1 month was observed in 45 pts (83%). Sensitivity of EE and DE for detecting significant stenosis of the infarct-related vessel was 65% and 70% respectively, while specificity was 87% with both methods. The positive predictive value of biphasic response to detect residual stenosis of the IRV was 100% with EE and DE. The positive predictive value of biphasic response to predict FR was 97% with both methods.

Conclusion: When observed, a biphasic response of wall thickening during EE or DE is highly predictive of residual stenosis of the IRV and functional recovery early after AMI.

DOPPLER TISSUE IMAGING

P3608 Long axis function of the left ventricle, a comparison of M-mode, pulsed tissue Doppler, colour tissue Doppler and strain rate

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Background: Long-axis function of the left ventricle assesses global function. Systolic Mitral Annulus Excursion (MAE) by M-mode and annulus Peak Systolic Velocity (PSV) by Doppler Tissue Imaging (DTI) both correlates with ejection fraction (EF). Velocity Time Integral (VTI) of systolic velocity should reproduce MAE. Synthetic M-mode can also be generated from 2D cine-loops. Tissue velocities are available from pulsed (pw) and colour (c) DTI, the first giving peak, the other mean velocities. Strain Rate Imaging (SRI) assesses regional function from Doppler. The aim of this study was to examine the relation of these variables with each other and EF.

Methods: 19 normals and 19 patients with AMI were examined with a GE Vingmed ultrasound scanner. None excluded for poor echo quality. Cine-loops from two- and four-chamber views were acquired in octave, cDTI and SRI modus. PwDTI and real-time M-mode curves from the mitral ring were obtained from septal, lateral, anterior and inferior points. Synthetic M-mode from octave loops (MAEr) and velocity curves from cDTI loops were generated from the same points. PSSR was averaged from 16 segments. EF was measured by Simpson's method. Measurements were compared for each point, and averages for each ventricle compared to EF.

Results: Comparison is shown in table I.In addition correlation coefficients of EF with the various methods were (95% CI): MAE 0.80 (0.73–0.85), MAEr 0.75 (0.67–0.82), pwVTI 0.66 (0.55–0.75), pwPSV 0.69 (0.58–0.77), cPSV 0.63 (0.51–0.72) and PSSR 0.80 (0.73–0.86).

Table I. Comparison of methods for long axis function

Comparison	BIAS	P	Limits of agreement	4-wall averages
MAE vs MAEr	1.9 mm	<0.0001	−1.9; 5.8	0.1; 4.2
MAEr vs pwTVI	−2.5 mm	<0.0001	−8.3; 3.3	−5.8; 0.5
pwPSV vs cPSV	2.58 cm/s	<0.0001	−1.83; 6.99	−0.41; 5.57

Bases between methods are constant, independent of absolute value.

Conclusions: The present study shows more scatter and weaker correlation than previous reports, probably due to non-selection of patients and early publication bias. Global averages reduce scatter by 30 to 50%, but it is still high. Measurements by different methods are not directly comparable due to biases. The bias between cDTI and pwDTI is to be expected. The bias between real-time and synthetic M-mode may reflect problems with aligning the beam in real-time.

P3609 Study of mitral annulus motion, by Doppler tissue imaging and m-mode echocardiography, for the assessement of left ventricular systolic and diastolic function in patients with coronary artery disease

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We compared Doppler Tissue Imaging (DTI) and m-mode echocardiography in the assessment of the systolic and diastolic function of left ventricle (LV), in patients with coronary artery disease (CAD).

Methods: Sixty patients with coronary artery disease (67 ± 12.2 years) were studied. All patients were examined by transthoracic 2D-Doppler echocardiography which included right upper pulmonary vein flow recordings. Tissue velocities in atrioventricular plane by DTI were recorded at five segments (septal, lateral, posterior, inferior and anterior) from the apical views. The velocity of systolic (Smax), diastolic wave (e) and the wave (a) produced by the atrial contraction were recorded. Left atrioventricular plane displacement (AVPD) was examined in the same segments, by m-mode.

Results: Angiographic Ejection Fraction (EF) was 46.4 ± 4.2%. The mean value of Smax in all five sites of the left ventricle was 16.5 ± 3.4 cm/sec and was significantly correlated with the ejection fraction, as assessed by angiography ($r = 0.7$, $p < 0.02$). The waves e, a and the ratio e/a, were significantly correlated with E and A velocities of transmitral flow, as well as with the ratio E/A (respectivelly $r = 0.5$, $r = 0.6$, $r = 05$, $p < 0.01$). e and a were correlated with the diastolic forward and reverse flow velocity of right upper pulmonary vein (0.3 and 0.5, $p < 0.05$)

The mean value of systolic AVPD was correlated with angiographic EF (0.35, $p < 0.01$). Mean AVPD in early diastole and mean AVPD during atrial systole were significantly correlated with E and A velocities of transmitral flow and their ratio (0.3, $p < 0.05$). The early and late diastolic AVPD were not correlated with the diastolic forward and reverse flow velocity of right upper pulmonary vein.

Conclusions: Study of the mitral annulus motion by Doppler tissue imaging is more accurate than m-mode atrioventricular plane displacement, for the assessment of systolic and diastolic function of the left ventricle in patients with coronary artery disease.

P3610 Detection of a pseudonormal Doppler-derived mitral inflow pattern by Doppler tissue imaging

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Background: It was suggested that the assessment of mitral anular dynamics by DTI permits a load-independent evaluation of left ventricular function.

Methods and Results: According to their symptoms of heart failure and their clinical history three groups (g) of patients (pts.) with normal systolic function (EF > 48%) were separated: ten asymptomatic subjects (60 ± 10 y., g A), 15 pts. with coronary artery disease (60 ± 11 y., NYHA class 1.4 ± 0.4, g B) and 15 pts. with arterial hypertension (58 ± 9 y., NYHA class 2.4 ± 0.5, g C). The mitral inflow profile (E, A, E/A) was obtained by pulsed Doppler. Peak diastolic velocities of the septal mitral anulus (E_T, A_T, E_T/A_T) and the time interval from Q in the ECG to the onset of E_T were derived from pulsed DTI. All patients had invasive measurement of left ventricular enddiastolic pressure. (LVEDP).

Group	E (cm/s)	A (cm/s)	E/A	E_T (cm/s)	A_T (cm/s)	E_T/A_T	Q-E_T (ms)	LVEDP (mmHg
A	70	73	0.97	11.7	11	1.11	289	8
(n = 10)	± 17	± 11	± 0.25	± 4.7	± 4.6	± 0.36	± 38	± 3
B	55	65	0.88	8.9	10.7	0.85	302	12
(n = 15)	± 20	± 13	± 0.3	± 5.4	± 6.1	± 0.26	± 40	± 6
C	77	81	1.02	6.9*	10	0.71*	375*	16*
(n = 15)	± 33	± 28	± 0.52	± 4.8	± 6.2	± 0.28	± 55	± 8

$p < 0.05^*$; B/C vs. A, Q-E_T after correction for heart rate. E_T was only poorly correlated to LVEDP ($r = 0.12$, $p > 0.05$).

Conclusion: DTI is a preload-independent tool for the assessment of LV diastolic dysfunction in symptomatic patients with preserved systolic function, a pseudonormal mitral inflow and elevated filling pressures.

P3611 Energy mode Doppler tissue imaging analysis of the left ventricular wall function and intra-myocardial differences between the endocardial and epicardial layers: normal pattern description in a clinical scenario

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Energy mode of the color Doppler tissue imaging (DTI) reflects the Doppler intensity shift of the myocardium and its is a new modality in the non invasive assessment of regional myocardial wall diastolic performance. The advantage and potential clinical applicability of this new imaging method are still unknown. The aim of this study was to analyze the differences between the endocardial (Endo) mesocardial (Meso) and epicardial (Epic) layers during the cardiac cycle in normal individuals using the new energy DTI mode and to establish its normal pattern. After appropriate DTI M-mode energy acquisition using the left ventricular posterior wall and the parasternal long axis view, we divided the cardiac cycle in seven consecutive phases, the QRS complex (Q), the early systole (S1), mesosystole (S2), endsystole (S3), early diastole (D1), mesodiastole (D2) and enddiastole (D3). In a population with 10 normal subjects, for each phase of the cardiac cycle the energy DTI images were quantitatively evaluated in each one of these three myocardial layers (Endo/Meso/Epic) and its correspondent absolute differences (Δ) were also calculated. Our results showed that the more significant statistical differences in intra-myocardial energy mode DTI analysis were obtain always between the Endo and Epic layers, and specially for the Q phase (Δ = 5.7 ± 3.7; p = 0.006), S2 phase (Δ = 4.9 ± 3.6; p = 0.006), D2 phase (Δ = 6.6 ± 6.1; p = 0.008) and D3 phase (8.5 ± 6.2; p = 0.005), a pattern that was constant in all individuals without cardiac pathology.

Conclusion: The regional intra-myocardial energy Doppler tissue imaging analysis of the left ventricle under physiological conditions is feasible in a clinical scenario, registered an heterogeneous pattern within the myocardial wall thickness and during the cardiac cycle, and can establish and quantitate the intra-myocardial differences or gradient between the endocardial and epicardial layers.

P3612 Can assessment of long-axis function differentiate between pathological and physiological left ventricular hypertrophy? A study using tissue Doppler echocardiography

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In some athletes with an increased left ventricular wall thickness, it is difficult to distinguish between physiological hypertrophy due to athletic training and pathological hypertrophy due to hypertrophic cardiomyopathy (HCM) or coincidental arterial hypertension (HT). This discrimination is clinically important because undiagnosed HCM is one of the most common causes of sudden cardiac death in young athletes.

Methods: We studied long-axis function in 30 patients with different types of left ventricular hypertrophy (LVH) (Gp 1 = 10 pts with HCM; Gp 2 = 10 pts with HT; Gp 3 = 10 weightlifters), and compared these with 10 normal subjects (Gp 4), to identify echo criteria which might differentiate between physiological and pathological LVH. The peak systolic velocities of mitral annular motion by tissue Doppler echocardiography were measured from the apex at 4 sites: lateral – L; medial – M; anterior – A; inferior – I; 4-site average – Mean.

Results: Global EF was normal and similar in all groups (mean: 65%, 65%, 63%, 68% respectively). There were no differences in mean age between groups, apart from Gp 2 who were older (mean: 36, 46, 30, 35 years, respectively). LV mass index (LVMI) and long-axis velocities are shown in the table. A peak systolic < 9 cm/s for mean systolic annular motion differentiated well (sensitivity 85%, specificity 100%) between pathological and physiological LVH.

LV mass index and long-axis velocities

Group	LVMI (g/m^2)	L (cm/s)	M (cm/s)	A (cm/s)	I (cm/s)	Mean (cm/s)
1	169 (58)	8.8 (2)	7.3 (2)	7.5 (2)	8.2 (2)*	7.9 (2)*
2	185 (44)	8.2 (2)	7.6 (1)#	7.9 (2)#	7.8 (1)#	7.9 (1)#
3	181 (34)	10.7 (3)	10.5 (2)*#	10.3 (2)*#	10.8 (2)*#	10.5 (2)*#
4	115 (21)	10.3 (1)	9.6 (1)	10.2 (1)	9.8 (1)	10.0 (1)

*p < 0.05: HCM vs. athletes; #p < 0.05: HT vs. athletes

Conclusion: Long-axis systolic function is decreased in patients with pathological LVH, but preserved in athletes. This simple new echocardiographic parameter may discriminate between pathological and physiological LVH.

P3613 Long-axis parameter changes during low-dose dypiridamole-dobutamine stress echocardiography

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The **aim** of the study was to examine long axis M-mode (LAM-m) parameter changes during combined low-dose Dipyridamole-Dobutamine stress echocardiography (DDSE) for the evaluation of myocardial viability. This method was compared with the accepted Thallium-201 rest and late redistribution scintigraphy.

Methods: DDSE was performed on the 35th day (± 2.2) of myocardial infarction (MI) in 60 patients (48 males, mean age 54.7 ± 10 years). Infusion of 0.28 μg/kg Dypiridamole over a 4 minute period, than 5 μg/kg/min Dobutamine (DBA) for 3 minutes and 10 μg/kg/min DBA for another 3 minutes were administered. The LAM-m pictures of the mitral annulus movement were obtained (depending on the location of MI) in four different sections (infero-septal, anterior, antero-lateral, inferior). We measured in 122 MI sections the following LAM-m parameters at rest: the total excursion of the mitral annulus *(d1)* and the mean velocity of the mitral annulus systolic movement *(v1)*, than we repeated the measurements in the 10th minute of DDSE *(d2, v2)*. The *d2/d1* and the *v2/v1* quotients were calculated to describe the changes during the DDSE. The rest and the late redistribution Th*201* images were done in all patients following DDSE. According to the isotope results the LAM-m sections were divided into viable (group A: 91 regions) and non-viable territories (group B: 31 regions).

Results: We found significant differences between the two groups in the values of *d2, v2, d2/d1, v2/v1*.

	d1 (cm)	d2 (cm)	v1 (cm/s)	v2 (cm/s)	d2/d1	v2/v1
Group A	1.04 ± 0.29	1.41 ± 0.38	3.31 ± 1.04	4.84 ± 1.51	1.38 ± 0.28	1.53 ± 0.46
Group B	1.12 ± 0.37	1.14 ± 0.39	3.52 ± 1.39	3.64 ± 1.61	1.05 ± 0.25	1.05 ± 0.28
p <	NS	0.002	NS	0.0005	0.0001	0.0001

The best parameter to distinguish viable from non-viable myocardium were *d2/d1* (chi square = 29.9, Wilks lambda = 0.778). We determined the discriminant function of *d2/d1* for the evaluation of viability: sensitivity 78.0%, specificity 83.9%, positive predictive value 93.4%, negative predictive value 56.8%, accuracy 79.5%.

Conclusions: The *d2/d1* quotient has a high positive predictive value in the determination of viable myocardium. If the *d2/d1* value does not suggest viability further imaging processes are necessary to exclude it.

P3614 Assessment of left ventricular myocardial viability using mitral annular descent velocity: a study with dobutamine stress pulsed tissue Doppler imaging

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Systolic mitral annular motion velocity (MAV) usually reflects left ventricular (LV) asynergy corresponding to the infarct regions in patients with myocardial infarction (MI). However, the relationship between MAV and myocardial viability has not been clarified.

Methods: The study population consisted of 24 patients with previous MI who had one major coronary lesion by coronary angiography and 10 normal subjects (mean age 65 ± 12 and 61 ± 14 years, respectively). We performed Tc-99m-methoxyisobutyl isonitrile scintigraphy in all 24 patients, and divided them into the two groups (A group; 13 patients with myocardial viability, B group; 11 patients without viability). Dobutamine was administered intravenously (2, 5, 10, 20 μg/kg/min, 10 minutes intervals), and peak first and second systolic MAVs (Sw1 and Sw2, respectively) were measured at the 6 mitral annular sites (anteroseptal, posterior, inferior, anterior, posteroseptal and lateral sites) by pulsed TDI. LV wall motion score index (WMSI) was determined according to the classification of American Society of Echocardiography.

Results: At baseline, WMSI was significantly greater, and mean systolic MAV was significantly lower in both A and B groups than in the control group, but there were no significant differences between A and B groups. After dobutamine infusion, WMSI improved in only A group. Sw1s and Sw2s at the mitral annular sites corresponding to the infarct regions increased significantly with 2 μg/kg/min and with 5 μg/kg/min, respectively, compared to baseline in group A. However, there were no significant increases in both systolic velocities even with 20 μg/kg/min in B group.

Conclusion: Systolic MAV, especially Sw1, is a useful and feasible parameter for detecting the regional LV myocardial viability using dobutamine stress pulsed TDI in patients with MI.

P3615 The effect of β-blockade on regional myocardial function in patients with coronary artery disease evaluated with colour Doppler myocardial imaging

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Quantititative assessment of regional myocardial function and the evaluation of β-blockade effects in patients with coronary artery disease (CAD) is of great clinical importance. Currently 2-D echo recognition of wall motion abnormalities (WMA) is based on a qualitative visual assessment of wall motion. With Colour Doppler Myocardial Imaging (CDMI), however, regional myocardial motion can be quantified by measuring peak systolic motion velocities (SVs) within the myocardial wall.

Aim of the study was therefore to evaluate regional myocardial motion with CDMI in patients with CAD and to study the β-blockade effect on normal and less perfused myocardial regions.

Methods: 32 pts with invasive proven CAD (>70% stenosis) and WMA in 2-D-echo were examined with CDMI. 18 pts received a β-blocker therapy. WMA in 2-D echo and SVs of myocardial motion were determined in the 16 standard myocardial segments by 2 blinded observers and compared to normal contracting corresponding segments of 32 age-matched volunteers with regard to normal and less perfused regions and β-blocker therapy.

Results: There was an agreement of 78% between visually assessed WMA by 2-D echo and reduced SVs (below 1 SD of normal segmental SVs) measured by CDMI and an agreement of 85% between angiographically defined stenotic vessel related segments and those with reduced SVs in CDMI. A mean of all SVs derived from 16 segments was significantly lower ($p < 0.001$) in pts with CAD (3.3 cm/s) compared to normals (4.7 cm/s). In pts with CAD mean SVs in segments supplied by stenotic vessels were significantly lower ($p < 0.001$) compared to corresponding segments in normals while mean SVs in segments supplied by non-stenotic vessels were significantly higher ($p < 0.01$). Comparing pts with and without β-blockade mean SVs were lower in normal perfused segments of pts with β-blockade while they were similar in less perfused regions.

Conclusions: CDMI could reliably identify both, segments with reduced contractility in 2-D-echo and segments supplied by angiographically proven stenotic vessels. Furthermore, CDMI allowed quantitative assessment of segmental myocardial motion in pts with CAD which showed reduced systolic motion velocities in regions supplied by stenotic vessels and increased SVs in normal perfused myocardial regions indicating compensatory hypercontractility. β-blocker therapy seems to affect normal and less perfused myocardial regions differently.

P3616 Early postoperative improvement of myocardial systolic velocities assessed by Doppler tissue imaging in patients with significant aortic stenosis

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The aim of this study was to assess changes in myocardial systolic velocities by Doppler Tissue Imaging (DTI) before and after surgery for valvular aortic stenosis (AS). 10 patients (6 M, 4 F), mean age 72 ± 9 y with a significant AS (mean gradient 63 ± 13 mmHg, valve area 0.6 ± 0.3 cm2), good LV function (M-mode echo fractional shortening 34 ± 8%) and no coronary artery desease were studied before and early (6 ± 2 d) after isolated aortic replacement. Radial epicardial, endocardial velocities as well as transmural LV gradient were calculated by M-mode DTI in posterolateral wall (short axis view), and longitudinal LV velocites were calculated by pulsed DTI in inferior wall (apical 2C view).

Systolic radial velocities (cm/s)

	Epicardium		Endocardium		Gradient	
	Before	After	Before	After	Before	After
	1.6 ± 0.7	3.0 ± 1.3	3.6 ± 1.2	7.3 ± 4.9	1.9 ± 1	3.1 ± 2.
p	0.003		0.04		0.16	

Systolic longitudinal velocity (cm/s)

	Before	After
	5.6 ± 1.1	8.2 ± 1.5
p	0.001	

Valvular replacement for aortic stenosis was associated with early improvement in both radial and longitudinal systolic LV velocities, presumably because acute decrease in left ventricular afterload.

P3617 Early changes in left ventricular long axis function following aortic valve replacement for aortic stenosis in patients with left ventricular dysfunction

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Chronic aortic stenosis (AS) may cause progressive left ventricular (LV) dysfunction. In many cases, LV function can be salvaged by aortic valve surgery. The best type of valve replacement in this situation is uncertain.

Methods: We studied 19 patients (mean age 64 ± 14 years, 16 males) with significant AS and impaired LV systolic function (fractional shortening < 25%), as assessed by trans-thoracic Doppler echocardiography. No patient had other valvular disease or significant coronary artery disease. Patients were studied pre-operatively and 5 days post-operatively. Patients were divided according to valve received into: Group I – 10 patients receiving a stentless valve and Group II – 9 who had a stented valve.

Results: Before surgery peak aortic gradient was 72 ± 19 mmHg in group I and 67 ± 14 mmHg in group II. Post-operatively, peak aortic gradient was 12 ± 6 mmHg in group I and 38 ± 10 mmHg in group II ($p < 0.001$). Pre-operative LV free wall excursion, peak shortening (SR) and lengthening (LR) rates were not significantly different between the 2 groups. All pre-operative values were lower than values from 21 normals ($p < 0.001$). (See table). Relative to Group II, the increase in LV free wall excursion was 0.2 cm greater in Group I (95% confidence interval −0.2 to 0.7). Increases in peak SR and LR rates were also greater, 1.3 cm/s (−1.7 to 4.3) and 0.9 cm/s (−1.5 to 3.2) respectively.

	Normal Group	Group I (n = 9)		Group II (n = 10)	
		Pre-op	Post-op	Pre-op	Post-op
Excursion (cm)	1.5 ± 0.25	0.8 ± 0.3	1.1 ± 0.4	1.0 ± 0.4	1.0 ± 0.3
SR (cm/s)	8 ± 1.5	3.9 ± 1.6	6.1 ± 2.2	4.5 ± 1.5	5.7 ± 2.4
LR (cm/s)	10 ± 2.5	3.6 ± 2.7	4.9 ± 1.4	3.9 ± 1.4	4.9 ± 1.5

Conclusion: In this small sample of patients, there was a greater early improvement in LV systolic and diastolic function in those receiving stentless valves compared to those receiving stented valves. In patients with poor LV function and AS, this improvement may be clinically important.

P3618 Myocardial velocity gradient as an indicator of regional myocardial contraction after cardiac surgery: a study with tissue Doppler imaging

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Background: It is common finding that ventricular septum (VS) after cardiac surgery indicates a systolic abnormal motion in the M-mode echocardiogram. Recently, it has been reported that the myocardial velocity gradient (MVG) obtained from tissue Doppler imaging (TDI) is useful as a noninvasive index in evaluating myocardial thickening or thinning. We evaluated the systolic MVG in the VS in patients after cardiac surgery.

Methods: We recorded the left ventricular (LV) M-mode color-coded TDI in 20 postoperative patients who showed a systolic abnormal ventricular septal motion in the M-mode echogram and 10 normal controls. There was no evidence of clinically significant abnormal findings following the cardiac surgery in all patients. The myocardial velocity profile in the VS and posterior wall was extracted during a cardiac cycle, and the MVG was measured as the slope of the regression line for each velocity profile across the myocardium.

Results: There was no significant difference in LV ejection fraction determind from the 2-dimentional echocardiogram between the patient and normal groups (60 ± 12 vs $62 \pm 8\%$). The systolic peak MVG derived from the posterior wall showed no significant difference between the two groups (3.0 ± 0.7 vs 3.2 ± 0.9 cm/s/cm). The systolic peak MVG derived from the VS also showed no significant difference between the two groups (1.9 ± 0.7 vs 2.2 ± 0.5 cm/s/cm).

Conclusions: The systolic thickening in the VS is preserved in patients after cardiac surgery despite the abnormal motion in the M-mode echocardiogram. The MVG is a clinically feasible index in evaluating the regional myocardial contraction, which is hardly affected by the translation of the heart.

P3619 Evaluation of myocardial Doppler imaging in the detection of bypass tracts in Wolff-Parkinson White syndrome

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Myocardial Doppler Imaging (MDI) provides a new sensitive technique for detecting wall motion and may be useful in characterising the ventricular contraction sequence. In Wolff-Parkinson White (WPW) syndrome there is abnormal premature activation of the ventricles in sinus rhythm and using MDI it should be possible to localise the antegrade conducting bypass tract. Algorithms exist to predict the site of overt bypass tracts from the surface ECG (sECG) but are less useful when pre-excitation is minimal. This study was conducted to evaluate whether MDI could add to non invasive mapping of bypass tracts. The pattern of ventricular activation was studied using MDI in 13 patients with WPW and 35 normal controls to identify the onset and sequence of contraction. The sECGs of the WPW group were analysed to predict the position of the pathway. There was a significant difference in the time interval from onset of atrial depolarisation to earliest onset of ventricular contraction between the WPW group and controls (159 ms vs 210 ms, $p < 0.05$). The sequence of contraction also differed in WPW compared to the controls. In the WPW group, the sECG identified 8 left sided pathways. There was close correlation with MDI data in 2 cases. In a further 5 cases MDI identified a region of myocardium adjacent to the location of the pathway as predicted by the sECG. No correlation was observed in 1 case. The sECG identified 5 right sided pathways and in 4 of these cases the RV was observed to contract prior to the LV. However, precise location of the region within the RV to contract was not possible. In 1 case the LV myocardium, adjacent to the RV insertion contracted first. In WPW, MDI demonstrates early, abnormal activation of ventricular myocardium. Left sided pathways can be predicted more reliably than right sided pathways due to the oblique echocardiographic plane obtained through the RV. However, at present, the predictive accuracy of algorithms to locate bypass tracts from sECGs appears more consistent and accurate than MDI.

MYOCARDIAL CONTRAST ECHOCARDIOGRAPHY

P3620 The influence of parallel beamforming on radio frequency signals – clinical implications

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Introduction: Tissue characterization (TC) based on processing radio frequency (RF) data has been investigated by extracting parameters such as integrated backscatter (IB) and its cyclic variation (CV) and by defining statistics of the amplitude distribution of these signals. Recent data has shown that IB is not a simple sinusoidal curve but has multiple reproducable peaks and troughs thoughout the cardiac cycle. This requires data acquisition at frame rates over 100 Hz. This can be achieved by parallel beamforming. However, as this implies different processing of the received signals, the beamforming itself could influence extracted parameters. Our aims were to study the influence of parallel beamforming on the properties of the radio frequency signals.

Methods: A computer simulation environment was used to calculate B-scan images (40 lines, 30 degrees scan angle) of 30 independent, homogeneous, scattering regions (3 cm × 3 cm) with scatterer density of 20, 40 or 80 scatterers/mm^2, imaged with a dynamically focused phased array transducer (64 crystals). The emitted pulse was Gaussian and had a mean frequency of 3.5 MHz and a 100% bandwidth. Each image was calculated 3 times using 1, 2 and 4 parallel beamformers in receive. IB values, skewness and kurtosis of the resulting RF data were calculated within a region of interest of 1 cm × 1 cm. IB values were expressed on a dB-scale using the maximal reflected energy occurring as a reference.

Results: Absolute IB values decreased with increasing number of parallel beams (cf. table). However, this increase was independent of the scatterer concentration. Skewness and kurtosis of the amplitude distribution of the RF signals did not change significantly.

Mean IB values

	1	2	4
20/mm^2	-6.3 ± 0.6	-6.7 ± 0.6	-7.9 ± 0.6
40/mm^2	-3.4 ± 0.6	-3.9 ± 0.5	-4.8 ± 0.8
80/mm^2	-0.5 ± 0.3	-0.9 ± 0.3	-2.2 ± 0.2

Measured IB value (dB) as function of number of parallel beams (columns) and scatterer concentration (rows)

Conclusion: Since absolute IB levels cannot be defined in the clinical setting and have a large intrinsic variability and since changing scattering densities may be an appropriate model for CV, this study shows that parallel beamforming should not influence the measures extracted from RF for TC.

P3621 Experimental studies on an isolated pig heart model: assessment of absolute myocardial blood flow with myocardial contrast echocardiography

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Backround: The measurement of absolute myocardial blood flow (MBF), i.e. in ml/min/g, has gained increasing importance in the evaluation of patients with coronary artery disease. It has been suggested that contrast echocardiography (MCE) can be used to assess changes in myocardial perfusion.

Methods: 5 isolated pig hearts were perfused with a nonrecirculating Krebs-Henseleit solution mixed with blood, containing 15 mM KCl to provoke cardiac arrest. To obtain a reasonable linear relation between bubble concentration and myocardial videointensity, an optimal concentration was defined. 0.01 mg of Levovist® (Schering SA), a saccharide echo contrast agent, was injected as a bolus into the perfusion line through a mixing chamber placed just upstream from coronary arteries cannula. The hearts were imaged in the short-axis with a phased array transducer emitting at a mean frequency of 1.8 MHz and receiving at a mean frequency of 3.6 MHz (second harmonic). Ultrasounds were transmitted once every second (intermittent imaging). Echocardiographic imaging were analysed off line with a videodensitometry software (Sonos 5500, Hewlett Packard Corp). The time-intensity curves from myocardial regions of interest were fitted to a gamma-variate function.

Results: The hearts were studied at different MBF from 0.4 to 3.50 ml/min/g. Excellent correlations were found between myocardial peak videointensity (PMVI), initial slope of the curve, inverse of mean transit time (1/MTT), time to peak contrast effect (TP) and MBF.

	PMVI	Slope	1/MTT	TP
r value	0.92	0.92	0.87	−0.84
p value	<0.0001	<0.0001	<0.0001	<0.0001

Conclusion: Our results suggest that when echocardiographic contrast agent is injected selectively into main coronary arteries, it might be possible to quantify MBF from time-intensity curves.

P3622 Ventricular and supraventricular premature beats induced by contrast echocardiography in an animal model

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In a phase I ultrasound contrast study in healthy human volunteers, the occurrence of ventricular premature beats (VPB) was observed during end-systolic triggered imaging with high ultrasound output. To study this effect in detail, an animal model was developed.

Methods: Rabbits of 2.5–3.5 kg developed heart failure after a traumatic aortic regurgitation via a catheter was created and the abdominal aorta was partially ligated. Control rabbits did not undergo surgery. Rabbits were anaesthetized and received an intravenous infusion with an ultrasound contrast agent (AIP101, Andaris, Nottingham, UK) at 12 ml/hr in a 1:5 dilution. Before the start of the infusion baseline imaging was done using an ATL HDI 3000 with second harmonic imaging (2.7–5.4 Mhz), at an MI of 1.6, imaging depth of 5.4 cm, and focus 5 cm. Triggering was done end-systole, either every heart cycle, 1:5, and 1:10 heart cycles. During contrast infusion images were made using the same protocol. A one lead ECG was registered on the videotape of the ultrasound machine.

Results: No spontaneous VPBs or SVPBs were registered during baseline. It was possible to induce both VPBs and SVPBs, occurring directly after the trigger pulse that indicated the end of a 2D-sector sweep. With 1:10 triggering, the maximum VPB rate obtained for every trigger was 90% in heart failure rabbits. With 1:5 triggering it was 75%, while with 1:1 triggering the maximum was 7%. In control rabbits, the maximum VPB rate was 42%. The maximum SVPB was 100% with 1:10 triggering.

Conclusion: VPBs and SVPBs can be induced in a rabbit model with ultrasound and an intravenous ultrasound contrast agent, when using a high MI, and end-systolic triggering. The failing heart is more susceptible then the normal rabbit heart. A long trigger interval is necessary to allow refill of the myocardium with contrast.

P3623 Improvement of microbubbles detection using NC100100 combined with harmonic power imaging

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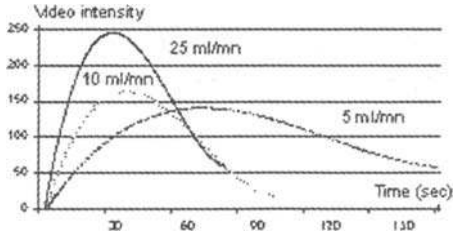
NC100100 is a new echocardiographic contrast agent based on a perfluorocarbon emulsion. Harmonic Power Imaging (HPI) has been developed from the Power Doppler technology to increase the stimulated acoustic emission (SAE) which allows high detection of first generation contrast agents. We sought to improve NC100100 detection by the HPI technique inducing a SAE phenomenon. Then, we assessed the effect of flow rate variations on microbubble HPI signals.

Methods: A phantom mimicking myocardial tissue was perfused by saline solution with a constant flow rate. NC100100 was injected by bolus of 0.05 ml. Echocardiography was performed with an HDI3000 system (ATLÒ) equipped with a P3-2 probe. First, the images were acquired in both triggered harmonic imaging and HPI mode for off line videodensitometry analysis and pixel intensities (PI) were compared between the two modalities. Second, flow rate variations (range: 5–20 ml/min) were assessed in terms of PI.

Results: Before NC100100 injection, the mean PI was 22 ± 1.5 with harmonic imaging and 29 ± 0.7 with HPI. The Peak PI was significantly higher in the two modes after the injection of NC100100 but dramatically much more with HPI mode than with harmonic imaging (215 ± 15 vs 55 ± 15, $p < 0.001$). In HPI mode, the peak PI significantly changed depending on the flow rate variations (146 ± 13, 159 ± 21, 248 ± 19) (figure).



HPI NC100100.

Conclusion: HPI mode provides a substantially more sensitive NC100100 detection compared with harmonic imaging. Moreover, the contrast HPI signal is significantly modulated by flow rate variations.

P3624 How does respiration interfere with measuring myocardial signal intensity during contrast studies?

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Background: Quantification of myocardial perfusion by means of contrast echocardiography is usually based on measurements of myocardial signal intensity (SI) changes. Since those changes may be very small, this study was designed to determine the influence of breathing on the quantitative assessment of contrast effects.

Methods: We acquired ECG-triggered images from an apical four chamber view in 10 healthy volunteers before and during continuous infusion of Levovist® (400 mg/ml, mean infusion rate 100 ml/h) using a HP Sonos 5500 ultrasound system (1.8 MHz, AD Contrast Mode). At least 10 frames were recorded each in apnoea, with intermittent breathing just after the ECG-trigger and with spontaneous breathing. Mid- and endsystolic as well as mid- and enddiastolic ECG-trigger points were used. A total of 1200 myocardial segments was analysed with the HP Acoustic Densitometry software package. In each setting, standard deviation (SD) of the mean SI was used as a measure of the signal variation.

Results: Independent of the selected trigger point, myocardial SI significantly increased with the infusion of contrast by 1.9 ± 2.5 dB ($p < 0.01$). The maximal contrast effect was measured in the septal and lateral apex (2.88 ± 2.1 dB and 3.47 ± 2.7 dB, $p < 0.01$). In the basal lateral wall, however, SI slightly decreased due to attenuation artefacts (−0.67 ± 2.1 dB, n.s.). SD of the mean SI was lowest at apnoea (± 0.49 dB) and not significantly different from SD at intermittent breathing (± 0.58 dB). With uncontrolled breathing, however, SD raised to ± 0.78 dB ($p < 0.001$).

Conclusion: Spontaneous breathing during myocardial contrast studies causes SI changes of more than 40% of the expected contrast effect and may mask this effect completely. The acquisition of images in apnoea or – for longer acquisition periods – with intermittent breathing reduces this source of variance significantly. We therefore conclude that the control of respiration is essential during myocardial contrast studies.

P3625 Incidence of artifacts during myocardial contrast echo and nuclear scintigraphy during dobutamine stress echocardiography

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NC 100100 (Nycomed) is a new gas filled contrast agent with the ability of myocardial opacification.

Methods: In this study we compared MIBI SPECT to myocardial contrast echocardiography (MCE) in 20 patients (mean age 63.4 ± 14.6) years with a positive (within six months) coronary angiogram who underwent dobutamine stress echocardiography (DSE). Imaging was performed with an ATL HDI 5000 using only harmonic (H) mode at progressive ECG trigger intervals from 1:1 to 1:6. All patients at peak stress had a MIBI SPECT injection, followed by a resting injection 24 h later. NC100100 was also injected at rest and peak stress at the dose of 0.03 ml/kg in the Ap 4–2 ch and parasternal LAX and SAX views. Images were stored and analyzed in digital format.

Results: MCE correctly diagnosed perfusion defects in at least one of the coronary artery territories involved in 14 out of 20 (70%) patients. Artifacts were seen in 5 patients, involved the lateral wall in both Ap4ch and SAX views and in the inferior walls and were due to rib attenuation and lateral anisotropism. Nuclear scintigraphy correctly diagnosed 15 perfusion defects and showed artifacts involving the anterior wall in 3 patients that were considered as motion artifacts and in the inferior wall in 4 patients that were considered as attenuation from the gut or liver and in one case maybe due to breast apposition.

Conclusion: Artifacts which can mimic perfusion defects can occur with both MCE and SPECT due to a variety of reasons. To avoid false positive results with MCE it is essential to understand these artifacts as nuclear scintigraphy does.

P3626 The effect of optison on sensitivity and specificity of dobutamine contrast echocardiography in technically difficult patients

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Optison, a recently approved echo contrast (C), improves endocardial visualization during Dobutamine Stress Echocardiography (DSE); whether this improvement leads to improvement in sensitivity and specificity of DSE is not well known. Therefore we studied total of 204 patients; 92 with technically difficult studies underwent intravenous contrast adminitration during DSE were compared with 112 patients without contrast. All patients (pts) underwent coronary angiography. Color coded perfusion analysis, regional wall thickening, and percentage of endocardial border visualization (EBV) were performed off-line There were no differences between the groups with respect to age sex, history of myocardial infarction (MI), resting wall motion abnormalities (RWMA) and stenosis severity, extent and location. In the group of DSE with contrast, EBV improved from 52 ± 8% to 87 ± 7% after contrast injection.

	Age	Male%	3 vessel	Hx/MI	LAD	RWMA
DSE with C	62 ± 8	54	40%	42%	59%	59%
DSE without C	60 ± 9	58	38%	40%	64%	54%
p	NS	NS	NS	NS	NS	NS

Sensitivity of DSE for detecting coronary artery disease ≥70% was significantly higher with Optison with additive information obtained from quantitative perfusion and wall thickening analysis performed (65% versus 89%, p = 0.01). Likewise, specificity was significantly improved with echo contrast (72% vs 91%, p = 0.01)

In conclusion, Optison administration during DSE combined with perfusion analysis in technically difficult studies leads to improved sensitivity and specificity as compared to pts with good quality non contrast images.

P3627 Venous myocardial contrast echocardiography can guide clinical decision making in the cardiac catheterization laboratory

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In the experimental setting, venous myocardial contrast echocardiography (VMCE) combined with pharmacological stress has been demonstrated to detect myocardial blood flow mismatch in the presence of coronary stenosis. We therefore hypothesized that, similar to nuclear cardiac imaging, the functional relevance of a coronary stenosis can be detected in patients by VMCE during pharmacological stress.

In 50 patients, coronary stenoses on cardiac catheterisation were considered of uncertain functional relevance. As clinical routine, these patients were subsequently sent for TC 99 m Sestamibi SPECT imaging (SI) at rest and with exercise to determine the need for PTCA in case of stress induced hypoperfusion. Before nuclear imaging, VMCE (continuous infusion of 8 g (300 mg/ml) of Levovist at 200 ml/h) at rest and with pharmacological stress (140 μg adenosine/kg for 5 min) was performed in the 4- and 2-chamber views (5 segments each). Each segment was scored as normal or abnormal for VMCE and SI by two observers blinded to the results of the other method. On SI, 19 patients (68/600 segments) showed abnormal perfusion at rest and deterioration of perfusion with stress was noted in 33 patients (80/600 segments). There was excellent concordance with the findings of VMCE for normal perfusion, reversible and irreversible hypoperfusion for the patient (88%, k = 0.82) and segmental (82%, k = 0.78) comparison. Intra- and interobserver concordance for VMCE was 92% (k = 0.82) and 88% (k = 0.78) respectively. In the 33 patients with positive SI, PTCA of the vessel showing stress induced hypoperfusion was performed.

We therefore conclude, that VMCE is a promising clinical tool for the evaluation of the functional relevance of coronary stenoses. Its impact on the decision between treatment options for coronary lesions can be similar to SI.

P3628 Automatic LV volume and ejection fraction by contrast harmonic color Doppler imaging compared to radionuclide ventriculography

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Background: Radionuclide ventriculography (MUGA) is a gold standard for measuring LVEF because it is accurate and machine interpreted. Echo LVEF measurements are subjected to variability in image acquisition, interpretation and to the limitations of 2D vs. 3D imaging.

Methods: The LV end diastolic (ED) volume (VOL), end systolic (ES) VOL and LVEF were determined by contrast harmonic color Doppler (CHCD) to MUGA in 35 patients. CHCD 3D VOLs were machine derived from Simpson's rule and an automatic edge detection algorithm that averages the 2D VOL from 3 apical views. The CHCD data was compared to MUGA using linear regression and Bland-Altman analysis.

Results: CHCD produced images with vivid endocardial definition in all patients regardless of precontrast image quality (9% inadequate contrast harmonic 2D) and the exams were completed in less than 3 min. The MUGA LVEF range was 9 to 70% and the MUGA LV VOL ranges from 55 to 320 ml and 20 to 249 ml at ED and ES, respectively. CHCD LVEF showed excellent correlation with MUGA LVEF (regression slope 1.004, R2 = 0.973), as did LV VOL (ED slope 1.17, R2 = 0.92 and ES slope 0.12, R2 = 0.912).

Conclusions: CHCD accurately measures LV VOL and LVEF using machine detected LV borders. Vivid endocardial delineation is seen even in cases that are technically difficult.

P3629 Echo contrast lung transit time: a sensitive new parameter for left ventricular dysfunction

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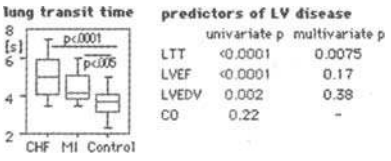
Detection and follow-up of left ventricular (LV) dysfunction are important indications for echocardiography. The limited accuracy of echo for systolic LV function, the difficulties of assessing diastolic function, and the subjectivity of the assessment make this task difficult.

Hypothesis: We hypothesized that forward LV failure (increased circulation time) as well as backward failure (increased lung blood pool) prolong the lung transit time (LTT) of echo contrast agents, and that therefore the LTT could serve as a useful quantitative parameter for LV function assessment.

Method: In 74 patients (23 with heart failure [CHF], 20 after infarction [MI] but without CHF, 31 controls), LTT from the right ventricular outflow tract to the left atrium was measured after IV injection of the fluorocarbon echo contrast agent Nycomed NC100100 (0.03 μL/kg). Enddiastolic LV volume (EDV), ejection fraction (EF), and cardiac output (CO) were measured using the biplane method of disks with contrast enhanced endocardial delineation.

Results: LTT was significantly prolonged in LV disease (CHF or MI; figure) compared to controls. In comparison with LVEF, LVEDV and CO, LTT was a stronger and independent predictor of LV disease by univariate and multivariate analysis (table). LTT was inversely correlated with LVEF (p < 0.0001, r = 0.45).



predictors of LV disease	univariate p	multivariate p
LTT	<0.0001	0.0075
LVEF	<0.0001	0.17
LVEDV	0.002	0.38
CO	0.22	-

Lung transit time.

Conclusion: Determination of the echo contrast lung transit time, a novel quantitative application of contrast echocardiography, proved highly valuable in assessing left heart disease and compared favorably with conventional noninvasive parameters. This parameter is rapidly available at bedside and promises improved objective evaluation of LV function.

STRESS ECHOCARDIOGRAPHY – MISCELLANEOUS

P3630 International "Stress Echo Horror Poll" registry: "ad interim" results on 47,858 examinations

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Background: The safety of any test is a major issue in deciding its practicability and cost-effectiveness – yet, many major complications remain transparent to published literature, due to the "file drawer" bias, lack of time ("busy agenda bias") or unfamiliarity with the technicalities of scientific communication.

Aim and Methods: To evaluate the safety of various stress echo modalities in the "real life" an international "Stress Echo Horror Poll" registry was started. Up to January 1999, 33 echo laboratories have reported about 47,858 examinations.

Results: Exercise was used in 13,885, dobutamine in 20,280, dipyridamole in 13,693 cases. Life threatening events occurred in 30 patients: during exercise in 1 patient (event rate: 1/13,885), during dobutamine infusion (low dose for viability or high dose for ischemia) in 20 patients (event rate: 1/1,014) and during dipyridamole stress test in 9 patients (event rate: 1/1,521). Of the 30 patients with complications, 2 died during dobutamine stress test (ventricular fibrillation and cardiac rupture) and 1 following a dipyridamole test (hypotension).

In conclusion, dreadful complications may occur during exercise and, to a greater extent, during pharmacological stress echo. Stress echo should always be performed with an attending physician, with know-how and facilities for basic and advanced life support.

P3631 Safety of ergotaminergic pharmacological stress echocardiography for vasospasm testing in the echo lab: 15 years experience on 543 tests in 529 patients

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The safety of pharmacological stress testing for coronary vasospasm when performed outside the cath lab has been vigorously questioned. Aim of the study was to assess the safety of ergonovine/ergometrine stress testing performed in the echo lab. To this purpose, we retrospectively reviewed the data prospectively collected in the echo lab of the Institute of Clinical Physiology from January 1, 1985 up to December 31, 1998 on 543 tests performed by either ergonovine (n = 250) or ergometrine (n = 293) stress echo testing on 529 patients with history of chest pain, consistent with vasospastic angina. Ergonovine or ergometrine maleate was injected up to a total cumulative dosage of 0.35 mg. Interpretable echocardiograms were obtained in all patients during stress. Transient regional myocardial dysfunction occurred in 76 patients (14%). Limiting ischemia-independent minor side effects were present in 16 patients (3%). The overall feasibility was 97%. One patient had non-sustained ventricular tachycardia associated with transient ST segment elevation 30 minutes after the test. Two patients had second degree AV block associated with positive echocardiography test and promptly reversed by nitrates administration. Pharmacological stress echocardiography with either ergonovine or ergometrine is technically simple, highly feasible and can be safely performed in echo lab in properly selected patients in whom coronary vasospasm is suspected.

P3632 Is transesophageal echocardiography a viable option in the stress echo lab? The Pisa experience

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In order to assess the practical domain of application of transesophageal echocardiography (TEE) in the busy reality of a large volume stress echo lab, the Pisa stress echo lab experience from January 1994 to January 1999 was retrospectively reviewed. A total of 2630 transthoracic stress echo studies were performed. Additional 173 stress TEE studies (6.5% of the total stress echo load) were requested for one of the following indications: 1) poor transthoracic acoustic window (n = 26); 2) ambiguous transthoracic stress echo results (n = 10); mapping of mitral insufficiency during low dose dobutamine prior to coronary artery bypass surgery (n = 7); 4) coronary flow reserve assessment in patients with normal coronary arteries and suspected microvascular disease or with left anterior descending coronary stenosis of intermediate severity (n = 135). The total stress time (from preparation to report) was consistently <30 min. In 3 cases the TEE was interrupted for intolerance. In the remaining 170 patients, interpretable images were obtained, yielding an overall feasibility of 98%. TEE stress echo was withheld in 2 cases, in which resting TEE documented a severe left main stenosis – subsequently confirmed by angiography. In 168 patients, pharmacological stress TEE was completed with dobutamine up to 40 mcg/kg/min (n = 21), dipyridamole up to 0.84 mg/kg (n = 76), or adenosine up to 0.14 mg/kg/min for 5 min (n = 71).

In conclusion, stress TEE is a feasible and effective option for versatile assessment of anatomic disease, wall motion abnormalities, functional evaluation of mitral valve and coronary flow reserve. The TEE allows to vanquish acoustically hostile transthoracic windows and flow reserve assessment help to document noninvasively a coronary microvascular disease. Identification of severe left main stenosis in resting TEE is an additional built-in safeguard against contraindicated stress testing.

P3633 Post-stress echo ischaemia in patients with coronary artery disease

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Pharmacological stress echocardiography (SE) has become an important diagnostic tool and/or a follow up study in patients (pts) with coronary artery disease (CAD) because of its feasibility, diagnostic impact and safety. The stress test is interrupted after the appearence of a new wall motion abnormality (WMA) and/or worsening of the baseline WMA. After the interruption of dobutamine or dipyridamole infusion and administration of the antidote, the examination is usually considered terminated. However, we observed in some patients appearence of a new WMA *after* the interruption of the examination and administration of the antidote. We studied the features of patients with this rare phenomenon of post stress-echo ischemia (PSI).

Patients and methods: *SE:* in the period from 1997 to 1999, we performed 794 SE (399 dobutamine-atropine echo test = DOBET, 360 dipyridamole-atropine echo test = DIPET, 35 ergonovine echo test). PSI (i.e. a new WMA or worsening of the baseline WMA 3 to 7 minutes *after* the interruption of the test and administration of antidote – beta blockers, nitrates or aminophilline) was observed in 13 pts: in 12 pts after DOBET (1.5%) and in one pt after DIPET (0.1%). In 9 pts SE was performed as a follow up procedure after the previous PTCA, in 4 pts it was performed before the first (diagnostic) angiography.

ECG during SE: significant changes of the ST segment (≥1 mm) were observed in all pts.

Exercise test: all pts had a positive bicycle exercise test.

Coronary angiography: a) *Diagnostic angiography:* the 4 pts (30.7%) had no significant coronary lesions; b) *control (6 monthes post PTCA) angiography:* 2 pts (15.4%) had no significant intraluminal proliferation and no new lesions, 4 pts (30.8%) had an intraluminal proliferation of the stent or worsening of the coronary stenosis; in 3 pts (23%) no control coronary angiography was performed after the PTCA.

Discussion and conclusions: PSI is a rare phenomenon (only 1.6% of SE), observed almost only after DOBET; it is more frequent in pts with previous PTCA + stent (69% pts); it can be a sign of a severe endoluminal proliferation, but is present also in pts with a good post-PTCA result or without angiographically significant lesions. Although the pathophysiological mechanism is not clear, PSI is probably due to vasospastic effect of dobutamine on damaged and/or previously treated coronary arteries. This study indicates the importance of continuous monitoring of pts' symptoms, ECG and wall motion also after the SE for at least 10 minutes.

P3634 The value of QTC interval increase during dipyridamole stress echocardiography in predicting restenosis after percutaneous transluminal coronary angioplasty

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The aim of our study was to estimate whether provoked myocardial ischaemia during dipyridamole stress echocardiography (DIP-test) causes QTc interval increase in ECG leads: II, V2, V5 and if QTc changes increase sensitivity and specificity of the DIP-test.

Methods: 50 pts(19 women, 31 men) who previously underwent PTCA with recurrent angina: CCS class II – 18 (36%), class III – 29(58%), class IV – 3 (6%). Mean time from PTCA was 12.7 SD = 13.0 mth. DIP-test and elective angiography were performed in all pts. The following parameters: heart rate (HR), ejection fraction (EF), systolic volume (SV) and wall motion score index (WMSI) were measured during TTE at baseline, after the first dose of dipyridamole (0.56 mg/kg/4 min/, after the second dose of dipyridamole (0.28 mg/kg/2 min) and 6 min after termination of drug infusion. QTc intervals increase (at least 40 ms) were measured in leads II, V2, V5 during DIP-test at baseline and after the second dose of dipyridamole. DIP-test was regarded as positive in case of WMSI increase during the test.

Results: QTc increases in lead V5 were the most significant. Among 39 pts with restenosis confirmed by angiography, QTc increase was observed in 33 pts ($p < 0.05$), and positive DIP-test in 27 pts. In 11 pts without restenosis 4 pts had QTc increase and 7 pts had positive DIP-test. In pts without restenosis QTc interval in lead V5 was increased only in subgroup with positive DIP-test ($p < 0.05$), compared with subgroup with negative DIP-test ($p = 0.99$). Combined analysis of QTc increase and positive DIP-test improved the sensitivity from 75% to 89% without changing specificity: 41% vs 42%. Positive predictive value of the combined test was 89% and negative predictive value was 54%.

Conclusion: QTc interval prolongation in lead V5 during dipyridamole stress echocardiography increases DIP-test sensitivity. We suggest that QTc interval prolongation in lead V5 should be considered as an additional marker of the presence of restenosis.

P3635 Dipyridamole induced QTc shortening in Q-wave leads predicts subocclusion of the infarct-related artery early after an acute myocardial infarction

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Background: At the moment we are not aware of simple noninvasive tests useful in predicting the impaired patency of the infarct related artery.

Purpose: to assess whether an unconventional, but extensively validated, ECG marker of transmural ischemia, i.e. the stress induced shortening of QTc interval, may identify patients (pts) with residual severe stenoses in the infarct related artery.

Methods: 109 consecutive pts (85 men, mean age 61 ± 11 years) underwent dipyridamole echocardiography test (DET) and subsequent coronary angiography within 2 weeks after Q-wave myocardial infarction. Dipyridamole was chosen as "stressor", because the appearance of transmural ischemia (and therefore QTc shortening) during DET needs a horizontal steal, in a collateral dependent myocardial region. The drug was infused up to 0.84 mg/kg over 10 min. The QTc interval was measured at rest and at peak stress, lead by lead, in leads showing ST-segment shift and the fractional difference percentage between the QTc intervals (ΔQTc) was calculated. ECG tracings were analyzed by 2 observers unaware of angiographic results.

Results: On the basis of angiographic findings, 2 groups were identified: pts with infarct related artery stenosis ≥ 95% (group I; n = 53) and with infarct related artery stenosis < 95% (group II,n = 56). The 2 groups were similar for rest WMSI (1.48 ± 0.26 vs 1.45 ± 0.27, P = n.s.) and chest pain during stress (6/53 vs 7/56, i.e. 11.3% vs 12.5%, P = n.s.). A significant difference between group I and II was observed regarding the mean max. ST-segment shift during stress (1.56 ± 1.05 vs 0.57 ± 0.9 mm, P < 0.0001) and the mean peak dipyridamole WMSI (1.86 ± 0.27 vs 1.69 ± 0.30, P < 0.005). Shortening of QTc interval occurred in 52/53 (98%) pts of group I, and in 5/56 (9%) pts of group II; mean ΔQTc group I = –20.6 ± 10% vs mean ΔQTc group II = +0.03 ± 5.7% (P < 0.0001).

Conclusion: Early after an acute myocardial infarction a significant ΔQTc shortening, measured in the infarct related leads, showing ST-segment shift during DET, is a noninvasive ECG parameter, useful in predicting a residual severe (occlusive or subocclusive) stenosis in the infarct related artery.

P3636 Low-dose adenosine stress echocardiography in detection of viable myocardium

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Background: Low-dose adenosine may recruit inotropic reserve by increasing coronary blood flow or by increasing extracellular level of adenosine.

Objective: The aim of this study was to compare evaluate the potential of low-dose adenosine (Ado) echocardiography (echo) to identify myocardial viability.

Methods: Thirty patients with resting dyssynergy, due to previous myocardial infarction, and angiographically proven coronary artery disease (diameter stenosis ≫50% of at least one major coronary artery), scheduled for coronary revascularization, underwent low-dose Ado (80, 100, 110 mcg/kg/min in 3 minutes intervals) echo test. A criterion for myocardial viability was improvement in systolic thickening of ≫1 dyssinergic segments of ≫ 1 grade. In all patients, echo follow-up was obtained after 3 months.

Results: Systolic blood pressure (rest: 142 ± 20 mmHg) decreased slightly, but nonsignificantly after low-dose Ado (134 ± 25 mmHg, p = ns vs rest), whereas diastolic blood pressure was unchanged (81 ± 8 mmHg to 82 ± 11 mmHg, p = ns). Heart rate (rest: 65 ± 7 bpm) increased significantly to 83 ± 4 bpm ($p < 0.01$) during low-dose Ado. No patient developed echo or ECG signs of ischemia during low-dose Ado. Wall motion score index (WMSI) improved significantly from rest 1.49 ± 0.33 to low-dose Ado (1.24 ± 0.28, $p < 0.01$). Of the 174 segments with baseline dyssinergy, 72 were responders, and 102 were non-responders. An improvement of one grade or more was shown in 68 segments (viable), while 106 segments showed no improvement (necrotic). Follow-up WMSI was 1.23 ± 0.30 ($p < 0.05$ vs. rest). The sensitivity of adenosine for predicting recovery was 89%, while specificity was 89%. Positive and negative predictive values were 85% and 93%, respectively.

Conclusion: Low-dose adenosine echo test is physiologic, hemodynamically neutral test, with high diagnostic value for predicting functional recovery following successful revascularization – thus providing adequate alternative to low-dose dobutamine test for evaluation of myocardial viability.

P3637 Usefulness of quantitative ultrasonic myocardial texture analysis for the prediction of myocardial contractile reserve in patients with idiopathic dilated cardiomyopathy

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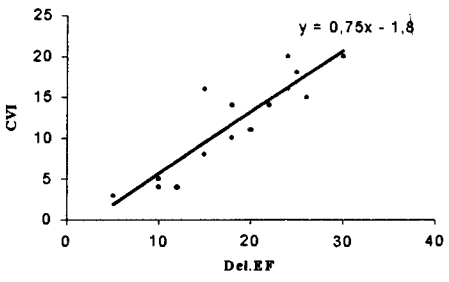
The aim of this study was to investigate the relation between videodensitometric parameters of patients with idiopathic dilated cardiomyopathy (IDC) and contractile reserve determined by low-dose dobutamine stress echocardiography (DSE). For this purpose 15 patients (mean age 42 ± 20) with IDC were enrolled in to the study. Baseline echocardiographic variables and left ventricular ejection fraction (EF) before and after 5 min. infusion of 10 mμg/kg/min dobutamine were collected. Quantitative analysis of echocardiographic digitized imaging was performed through a calibrated 256 grey level digitization system to calculate mid-septum and mid-posterior textural analysis. Systolic and diastolic Mean Grey Level (MGL) distribution of septum and posterior wall was observed and Cyclic Variation Index (CVI) was calculated according to formula: $(MGL_{diast} - MGL_{syst})/MGL_{diast} \times 100$. Baseline means of CVI obtained from septum and posterior wall were correlated to ejection fraction changes by DSE (ΔEF%) by using linear regresion analysis. The results are listed in the table and correlation between ΔEF% and CVI presented in the figure below.

	Pre-DSE values	Correlation with ΔEF%	p values
EF%	27 ± 5	0.41	NS
ESVI (ml)	124 ± 21	–0.47	NS
CVI	12 ± 6	0.89	<0.0001

NS: Not Significant



In conclusion, ultrasonic myocardial texture analysis of patients with IDC may help to predict the contractile reserve.

P3638 Value of harmonic imaging during dobutamine-atropin stress echocardiography

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Image quality exerts a major influence on the accuracy of dobutamine stress echocardiograms. This study examines the impact and value of harmonic imaging on segmental analysis of echocardiograms during dobutamine stress.

Methods: 50 consecutive DSEs according to standard protocols were performed in patients referred for the evaluation of chest pain. Digital images in cine-loop were acquired in 4-, 2-chamber views and LAX at rest and during maximal stress in fundamental (FUN; 2.0–3.5 MHz) and harmonic imaging mode (HI; 1.5–1.7/3.0–3.4 MHz). 800 segments were evaluated for left ventricular endocardial delineation and tracing (ENDO score 1–5, 5 = best imaging quality) and wall motion (WMSI score 1–4 according to ASE criteria).

Results: HI was superior to FUN in 76%, equal in 16% and inferior in 8%. The number of diagnostic segments increased from 62% (FUN) to 92% (HI). 12% of patients with non-interpretable echocardiograms during FUN became diagnostic with HI. Image quality for both FUN and HI decreased non-significantly during stress. HI increased imkage quality of especially lateral, anterior and basal-inferior segments. WMSI changed in 14% of patients.

Mean score	ENDO FUN	ENDO HI	WMSI FUN	WMSI HI
Rest	2.6 ± 0.3	3.7 ± 0.4	1.14 ± 0.09	1.11 ± 0.17
Peak stress	2.3 ± 0.2	3.3 ± 0.3	1.28 ± 0.16	1.32 ± 0.24

Conclusions: Harmonic Imaging significantly enhances image quality during DSE and increases the number of diagnostic LV segments.

P3639 Biphasic strain compression wave morphology during dobutamine stress echo relates to segment location and not ischaemia

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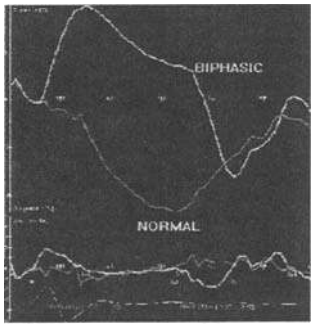
Myocardial strain is developing as an objective tool to assess regional LV function during dobutamine echo (DbE). Biphasic strain compression wave morphology (BSC) has been considered a characteristic of ischaemia, reflecting tardokinesis. We sought to examine the frequency of BSC morphology in normal vs diseased segts and address whether the phenomenon is site specific.

Methods: Digital images during DbE from 41 patients were acquired in tissue velocity image format from 3 apical views (Vingmed System FiVe) at rest, low dose dobutamine, prepeak, and peak stages. Wave morphology was examined post acquisition in 1264 base and middle myocardial segments for occurrence of BSC morphology. Comparison with wall motion scoring by an expert reader was analyzed.



Results: Biphasic morphology was identified *only* in normal basal segts (mainly anteroseptal). No abnormal basal or septal segts showed BSC;

Morphology	Abn mid LV	Norm mid LV	Abn basal LV	Norm Basal LV
Biphasic (12)	0	0	0	12
Normal (1252)	416	202	451	195

BSC expansion occurred between mitral closure and aortic opening.

Conclusion: Biphasic strain compression pattern appears unrelated to ischaemia. Possible explanations include detection of late atrial systole or generation of tension in the aortic root during isovolumic contraction.

P3640 Can off-line tissue Doppler echocardiography make dobutamine stress echocardiography objective?

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Dobutamine stress echocardiography (DSE) is now commonly used to establish the presence or severity of myocardial ischaemia, yet it relies on subjective interpretation of grey-scale images and has sub-optimal inter-observer and inter-centre reproducibility. Tissue Doppler echocardiography (TDE) may overcome these problems, since it can accurately quantify regional myocardial function.

The utility of real-time digital acquisition of TDE data with subsequent off-line quantification of spectral tissue Doppler profiles, to diagnose coronary artery disease, is being assessed prospectively in the MYDISE study (Myocardial Doppler in Stress Echocardiography). All patients undergo maximal DSE with data acquisition using the Vingmed System Five. To test the reproducibility of off-line measurements, 7 observers from 5 participating centres analysed studies from 8 patients. From apical 4- and 2-chamber (A4C, A2C) and parasternal long-axis(PLAX) loops, each observer measured peak systolic velocity V and other parameters, in two beats from all 16 segments (ASE model), at baseline, 20 ug/kg/min, and peak dose, using newly-developed software.

In A4C and A2C, V at rest was highest in basal segments and declined towards the apex; mean V was 6.7(sd 1.2), 4.6(0.9) and 3.1(1.2) cm/s in basal, mid and apical septum respectively ($p < 0.001$). The coefficient of variability for V showed a similar but opposite gradient, being 8–13% for basal segments (Table), 11–21% for mid-ventricular segments, and 15–47% for apical segments ($p < 0.05$). The reproducibility of anteroseptal segments in PLAX was very poor (104%).The reproducibility of V in basal and mid segments in patients with optimal images was <5%. At peak stress, reproducibility of V in basal segments remained good (coefficients of variability 10–18%).

Basal segment TDE data

	Septal	Lateral	Anterior	Inferior	Posterior
Peak velocity (cm/sec)	6.7	7.5	6.7	7.2	5.6
Pooled standard deviation (cm/sec)	0.6	1.0	0.9	0.6	0.6
Coefficient of variability (%)	9	13	13	8	11

We conclude that stress echocardiography with off-line quantification of regional myocardial function by tissue Doppler echocardiography is feasible, and that the best reproducibility and clinical value will be obtained by analysing basal myocardial segments on apical images.

P3641 Color kinesis-dobutamine stress echocardiography in the detection of involved coronary arteries

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To facilitate a more objective evaluation of regional left ventricular performance, Color Kinesis (CK) can be used instead of conventional methods during stress echocardiography. The present study aimed to compare the accuracy of CK-dobutamine stress echocardiography (CK-DbSE) with that of Tc-99m-MIBI SPECT scintigraphy (Db-MIBI) for the identification and localization of coronary artery disease (CAD). Twenty patients (16 males,mean age 57 ± 10) were studied at the time of coronary arteriography (CA). All completed a dobutamine (Db) stress test (5 to 40 mcg/kg/min dose increments) with the addition of atropine in 5. MIBI was injected at peak stress and images were obtained 1 to 2 hours later and compared with a resting scan. CAD was identified by worsening,unchanged or new wall motion abnormality during stress at CK-DbSE and by either fixed or reversible defects at Db-MIBI. Images were interpreted in respective departments by experienced observers blinded to all clinical data and presence of CAD which was defined as > 50% stenosis in CA. For both tests,left anterior descending (LAD), circumflex (Cx) and right coronary artery (RCA) territories were determined and findings were compared with that of CA.

Results are summarized in the table.

		Sensitivity	Specifity	Accuracy
LAD	CK-DbSE	8/9 (89%)	9/11 (82%)	85%
	Db-MIBI	8/9 (89%)	10/11 (91%)	90%
Cx	CK-DbSE	7/11 (64%)	9/9 (100%)	80%
	Db-MIBI	9/11 (82%)	7/9 (78%)	80%
RCA	CK-DbSE	9/11 (82%)	8/9 (89%)	85%
	Db-MIBI	10/11 (91%)	7/9 (78%)	85%
Total	CK-DbSE	24/31 (77%)	26/29 (90%)	83%
	Db-MIBI	27/31 (87%)	24/29 (83%)	85%

In conclusion,despite a lower sensitivity in Cx territory,CK-DbSE is as accurate as Db-MIBI for the identification and localization of CAD.

P3642 Evaluation of left ventricular regional function in stress echocardiography improves by combining anatomic M-mode with tissue second harmonic imaging. Preliminary results

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Background: Improved image quality by noncontrast harmonic imaging (HI) has been shown to reduce observer variability and increase the number of diagnostic two-dimensional (2D) examinations in dobutamine stress-echocardiography (DobSE) but interpretation of wall motion can still be difficult expecially at peak stress and in presence of subtle abnormalities. The aim of this study was to apply Anatomic M-mode (AnatMm), a new technique allowing motion and thickening of any myocardial segment to be evaluated in M-mode format, to assess segments where wall motion evaluation remains difficult or equivocal with tissue HI, particularly in the setting of DobSE.

Methods: Nine consecutive DobSE studies performed for myocardial ischemia were recorded in both fundamental (FUND) and HI modality (Octave Tissue Imaging, OTI). Four patients (pts) had a left bundle branch block. All pts underwent a nuclear stress-echo study. Two experienced observers were asked to evaluate independently all examinations, with FUND and OTI studies provided in a random sequence. After analysis of results, observers were asked to reevaluate by AnatMm the disagreement segments. Regional myocardial function was scored visually at rest and peak stress using a 1–5 scale according to the ASE 16-segments model for a total of 288 segments by each technique.

Results: The overall number of segments (rest+peak stress) considered uninterpretable (score 1) by one or both observers decreased from 5.5% (16/288) by FUND to 2.1% (6/288) by OTI ($p < 0.05$). Among the interpretable segments, interobserver disagreement decreased from 18.0% (49/272) by FUND to 11.3% (32/282) by OTI ($p < 0.01$). By applying AnatMm to this latter group (32 segments), overall observer disagreement became 4.6% (13/282) ($p < 0.01$ vs FUND). Evaluation based on AnatMm was in agreement with the nuclear examination results.

Conclusions: AnatMm reduces observer variability of DobSE particularly in segments where wall motion evaluation is difficult or equivocal even by HI. This is due to better appreciation of mild abnormalities and preserved myocardial thickening and may improve accuracy of DobSE.

P3643 In vitro validation of a new PISA method for assessing the effective regurgitant orifice area

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The present work has been designed to validate the calculation of the effective regurgitant orifice area (ERO) with the use of a new formula insensitive to any fixed error in the determination of the position of the regurgitant orifice Dr and that takes into account the velocity profile (Vr versus r) along different radius (r) of the flow convergence and the velocity at the orifice (Vo). Assuming an hemispheric model, ERO = 2p (r+Dr)2.Vr/Vo and the slope of a linear regression between Ö (Vo/Vr) and r is inversely proportional to the orifice diameter. Thus, ERO = 6.25/slope^2.This approach was tested in vitro in pulsatile conditions on circular, conical and slit-like orifices. The calculated ERO was compared with the actual jet cross sectional area derived from the transverse velocity profile at the jet origin. For the purpose of comparison the "classical" ERO was calculated for all the configurations, angulations and threshold velocities. The relationship between D(Vo/Vr) was linear (correlation > 0.98) over a wide range of velocities. The non hemispheric components were found to modify the constant and not the slope. The mean variation of the calculated ERO was 6.5%. The correlation between the calculated and the actual ERO was very close (>0.97) with slope equal to. 96. By comparison with the new method, the classical formula gave an underestimation of the ERO which dramatically increased when studying the flow closer to the orifice or in the case of error on the measurement of r.

In conclusion, a method using velocity profiles instead of isolated values improves the accuracy of the PISA method for measuring the ERO.

PROGNOSIS BY STRESS ECHOCARDIOGRAPHY

P3644 The elusive prognostic meaning of atropine addition to pharmacological stress echocardiography

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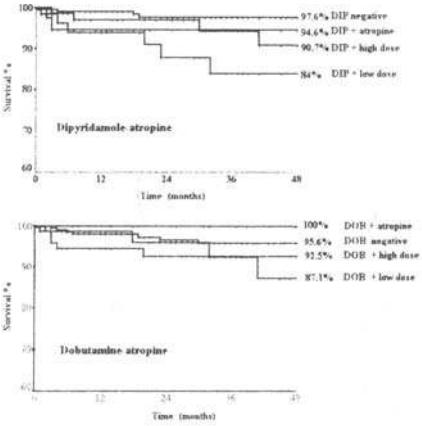
Background: Atropine coadministration increases the diagnostic accuracy both of dobutamine (DOB) and dipyridamole (DIP) stress echocardiography

Aim: To evaluate whether the addition of atropine increases the prognostic value of DIP and DOB stress echocardiography in patients with known or suspected coronary artery disease in a large scale, multicenter, observational and prospective study design.

Methods and Results: DIP (up to 0.84 mg/kg over 10′)-atropine (up to 1 mg over 4′) and DOB (up to 40 μg/kg/min)-atropine (1 mg over 4′) stress testing were performed on different days, in random order and within 15 days in 460 patients. During the follow-up (38 ± 21 months), there were 18 cardiac deaths. Survival was similar in patients with negativity and atropine-positivity



DIP + low dose vs DIP negative, $p < 0.0001$.

Conclusion: In patients at low-to-moderate risk of cardiac events, atropine addition to pharmacological stress echocardiography does not improve its prognostic value when cardiac death is considered.

P3645 Dipyridamole echocardiography test performed between third-fifth day in the uncomplicated acute myocardial infarction for early risk stratification

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Purposes: to evaluate if the dipyridamole echocardiography test(DET) performed between the 3th-5th day in the uncomplicated acute myocardial infarction(AMI) allows an early discharge in some cases or the indication of a faster coronarography in others.

Methods: in the period between febr. '97 and sept. '98 were admitted 190 patients with AMI, 138 males (72.6%), age = 59 ± 10.3 years. The DET was performed between the 3th-5th day with a dipyridamole(DIP) infusion of 0.84 mg/kg over 10′ followed by atropine 1 mg from the 12th to the 15th minute. The DET was considered positive in the presence of a new or worsening dyssynergy. Patients with heart failure, angina, mayor arrhythmias, poor acoustic window were excluded. In the follow-up events were defined as cardiac death, non-fatal myocardial reinfarction, unstable angina and revascularization procedures.

Results: 92 patients (48.4%) performed the DET, all without complications. 29 patients (31.5%) had a negative DET result; 63 patients (68.5%) a positive DET. The mean stay in hospital of the patients with a negative test was significantly lower in comparison with that of the patients with a positive test (7.55 + 1.32 days vs 9.29 + 1.61, $p < 0.0001$). Events occurred in 55 patients (59.8%), 6/29 patients with a negative DET (20.7%), 49/63 patients with a positive DET (77.8%). At the multivariate Cox analysis the DET positivity was the only independent predictor of events, with relative risk = 11.48 for heterozonal positivity ($p = 0.00001$), 2.98 for homozonal positivity after atropine ($p = 0.03$).

Conclusions: the DET between third-fifth day in the uncomplicated AMI is feasible, tolerable and safe. A negative DET allows an earlier hospital discharge with lower costs; the heterozonal positivity as well as the homozonal positivity after low and high doses of DIP, indicates a quick performance of the coronarography for the high risk of events in the follow-up.

P3646 Prognostic value of pharmacologic stress echocardiography in outpatients

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To investigate the prognostic importance of pharmacologic stress echocardiography (SE) performed in an outpatient setting, data of 1482 patients (pts) evaluated with either dipyridamole (n = 846) (up to 0.84 mg over 10′ + atropine up to 1 mg) or dobutamine (n = 636) (up to 40 mgr/kg/min+atropine up to 1 mg) SE were analyzed. A positive echocardiographic result (new or worsening of preexisting wall motion abnormality) was identified in 459 (31%) pts. During the follow-up (28 ± 24 months), there were 25 cardiac deaths, 34 infarctions and 228 coronary revascularizations. Adopting an interactive stepwise procedure, age > 70 years (OR = 2.7; 95% CI = 1.3–6.6; p = 0.0199), resting WMSI (OR = 3.0; 95% CI = 1.1–8.0; p = 0.0252) and male gender (OR = 3.2; 95% CI = 1.0–9.6; p = 0.0432) were independent predictors of cardiac death among clinical covariates; this clinical model had a global chi-square of 20.7. After the addition of SE data, SE positive result (OR = 6.2; 95% CI = 2.6–14.8; p = 0.0000) and resting WMSI (OR = 3.1; 95% CI = 1.2–7.9; p = 0.0252) were associated with cardiac death; the global chi-square at this second step increased to 46.1. The 4-year survival rate was 99% for pts with negative and 91% for pts with positive result of SE (log rank = 33.2; p = 0.0000). Considering hard cardiac events (death and infarction) as end-points, the clinical independent prognostic predictors were resting WMSI (OR = 2.2; 95% CI = 1.1–4.4; p = 0.0252), male gender (OR = 2.0; 95% CI = 1.0–3.9; p = 0.0427) and previous infarction (OR = 1.7; 95% CI = 1.0–2.9; p = 0.0650); the global chi-square of the clinical model was 22.5. In the second step, with the addition of SE findings, SE positive result (OR = 3.6; 95% CI = 2.1–6.2; p = 0.0000) and resting WMSI (OR = 2.3; 95% CI = 1.1–4.5; p = 0.0184) were independently correlated with prognosis; the global chi-square increased to 49.5. The 4-year infarction-free survival rate was 97% for pts with negative and 85% for pts with positive result of SE (log rank = 36.6; p = 0.0000).

In conclusion, pharmacologic SE has shown a strong prognostic power in pts evaluated in an ambulatory setting, incremental to that provided by clinical data.

P3647 Does the presence of multiple markers of myocardial ischaemia during dobutamine stress echocardiography identify patients at a higher risk of cardiac events during follow-up?

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Aim: To assess whether the presence of multiple markers of myocardial ischemia (I) (ECG, echo and chest pain) during dobutamine stress echocardiography (DSE) identifies pts at higher risk of cardiac events.

Methods: 265 pts with suspected or proven coronary artery disease (CAD), 91% men, aged 56 ± 9 yrs, 70% with angina, 57% with previous myocardial infarction (MI), 46% with previous PTCA or bypass, 37% with multivessel CAD, with a mean ejection fraction of 57 ± 14%, underwent DSE (5–40 mcg/kg/min + atropine) and were followed for 16 ± 15 months for major (cardiac death and MI), minor (unstable angina, PTCA or bypass at least 2 months after DSE) and total events. Criteria for a positive test were a >1 mm ST-segment shift for ECG and a new or worsening asynergy for echo.

Results: On the basis of DSE results pts were divided in 4 groups: Group (Gr) 1 (79 pts, 30%): Negative DSE; Gr 2 (71, 27%) positive DSE with 1 marker only (ECG or echo); Gr 3 (57, 21.5%): positive DSE with 2 markers (ECG and echo); Gr 4 (57, 21.5%): positive DSE with all 3 markers of I. During follow-up 17 major events (7 cardiac death and 10 re-MI) and 129 minor events (113 unstable angina, 16 PTCA or bypass) occurred. By Cox multivariate analysis ejection fraction (EF) (Hazard ratio (HR) = 0.96), diabetes mellitus (HR = 1.95), multiregional asynergy (HR = 1.22) and use of atropine during DSE (HR = 0.36) were found to be independent predictors of major events, while the presence of multiple markers of I did not increase the risk of major events. On the other hand, the presence of multiple markers of I during DSE was an independent predictors of minor and total events, together with EF (HR = 0.98), multivessel CAD (HR = 1.78) and diabetes (HR = 1.58); risk for events was higher in Gr 4 compared to Gr 2 (HR = 1.63, p < 0.04) and Gr 3 (HR = 1.50, p = 0.10), but not in Gr 3 compared to Gr 2 (HR = 1.09, p = 0.7).

Conclusions: The presence of multiple markers of I during DSE does not identify pts at a higher risk of major events, but is a significant independent predictor of minor and total events, with a risk increasing with the increasing number of markers of I detected during DSE.

P3648 T-wave positivization as a marker of higher cardiac risk in a prospective study of dobutamine stress echocardiography after acute myocardial infarction

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Aim: An increasing evidence is supporting T-wave positivization (TWP) during dobutamine stress echocardiography (DSE) after uncomplicated acute myocardial infarction (AMI) as a potential marker of myocardial viability. We focused on TWP in this setting as a predictor of cardiac events in a long-term prospective study.

Methods: Two-hundred twenty-nine patients (pts), mean (± SD) age 56 ± 9 years, 199 males, who underwent a standard DSE within 10 days after uncomplicated AMI, were selected for exhibiting negative T waves in the infarct area in at least 2 adjacent leads of resting ECG. A follow-up of 735 days (1 month-6 years) for hard: cardiac death, reinfarction, and soft cardiac events: unstable angina and coronary revascularization was completed. Cox multivariate analysis and Kaplan-Meier survival curves with log-rank test were applied.

Results: TWP appeared during DSE in 76 (33%) pts (at low dose in 69 pts). TWP agreement with DSE-elicited myocardial viability was 64%. At follow-up TWP discriminated 62% cardiac events (47 events/76 pts) in TWP pts vs 46% (70/153) in the remaining pts (p < 0.05), with a median event-free survival period: 490 days of TWP pts vs 1740 days of the remaining pts: ratio: 3.5 (95% CI 2.9–4.2). At univariate analysis basal wall motion score index (WMSI) (p < 0.01), low dose DSE WMSI: 10 μg/kg/min (p < 0.01), peak WMSI (p < 0.01), peak heart rate (HR) (p < 0.01), myocardial viability (p < 0.01) and TWP (p < 0.05) were predictors of cardiac events. Age, thrombolysis, ST shifting, dobutamine time, rest HR, rest or peak systolic or diastolic blood pressure did not reach significance. At Cox multivariate analysis TWP was no independent predictor. Rest WMSI (p < 0.05), peak WMSI (p < 0.01) and peak HR (p < 0.01) were independent predictors.

Conclusions: In case of doubtful or nondiagnostic DSE for myocardial viability, TWP can be helpful to sort pts at higher risk. TWP onset at low dose DSE and its agreement with myocardial viability may be clues to relate it to a viable substrate.

P3649 Stress echocardiography for prognostic stratification in patients with unability to exercise or uninterpretable electrocardiogram

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In aim to determine the prognostic value of stress echocardiography (SE) in patients (pts) with unability to exercise or uninterpretable electrocardiogram, data by 394 pts (149 men; age 69 ± 10 years) who underwent dipyridamole (n = 194) (up to 0.84 mg/kg over 10′ + atropine up to 1 mg) or dobutamine (n = 200) (up to 40 mgr/kg/min+atropine up to 1 mg) SE were analyzed. Of them, 318 were unable to exercise because of systemic disorders and 76 had left bundle branch block at baseline electrocardiogram or paced rhythm. SE was positive for echo criteria (new or worsening of preexisting wall motion abnormality) in 98 pts. During follow-up (34 ± 24 months), there were 14 cardiac deaths, 19 infarctions and 36 revascularizations. By using an interactive stepwise procedure, among the 9 clinical variables analyzed, resting WMSI (OR = 7.8; 95% CI = 2.4–25.8; p = 0.0008) and previous infarction (OR = 4.9; 95% CI = 1.5–16.5; p = 0.0096) were independently correlated with cardiac death; the global chi-square of this clinical model was 37.2. After the addition of SE findings, resting WMSI (OR = 14.5; 95% CI = 4.6–46.2; p = 0.0000) and SE positive result (OR = 24.6; 95% CI = 5.2–116.2; p = 0.0001) were predictive of cardiac death; at this second step the global chi-square was 68.0. The 4-year survival rate was 99% for the negative and 80% for the positive population (log rank = 39.0; p = 0.0000). When hard cardiac events (death and infarction) were taken as end-points, the clinical predictors of prognosis were resting WMSI (OR = 4.4; 95% CI = 2.0–9.8; p = 0.0002), previous infarction (OR = 3.5; 95% CI = 1.6–7.4; p = 0.0012) and age ³70 years (OR = 2.0; 95% CI = 1.0–4.3; p = 0.0557); the global chi-square was 53.6. After the addition of SE data, SE positive result (OR = 14.1; 95% CI = 6.0–32.9; p = 0.0000), resting WMSI (OR = 10.4; 95% CI = 4.5–24.1; p = 0.0000) and age ³70 years (OR = 2.2; 95% CI = 1.1–4.6; p = 0.0319) showed independent prognostic power; the global chi-square increased to 49.5. The 4-year infarction-free survival rate was 97% for the negative and 59% for the positive population (log rank = 67.8; p = 0.0000).

In conclusion, SE was effective for prognostic assessment of coronary artery disease in patients unable to exercise or with uninterpretable electrocardiogram.

EXERCISE STRESS ECHO

P3650 Harmonic imaging improves interobserver agreement and sensitivity of bicycle stress echocardiography in patients with impaired image quality

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Harmonic imaging (HI) has shown to improve image quality in patients (pts) with impaired image quality. Especially in bicycle exercise stress echocardiography (BESE) image acquisition is frequently reduced at peak stress due to hyperpnea.

Methods: To evaluate the impact of HI on sensitivity, specificity and interobserver agreement of BESE 90 pts with reduced image quality at rest (≥3 segments not visible, 16 segment model, ASE) were investigated. In all pts image acquisition was performed in fundamental imaging modality (FI) and HI during the same diagnostic procedure (Acuson, Sequoia, FI 3.5 MHz, HI 1.75 → 3.5 MHz). Images were acquired at rest and at peak stress. Examinations were separately stored on Quad-screen cine loop format BESE was performed until 85% of maximal age predicted heart rate was achieved. Interpretation of stress echos was performed independently by three stress echo experienced physicians. In all pts quantitative coronary angiography was performed.

Results: Interobserver agreement (concordant interpretation of three physicians), sensitivity and specificity were analyzed as follows:

	FI	HI	
Concordant Interpretation	65%	81%	$p < 0.02$
Kappa value	0.38	0.67	$p < 0.01$
Sensitivity	68%	87%	$p < 0.05$
Specificity	78%	80%	p = n.s.

Conclusion: HI significantly improves interobserver agreement of BESE in pts with impaired image quality at rest as well as diagnostic sensitivity. HI should therefore routinely be applicated in BESE in pts with impaired quality.

P3651 Exercise echocardiography : its accuracy and value in the prognosis of patients with known or suspected coronary artery disease

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Objectives: To determine the validity and prognostic value of exercise echocardiography in predicting the occurrence of coronary events among a cohort of patients with known or suspected coronary artery disease (CAD) followed-up within a span of 3–5 years.

Background: Exercise echocardiography had been added to the diagnostic tests used to detect CAD. While many studies have been published showing its superior capability in detecting CAD, only few show its potential in predicting coronary events.

Methods: Patients >44 years with known or suspected CAD seen at the National Kidney and Transplant Institute underwent exercise echocardiography and were followed-up regularly on an outpatient basis. Coronary events were recorded. Validity of the test in relation to coronary events was determined. Cox regression analysis was used to assess variables for prognostic significance.

Results: Of the 356 patients, 18 were lost to follow-up. There were 52 (15%) patients who developed coronary events. Forty three had spontaneous coronary event and 9 underwent revascularization. When patients without ischemia on exercise echocardiography but with submaximal exercise were excluded, sensitivity was 95% and specificity was 94%. Of the clinical and exercise test variables, male sex (relative risk [RR] = 3.2446; 95% confidence interval [CI] = 1.6506–6.3780), METs < 6 (RR = 2.1839; 95% CI = 1.1668–4.0874), age-predicted maximal heart rate < 85% (RR = 2.8893; 95% CI = 1.4304–5.8361), a decrease of one unit peak double product (RR = 1.0001; 95% CI = 1.00004–1.0002), and ST depression (RR = 1.8825; 95% CI = 1.0002–3.5431) were shown to be associated with increased risk for coronary event. However, the presence of ischemia on exercise echocardiography (RR = 14.7730; 95% CI = 7.0421–30.9912) was shown to be highly significant for the prediction of coronary event, and its presence made all other previously significant variables irrelevant.

Conclusion: The presence of ischemia on exercise echocardiography is sensitive and specific for subsequent coronary event. This study shows that exercise echocardiography has a prognostic value in patients with known or suspected CAD.

P3652 Labil subaortic obstruction during exercise stress echocardiography

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Although the development of subaortic obstruction (SO) has beeen extensively reported during dobutamine stress testing, it's appearance during physical dynamic exercise has not been equally studied. Since Exercise Echocardiography (EE) is an increasingly used method to evaluate patients with chest pain we hypothesized that non-suspected labil SO may be present in patients referred for this test.

To determine the frecuency of newly developed subaortic obstruction during exercise, and the clinical characteristics of these patients, we prospectively studied 2280 patients by color and pulsed Doppler before and immediately after treadmill EE (Bruce protocol). Exercise-induced SO was seen in 38, exercise-induced mitral valve systolic anterior motion (SAM) causing mitral regurgitation (MR) in 2, and exercise-induced SO together with MR was seen in 3. The LVOT Doppler-derived gradient increased from 10 ± 3 to 69 ± 29 mmHg (34–130) in the 41 patients with SO. In 8, SAM without septal contact was seen at rest and could again be demonstrated during exercise (n = 2) or postexercise (n = 8). New mitral valve SAM was recorded in 18 at both exercise and postexercise (n = 9), or only at postexercise (n = 9). The Doppler increased gradient was thought to be due to midventricular SO in another 8 patients, whereas no cause of SO could be demonstrated in 9. Concentric left ventricular hypertrophy (LVH) was seen in 23, asimetric LVH in 10 and normal baseline echo in 10. LVH was associated to high blood pressure (HBP) in 16 (37%), whereas was idiophatic in 17 (40%). LVH patients achieved lower exercise time than non-LVH (9 ± 3 min vs 11 ± 1 min), in spite of similar Doppler gradients, although age and% of females were higher in the former group (58 ± 10 vs 49 ± 7 years, $p < 0.05$; 24% vs 10%, p = NS).

In conclusion, exercise-induced subaortic obstruction and mitral regurgitation due to exercise-induced mitral valve SAM are relatively infrequent in patients submitted to Exercise Echocardiography. These findings are associated to LVH due to HBB or idiophatic. Doppler postexercise study may unmask this condition.

P3653 Is the exercise stress echocardiography able to identify patients with three-vessel disease?

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Objective: The aim of this study was to assess in a large population of CAD patients (pts) whether the echo-monitoring during exercise stress test could provide additional and independent diagnostic information for the detection of the three-vessel disease.

Methods: The study population included 281 pts (260 M and 21 F, mean age 58.1 ± 8.5 yrs) with CAD documented by angiography who underwent exercise stress echocardiography (EST-Echo). The left ventricular end-diastolic volume (LV-EDV), the end-systolic volume (LV-ESV), the ejection fraction (LV-EF) and the wall motion score index (WMSI) were calculated both in basal condition and at peak exercise. The development during exercise of a new wall motion abnormality or the worsening of baseline wall motion abnormalities was considered to be an ischemic response. The pts were divided into two groups: Group1 (G1) included 219 pts (204 M and 15 F, mean age 57.3 ± 8.3* yrs) with one and two vessel disease, Group 2 (G2) 62 pts (56 M and 6 F, mean age 60.8 ± 8.7* yrs) with three-vessel disease (*p = 0.003).

Results: On the rest echocardiogram the LV-EDV, the LV-ESV, the LV-EF and the WMSI were similar between the two groups (G1:146.3 ± 47.9, 68.4 ± 37.2, 54.1 ± 9.3 and 1.2 ± 0.3 respectively; G2: 152.3 ± 49.6, 74.9 ± 40.4, 53.2 ± 10.4 and 1.4 ± 0.4 respectively). At peak exercise pts of G2 showed lower LV-EF (50.5 ± 11.2 vs 56.1 ± 10.5, p = 0.02), larger LV-EDV and LV-ESV (165.5 ± 48.9 vs 147.3 ± 50.2, p = 0.02 and 82.1 ± 42.9 vs 66.5 ± 37, p = 0.03, respectively) and higher WMSI (1.7 ± 0.4 vs 1.4 ± 0.3, p = 0.001) than G1 pts. The multivariate logistic regression analysis identified as independent predictors of the presence of three vessel disease the WMSI at peak of EST-Echo (p = 0.0004), the occurrence of ventricular arrhythmias during exercise stress test (p = 0.001) and a low exercise tolerance (min of exercise) (p = 0.001).

Conclusion: In our experience it was demonstrated that the information coming from EST-Echo might be useful in the identification of pts with 3-vessel disease.

P3654 Accuracy of exercise echocardiography to detect coronary artery disease in non-infarcted left bundle-branch block patients

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Exercise ECG is not useful for the diagnosis of coronary artery diasease (CAD) in patients with left bundle branch block (LBBB), while thallium scintigraphy has limited specificity and accuracy. Exercise echocardiography (EE) has been proposed as an alternative test to detect coronary artery disease in these patients, but the diagnostic value in this context has not been extensively studied.

We studied 39 patients (25 male, 14 female; mean (±SD) age 63 ± 8 years; rest LVEF 55 ± 9) with complete LBBB and chest pain suspicious of CAD. All of them underwent treadmill EE and coronary angiography within 16 weeks. Patients with a clinical history of acute myocardial infarction, revascularization procedures or severe LV dysfunction (rest LVEF < 35%) were not included. The development of new or worsening regional dysfunction was considered as an ischemic response. Significant CAD on angiography was defined as a ≥50% luminal narrowing in ≥1 epicardial coronary artery.

Multivessel disease (MVD) was found in 12, one-vessel disease in 8, and non significant CAD in 19. EE sensitivity, specificity and global accuracy were 80% (CI: 69–91), 84% (CI: 74–94) and 82% (CI: 74–90), respectively; left anterior descending CAD 100%, 80%, and 87%; left circunflex CAD 50%, 78% and 67%; and right CAD 45%, 79% and 69%. Sensitivity was very high for MVD (100%), lower for one-vessel disease (50%).

In conclusion, treadmill Exercise Echocardiography is highly accurate in detecting coronary artery disease in non-infarcted patients with left bundle branch block and clinical suspicion of coronary artery disease. Sensitivity is very high for left anterior descending artery and multivessel CAD detection, lower for one-vessel CAD.

P3655 Relationship between exercise and dobutamine stress echocardiography wall motion abnormalities and stenosis severity and location

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Quantitative coronary angiography has been shown to allow the functional assessment of coronary stenosis, while exercise (ESE) and dobutamine (DSE) stress echocardiography are both widely accepted methods for assessing the functional significance of coronary stenosis. The relationship between ESE or DSE induced wall motion abnormalities and stenosis severity and location however remains controversial. 30 patients (mean age 58 ± 9 years, 23 male) with single vessel coronary artery disease with ≥50% minimal luminal reduction) and stable angina were studied. All patients had normal resting left ventricular function and no previous history of myocardial infarction. Coronary stenosis severity was assessed by computerized angiography. All patients underwent ESE and DSE on random order. Positive result was defined as occurrence of a new or worsening wall motion abnormality.

Results. At peak ESE 23 patients developed wall motion abnormalities (group 1) and 7 did not (group 2). A positive ESE was associated with stenosis severity ≥80% in 65% and with a proximal location in 94% of stenoses ($p < 0.01$). A significant correlation was found between stenosis area and wall motion abnormality difference score from baseline during peak exercise ($r = 0.53$, $p < 0.01$). During DSE 18 patients developed wall motion abnormalities (group 1) and 12 patients did not (group 2). A positive DSE was assosiated with stenosis severity ≥80% in 72% and with a proximal location in 81% of stenoses. A weak correlation was found between stenosis area and wall motion abnormality difference score from resting during peak dobutamine ($r = 0.37$, $p < 0.05$). There were fewer positive results with DSE than with ESE (60% vs 78%, $p < 0.01$). The proportion of positive ESE results was greater (62% vs 46%, $p < 0.01$) in stenoses with severity <80% and in middle and distal senoses (57% vs. 36%, $p < 0.01$) than in DSE

Conclusions. In patients with single vessel coronary artery disease, positive stress echocardiography tests are usually associated with a proximally located ≥80% stenosis. Patients with stenoses of <80% have a greater chance to have a positive exercise than dobutamine stress.

P3656 Silent and symptomatic myocardial ischaemia during exercise stress echocardiography

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Background: The results of the various studies, which attempted to verify if the magnitude of myocardial ischemia could influence the appearance of anginal pain, are contradictory.

Objective: This study aim was to evaluate the clinical, angiographic and echocardiographic features of CAD patients (pts) with and without anginal pain during exercise stress echocardiography-induced myocardial ischemia.

Methods and patients: Exercise stress echocardiography (EST-Echo) was performed in 339 pts (300 M, 39 F, mean age 59.5 ± 8.6 yrs) with angiographically documented coronary artery disease (CAD).The patients were classified into two groups: Group1 (G1) included 204 pts with silent ischemia during EST-Echo and Group 2 (G2) 135 pts who experienced moderate to severe chest pain during the test.

Results: Angina pectoris in history was present in 128 (62.7%) pts of G1 and in 120 (88.8%) of G2 ($p = 0.001$). The distribution of CAD was similar between the two groups. During EST-Echo pts of G1 showed higher rate-pressure products and greater work loads, both at the ischemia threshold (20555 ± 5600 vs 18200 ± 3917, $p = 0.001$ and 80.7 ± 28.9 vs 71.4 ± 23.6, $p = 0.005$, respectively) and at peak exercise (22870 ± 5733 vs 20654 ± 4715, $p = 0.003$ and 94.3 ± 26.9 vs 84 ± 25.6, $p = 0.01$, respectively) than G2 pts. A similar entity of ST segment depression at peak of EST-Echo was documented in G1 and G2 pts (1.7 ± 0.4 vs 1.5 ± 0.8, respectively). The left ventricular end-diastolic volume, the end-systolic volume, the ejection fraction and the wall motion score index were similar between the two groups both in basal conditions (G1: 146.2 ± 47.7, 70.1 ± 37.8, 54 ± 10.5 and 1.3 ± 0.3 respectively; G2: 145.8 ± 45.2, 67.3 ± 32.9, 54.8 ± 8.8 and 1.2 ± 0.4 respectively) and at peak of EST-Echo (G1: 151.2 ± 50.2, 68.9 ± 39.4, 54.7 ± 11.6 and 1.8 ± 0.3 respectively; G2: 151.7 ± 47.2, 72.4 ± 33.9, 53.5 ± 10.3 and 1.7 ± 0.4 respectively). At the multivariate analysis no echocardiographic parameter was predictive of silent myocardial ischemia during EST-Echo. The absence of anginal symptoms during daily life resulted the only variable predictive of silent ischemia during exercise ($p = 0.000$).

Conclusion: In our population the occurrence of anginal pain during EST-Echo was not related to the extension of the ischemic myocardium. Also the left ventricular function, both on baseline and in response to effort, was similar between the symptomatic and asymptomatic pts. These results confirmed that the pain sensitivity follows individual patterns.

EXERCISE TESTING OF HEART FAILURE IN NORMAL PEOPLE AND ATHLETES

P3657 Contributions of left ventricular systolic and diastolic functions on increase in cardiac output during constant work rate exercise in patients with chronic heart failure

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Left ventricular (LV) systolic function indicated by ejection fraction (EF) does not correlate with exercise capacity in patients with chronic heart failure, however, cardiac function would participate the increase in cardiac output during exercise, at least partially, even if it is not the main determinant. We investigated how LV systolic or diastolic function participates the increase in cardiac output during constant work rate exercise.

[Methods] Fifteen cardiac patients (resting LVEF: 25–77%, average 43 ± 17%) performed a constant work rate exercise testing using a supine bicycle ergometer for 6 min with a respiratory gas analysis under catheterizations to pulmonary and brachial arteries and left ventricle. Work rate was previously determined as an equivalent to 10 ml/kg/min of VO_2 by incremental exercise test. Cardiac output and pressures were measured, and left ventriculogram and blood sampling were performed before and at 6 min of exercise.

[Results] VO_2 at 6 min of exercise was 57 ± 12% of peak VO_2 obtained from incremental exercise test. Blood lactate was 2.8 ± 1.2 mmol/L and norepinephrine was 4.3 ± 2.4 pmol/mL at 6 min. Cardiac index at 6 min was 3.9 to 8.8 L/min/m^2, which did not correlate with LVEF both at rest and at 6 min. The rate of increase in cardiac output from the resting state correlated with the rate of decrease in systemic vascular resistance ($r = 0.84$, $p < 0.01$) and the rate of changes in LVEF ($r = 0.72$, $p < 0.05$), and inversely correlated with the rate of changes in LV end-diastolic pressure/volume ($r = -0.68$, $p < 0.05$) as an index of LV diastolic compliance, however, did not correlate with either the rate of changes in LV end-systolic pressure/volume as an index of LV contractility or the changes in heart rate. Moreover, the rate of changes in LVEF did not correlate with the rate of changes in LV end-systolic pressure/volume, but correlated with the rate of decrease in systemic vascular resistance ($r = 0.81$, $p < 0.01$). In conclusion, the increase in cardiac output during constant work rate exercise would be mainly dependent on the decrease in systemic vascular resistance reflecting vasodilation in the working skeletal muscle, and on LV diastolic function, but not systolic function in chronic heart failure. In addition, change in LVEF might be dependent on the change in peripheral vascular resistance.

P3658 Undetermined anaerobic threshold in chronic heart failure: incidence and clinical implications

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Peak oxygen consumption (pVO_2) is an indipendent predictor of prognosis in chronic heart failure (CHF) and is a useful guide for timing heart transplantation. The detection of the anaerobic threshold (AT) is mandatory to validate pVO_2, but it's undetermined in a substanstial percentage of patients.

Methods: To investigate the incidence and the clinical features of patients (pts) with undetermined (noAT), 520 CHF pts (89% male, 57 ± 8 yrs), in NYHA class I–IV, who performed an incremental bicycle exercise test limited by fatigue or dyspnea were reviewed: mean EF and peak VO_2 were 24 ± 8%, 14.5 ± 3 ml/kg/m′, respectively. AT was detected using the V-slope method. 134 pts (26%) had noAT: noAT pts compared to AT pts were in more advanced NYHA class (2.5 ± 0.5 vs 2.0 ± 0.6, $p < 0.001$), treated with higher Furosemide dose (126 ± 112 vs 82 ± 68 mgr, $p < 0.05$), were studied at a shorter time from last acute episode (206 ± 236 vs 365 ± 128 days, $p < 01$), had a higher end-diastolic volume index (141 ± 54 vs 127 ± 47 ml/m2 $p < 0.01$), a lower EF (22 ± 7 vs 26 ± 9%, $p < 0.001$) a shorter mitral flow deceleration time (153 ± 49 vs 168 ± 51 msec, $p < 0.01$), and more impaired resting spirometric data (FVC% 84 ± 16 vs 92 ± 17, $p < 0.001$, FEV −1% 82 ± 17 vs 89 ± 19, $p < 0.01$). At peak exercise, gas exchange ratio and Borg scale score (0–10) were not different in the two groups (1.1 ± 0.1 vs 1.1 ± 0.09, 7.5 ± 1.1 vs 7.5 ± 1.0. NS), but noAT pts showed a significant reduced peak VO_2 and a steeper VE/VCO_2 slope (12.1 ± 3 vs 15.3 ± 3 ml/kg/m′, 37 ± 10 vs 30 ± 5, $p < 0.001$). Moreover, noAT was observed in 50% (58/116) of pts with atrial fibrillation (AF), in 52% (18/35) of pts with AF and advanced NYHA class III–IV, and in 56% (14/25) of those pts with AF, NYHA class III–IV evaluated within 30 days of last acute episode.

In conclusion, noAT is frequent in CHF, particularly in pts with AF, advanced NYHA class, recent clinical instability and severe functional impairment. In these subsets of pts, incremental symptom-limited test should be postponed till better clinical conditions are achieved, or replaced with a submaximal trial.

P3659 Long term clinical outcome with low and high dose captopril in heart failure

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Background: Although angiotensin converting enzyme inhibitors (ACE-I)are recommended as first line therapy in patients with chronic heart failure, the target doses proven to be effective in major morbidity and mortality trials are not much used in daily practice in Belgium. This study was undertaken to assess the long-term effects of a low dose (25 mg b.i.d.) and a high dose (50 mg b.i.d.) of captopril in mild to moderate heart failure.

Methods: After a titration period, patients who tolerated 50 mg b.i.d. were randomized and followed up to 2 years.

Results: 298 patients were included and were followed up for a mean of 12 months. Progression in heart failure were respectively 31.5% and 22.4% for low and high dosage ($p = 0.088$). Treatment with high dose showed a reduction in the number of hospitalisations for all causes from 18.5 to 11.8% ($p = 0.1$) and for congestive heart failure from 14.7 to 7.2% ($p = 0.06$); moreover, the incidence of fatal and nonfatal cardiac events showed a trend in favour of the high dose of 21% ($p = 0.142$). The total number of adverse events was the same for both dosages and no difference in renal function was observed.

Conclusion: Although the statistical significance has not been reached, this study supports the trend seen in ATLAS study, that the use of higher dose of ACE-I such as 50 mg captopril b.i.d. improves clinical outcome. Therefore, clinicians should be encouraged to achieve target dose studied in large randomised trial.

P3660 The six-minute walking test in advanced chronic heart failure: an accurate procedure to assess clinical severity, functional capacity and daily physical activity

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The six-minute walking test (WT) is a simple, noninvasive, inexpensive and safe method to assess functional capacity in chronic heart failure (CHF) patients (pts).

Methods: The potential role of WT to detail clinical severity, functional capacity and daily physical activity was invastigated in 130 pts (59 ± 9 yrs, 81% male), with advanced CHF, in NYHA class II–IV, who performed an incremental bicycle symptom-limited exercise test and two WT (repeated within 1 week): mean EF, end-diastolic volume index (EDVi), and peak oxygen consumption (pVO_2) were 22 ± 7%, 131 ± 44 ml/m2, 11.1 ± 2 ml/kg/m′, respectively. Mean walking distance (Wd) was 365 ± 50 mt. Habitual daily physical activity level was evaluated by an interviewer-determined scoring (Activity score, AcS: range 0–9) considering leisure-time, occupational activities and hospital admissions. Wd correlated significantly with pVO_2 ($r = 0.40$, $p < 0.0001$) and AcS ($r = 0.37$, $p < 0.0001$). Pts were divided according to the Wd: pts with Wd > 365 mt (group A, 59 pts) and Wd > 365 mt (group A, 71 pts): group A pts were older (62 ± 8 vs 57 ± 9 yrs, $p < 0.01$), had a reduced peak VO_2 (10.5 ± 2 vs 11.7 ± 2 ml/kg/m′, $p < 0.01$), a steeper VE/VCO_2 slope (39 ± 11 vs 34 ± 8, $p < 0.01$), a more impaired spirometric data (FVC% 79 ± 12 vs 86 ± 13, $p < 0.01$, FEV 1% 78 ± 14 vs 83 ± 13, $p < 0.05$) and were studied at a shorter time from last acute episode (146 ± 81 vs 314 ± 144 days, $p < 01$). Moreover group A pts had a significantly lower AcS in (3.1 ± 1.5 vs 4.1 ± 2.9, $p < 0.01$) and shorter mitral flow deceleration time (DecT: 132 ± 45 vs 144 ± 37 msec, $p < 0.05$) and a higher daily Furosemide dose (125 ± 95 vs 90 ± 75 days, $p = 0.06$), whereas NYHA class, EDVi, EF were similar in two groups.

In conclusion: WT is reliable functional test in advanced CHF pts and allows an appropiate definition of clinical severity, exercise tolerance and daily physical activity. WT may substitute incremental symptom-limited exercise test in advanced CHF pts.

P3661 Atrial fibrillation in chronic heart failure: influence on exercise capacity and therapeutic implications

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Atrial fibrillation (AF) complicates chronic heart failure (CHF) and may promote its progression due to uncontrolled heart rate (HR), loss of atrial contribution and irregularity of ventricular rhythm. Few data are available on the influence of AF on exercise tolerance in CHF.

Methods: We studied 104 CHF pts (89% male, 54 ± 8 yrs), in NYHA class II–III, who performed an incremental bicycle exercise test with invasive haemodynamic evaluation limited by fatigue or dyspnea: mean EF and peak oxygen consumption (VO_2) were 22 ± 7%, 14.9 ± 4 ml/kg/m′, respectively. 17 pts (16%) were in AF: etiology of CHF, age, sex, NYHA class, daily diuretic dose, end diastolic volume index, and EF were similar in AF pts compared to pts in sinus rhytm (SR), Resting heamodynamic variables were similar in the two groups, but AF pts had a significant lower stroke volume (SV: 56 ± 11 vs 69 ± 20 ml, $p < 0.05$) and cardiac index (CI: 2.1 ± 0.2 vs 2.6 ± 0.6 5 ml/min/m2, $p < 0.05$). At peak exercise, gas exchange ratio, Borg scale score, peak VO_2 (13.9 ± 5 vs 14.8 ± 4 ml/kg/m′, NS) and CI (4.1 ± 1.1 vs 4.9 ± 1.5 ml/min/m2, NS) were not different in AF and SR pts, whereas AF pts had a significant higher peak HR (149 ± 22 vs 122 ± 21 beat/min $p < 0.01$), greater chronotropic response (difference between peak exercise and rest: 62 ± 22 vs 49 ± 20 beat/min, $p < 0.05$) and lower SV (59 ± 13 vs 75 ± 10 ml, $p < 0.05$). After adjusting for chronotropic response, a 24% decrease in peak VO_2 was observed in AF pts (9.5 ± 3 vs 12..6 ± 3 ml/kg/m′, $p < 0.05$).

In conclusion: CHF pts with AF show similar functional capacity compared to pts in SR and chronotropic response is crucial to maintain cardiac index and exercise tolerance. Medications that inhibit exertional chronotropic compensatory response may modify the ability to work in these pts.

P3662 Is the chronotropic response in dilated cardiomyopathy dependent on left ventricular function and gives implications for rate adaptive pacing?

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The heart rate (HR) to work rate (WR) relationship has been reported in normals, but not in pts with dilated cardiomyopathy (DCM). We studied the influence of LV dysfunction on the HR/WR-slope below and above the anaerobic threshold (AT) in such pts, which may potentially impact pacemaker sensor programming.

Methods: We included 31 male pts (age 51 ± 13 y) with DCM and an ejection fraction (EF) < 0.40, all on stable therapy with diuretics, digitalis and ACE-inhibitors, but not on beta-blockers. Based on LV dysfunction, two groups were defined: A: EF ≤ 0.25 (n = 19) and B: EF > 0.25 (n = 12). Symptom limited cardiopulmonary peak exercise testing was performed starting at 20 W with an increase of 10 W/min. The HR/WR slope was determined using linear regression analysis.

Results: The mean EF was A: 0.22 ± 0.02 vs. B: 0.34 ± 0.06 ($p < 0.05$). There was no difference for NYHA class (A: 2.6 ± 0.5 vs. B: 2.0 ± 0.5), HR at rest (A: 89 ± 16; B: 82 ± 17 bpm), or HR at AT (A: 122 ± 23; B: 122 ± 29 bpm) and HR at peak exercise (PE) (A: 143 ± 20; B: 125 ± 22 bpm), but a trend towards a steeper HR/WR slope from rest to PE in group B (0.74 ± 0.24 bpm/W), as compared to group A (0.52 ± 0.29 bpm/W) (n.s.). The HR/WR slope from rest to AT was significantly steeper (+38%) in group B (0.64 ± 0.28 bpm/W) with less severe LV dysfunction, as compared to group A (0.46 ± 0.25 bpm/W) ($p = 0.02$). In both groups a further increase in the HR/WR slope was measured above the AT (A: +26% to 0.62 ± 0.41 bpm/W; B: +20% to 0.80 ± 0.36 bpm/W) (n.s.).

Conclusion: Pts with DCM and moderate LV dysfunction show a steeper HR/WR response below the AT, as compared to those with severe dysfunction. The HR/WR slope in both groups does not down regulate above the AT, as observed in healthy subjects. To mimic this rate response with pacemaker sensors, other rate response slopes may be required, as compared to patients with normal LV function.

P3663 Left ventricular function in dilated cardiomyopathy – acoustic quantification assessment

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Left ventricular(LV) function was assessed in 41 pts with dilated cardiomyopathy (DCM) aged 37.0 ± 10.7 yrs and 33 controls aged 38.6 ± 9.0 yrs with good quality echocardiograms. Automated boundary detection (ABD) with modified Simpson's rule was used for LV volume estimation from apical 2-chamber view. We evaluated: LV enddiastolic volume (LVEDV), ejection fraction (EF%),% volume change during rapid filling (RF%) and filling due to atrial contraction (AF%)in relation to total filling volume, peak volume changing during rapid filling (dV/dtRF) and filling due to atrial contraction (dV/dtAF), normalized peak filling rate (PFR), time to PRF (tPFR) and normalized peak ejection rate (PER). Mean pulmonary wedge pressure (mPWP) and ejection fraction were determined invasively after echocardiographic study in DCM pts. Results are shown below.

We found negative correlation between mPWP and PFR (r = −0.49)as well as PER (r = −0.54). The DCM pts we divided into 2 groups: A – with mPWP ≥20 mmHg, B – with mPWP < 20 mmHg. We noticed significantly reduced PFR (2.0 ± 0.65 vs 2.6 ± 0.77EDV/s, $p < 0.03$) and PER (1.4 ± 0.5 vs 2.2 ± 0.93EDV/s, $p < 0.02$) in group A compared to group B. The correlation between LVEF obtained invasively and from ABD was strong (r = 0.84).

LV function in DCM and control group

		DCM	Control	p
LVEDV	(ml)	183.0 ± 83.3	71.7 ± 20.7	<0.0001
LVEF	(%)	25.2 ± 10.0	58.2 ± 7.1	<0.0001
RF	(%)	61.7 ± 15.6	70.7 ± 9.2	<0.05
RF	(%)	40.0 ± 11.2	29.6 ± 12.9	<0.04
dV/dtRF	(ml/s)	355.5 ± 150.2	276.4 ± 95.6	<0.02
dV/dtAF	(ml/s)	243.4 ± 110.2	168.4 ± 67.8	<0.0004
PFR	(EDV/s)	2.4 ± 0.71	4.2 ± 0.83	<0.001
tPRF	(ms)	77.2 ± 35.8	114.0 ± 63.4	<0.01
PER	(EDV/s)	1.8 ± 0.79	3.5 ± 0.47	<0.0001

Conclusions: Acoustic quantification is an effective noninvasive method to assess LV function in pts with DCM in which reduced peak filling rate, time to peak filling rate and peak emptying rate are observed. Markedly reduced PFR, tPFR and PER suggest significantly increased filling pressure with increased chamber stiffness of enlarged LV and can be a marker of poor prognosis.

P3664 Usefulness of VO_2 half-time after exercise as an indicator of functional status

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Delayed VO_2 kinetics after exercise have been characterized in patients with cardiocirculatory disorders such as seen in heart failure patients, its clinical significance, however, is not fully established. Since VO_2 following exercise does not necessarily decay in an exponential fashion, simple half-time (1/2T) of the VO_2 recovery might be a convenient, proper parameter. To further clarify its significance as an index of functional status, we first determined possible age-related changes in 1/2T in healthy controls and then examined its diagnostic significance as an index for therapeutic effects (exercise training).

Methods: We measured 1/2T in 229 control subjects at various ages (40 ± 17 yo.) with normal exercise tolerance (%peak VO_2 > 80%) and no structural cardiac disease. Then we evaluated the changes in 1/2T after 3-month exercise training in patients with recent myocardial infarction (MI, n = 119) and coronary artery bypass graft (CABG, n = 36). 1/2T was defined as the elapsed time (s) required for a 50% fall in the peak value.

Results: In controls, age-related increases in 1/2T were observed as evidenced by a significant correlation (y = 0.33×age ± 42, r = 0.48). 1/2T before training were much greater in CABG patients (109 ± 41 s) than in MI patients (78 ± 20 s, $p < 0.001$). After exercse training, 1/2T was shortened in all but 6 (unchanged in 4)in CABG patients (87 ± 30 s, $p < 0.001$), but remained unchanged in MI patients. The changes in peak VO_2 after training correlated with those in 1/2T in neither MI nor CABG patients.

Conclusions: VO_2 kinetics after exercise is delayed with aging in normal subjects. 1/2T seemed to reflect the deconditioning of the skeletal muscle rather than the cardiac dysfunction.

P3665 Doppler tissue echocardiography during exercise stress test in normals and athletes

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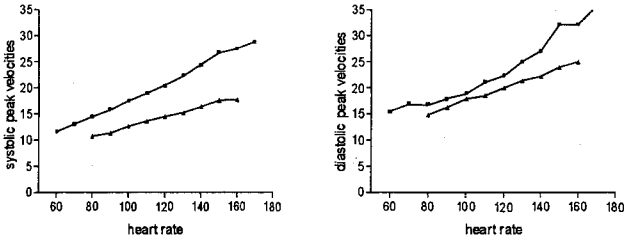
DTE is a new ultrasound technique allowing myocardial velocity measurements during cardiac cycle. Aim of the present study was the assessment of the heart function during all phases of exercise stress test measured by DTE in Normals (N) and in trained Athletes (AT).

Methods: 15 sedentary subjects and 12 Athletes underwent a DTE from the apical 4-Ch view during supine exercise test; the sample volume was positioned at the lateral mitral annulus within the color Doppler image and systolic (S) and diastolic (D, including both early and late ventricular filling) tissue waves were recorded from rest to the peak of exercise (90% of the maximal age-predicted heart rate) The peak velocity, mean velocity, time-velocity integral and duration of S and D waves were calculated and referred to the heart rate. As the figures show, in both groups (AT, solid square, N solid triangle) we observed during the test an increase of systolic and diastolic peak velocities, which was more relevant in AT. In both groups the percent increase of D wave was higher than that of S wave. Similar results were obtained with integrals and mean velocities.



Conclusions: Systolic and diastolic tissue velocities can be monitored during all steps of exercise test, DTE appears to be a new tool to quantify the ventricular response of different groups to exercise, for which clinical applications are foreseeable.

P3666 Long-term modification of cardiopulmonary performance after mitral valvuloplasty

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Percutaneous transvenous mitral valvuloplasty (PTMV) has been proved as an effective method in the treatment of patients (pts) with mitral stenosis (MS). In order to evaluate the evolution of cardiopulmonary performance in the long-term follow-up (5 yrs) after successful PTMV we performed a prospective study of 108 pts with pure or dominant MS. PrePTMV, early and late postPTMV echocardiography, exercise ECG and pulmonary function (PF) were compared in the whole group and in the subgroups created according to the valve echo score.

Results: The analysis revealed:

(1) Substantial increase of mitral valve area, fell of mitral gradient and pulmonary hypertension (PH) in the whole group, with higher significance in the subgroup with lower echo score ($p < 0.01$ vs 0.001)

(2) Significant improvement ($p < 0.05$) of some PF parameters (FVC, FEV_1) in all pts early post PTMV, in the late period significant only in the subgroup with mild to moderate PH and lower echo score (8 vs 11) (3) In pts with high echo score, severe PH prePTMV and/or persisting moderate to severe PH postPTMV: a) no improvement of DICO b) worse ($p < 0.01$) PF in comparison to the pts with mild PH

(4) Improvement of exercise capacity ($p < 0.01$) and functional status

Conclusion: PTMV is safe and effective method in the treatment of MS in pts with pliable valves and reversibility of pulmonary hemodynamics abnormalities. But PTMV seems to provide also in pts with less suitable valves acceptable results with improvement of cardiopulmonary performance persisting in the follow-up period. The long-term modifications of PF are determined probably by the degree of organic changes of pulmonary interstitium, what implies also no improvement of diffusing capacity and irrelevant changes of PF in the subgroup with severe PH.

DIAGNOSIS RISK STRATIFICATION IN CORONARY HEART DISEASE

P3667 Exercise tolerance is depending directly on coronary reserve and inversely on rate-pressure product response to exercise in hypertensive patients without myocardial ischaemia

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A reduced coronary flow reserve (CFR) is reported in patients with essential hypertension (HT) even in absence of angiographically significant coronary stenosis. Whether or not such an impairment in coronary vasodilator capacity may affect exercise tolerance (ET) even in absence of myocardial ischemia is not yet established.

Aim of this study was to evaluate the relationship between ET and CFR in patients with HT, angiographically normal coronary arteries and ECG on effort negative for myocardial ischemia.

Methods: in 30 lean patients with mild to moderate untreated HT (office BP > 150/90 mmHg and <180/110 mmHg; mean age 53 ± 10; 25 males), angiographically normal coronary arteries and ECG on effort negative for myocardial ischemia, blood flow velocity in left anterior descending coronary artery was monitored by transesophageal Echo-Doppler in basal condition and during i.v. adenosine infusion (140 μg/kg/min in 5 min): the adenosine/basal flow velocity ratio was computed as an index of CFR. All patients underwent a maximal exercise test by cycloergometer, with stepwise increments of 25 W every 2 minutes, until exhaustion: blood pressure (BP), heart rate (HR) and rate-pressure product (RPP) were measured every minute, while 12-lead ECG was continuously recorded during exercise and 5-min recovery.

Results: CFR was significantly lower in HT patients, as compared to a group of normotensive controls of similar age (2.63 ± 0.61 vs 3.32 ± 0.64; $p < 0.001$). Exercise test, negative for chest pain and electrocardiographic ischemia, was interrupted due to exhaustion at the 88.1 ± 11.3% of age-adjusted maximal HR. Exercise time was 10.2 ± 3.6 min in average, and correlated directly with CFR ($r = 0.56$, $p < 0.01$), and inversely with the slopes of the linear regression lines of HR, systolic BP and RPP vs. increasing workload ($r = 0.55$, 0.68 and 0.61, respectively).

Conclusions: in patients with mild to moderate essential HT and angiographically normal coronary arteries, ET seems to be limited by a reduced CFR and a steeper rate of increment of HR and systolic BP during exercise even in absence of detectable myocardial ischemia.

P3668 Prediction of culprit lesion localization by using a new index on predischarge exercise stress test in patients with acute inferior myocardial infarction

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In patienst with acute inferior myocardial infarction localization of culprit lesion is directly related with prognosis. Aim of this study is to test ST segment index that is calculated by dividing ST segment elevation in limbs lead D2 with D3, as a new marker for prediction of culprit lesion localisation if it is in right coronary artery (RCA) or left circumflex coronary artery (LCX). For this purpose 82 patients with acute inferior myocardial infarction who have ST segment elevation on predischarge symptom limited and/or submaximal treadmill exercise test by using modified Bruce protocol were included in the study. ST segment index was calculated from the ratio of ST segment elevation in limbs lead D2 and D3 on the peak exercise level.Patients were classified according to ST segment index in two groups. Group 1 consisted of the patients with ST segment index > 1 (n = 24) and group 2 the patients with ST segment index < 1 (n = 58). All patients were underwent coronary angiography.

Results: Both group 1 and 2 patients were similar in age gender, peak exercise level and double products they were achieved. Group 1 patients had LCX lesion (specificity% 87, sensitivity 87%, positive predictive value 75%, negative predictive value 94%, accuracy 88%) and group 2 patients had RCA lesion more frequent (sensitivity 87%, specificity 87%, poditive predictive value 94%, negative predictive value 75%, accuracy 88%) ($p < 0.001$).

Relation between culprit coronary artery and ST segment index

	Cx (n = 28)	RCA (n = 54)	p
Group 1 (n = 24)	21	3	<0.001
Group 2 (n = 58)	7	51	<0.001

In conclusion ST segment index can be used to predict culprit lesion localisation on predischarge exercise tests in patients with inferior myocardial infarction.

P3669 Pronounced post-exercise HRV in inferior ischaemia – determinants of its appearance and revascularization effects

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Exercise-induced inferior ischemia, possibly experienced in daily activities, might result in vagal activation as well as acute inferior myocardial infarction. Our recent data indicating more pronounced HRV and shorter decay of HR after exercise in patients with inferior ischemia compared in those with anterior ischemia supports this possibility, however, these indexes could not completely differentiate two lesions. To further establish our notion, we examined various factors possibly affecting this phenomenon in patients with inferior ischemia, and then evaluated the effects of revascularization (RV) on these parameters in patients with inferior and anterior ischemia.

Methods: In 52 patients with exerise-induced significant ST depression and documented inferior ischemia, we measured post-exercise HRV (6 min) with use of A/D converted ECG. They were divided into 2 group with (G-P, n = 26) and without (G-N, n = 26) pronounced post-exercise HRV accoring to Delta-RR (successive RR differences averaged at 60–90 sec, cut-off = 15 ms/beat), HR decay was also measured as a time constant (TC). Clinical characteristics including sex, risk factors, medications, exercise test results, angiographic findings, and ventricular function, were compared between the 2 groups. Furthermore, by repeating the test in patients with inferior (n = 11) and anterior (n = 10) ischemia after successful RV, pre-RV and post-RV data were compared.

Results: Except for age and resting HR (both, $p < 0.05$), all other factors were comparable between the 2 groups, suggesting prerequisite of preserved vagal activity in the appearance of this phenomenon. After RV, Delta-RR in patients with inferior ischemia attenuated in all but one (22 ± 13 to 8 ± 5 ms, $p < 0.05$). TC concordantly prolonged in all but 3 (73 ± 20 to 98 ± 29 s, $p < 0.05$). Both parameters changed toward the same level as those in patients with anterior ischemia, in whom both remained unchanged. This indicated a direct role of ischemia localized in inferior wall on this phenomenon.

Conclusion: The data supports our previous notion that inferior ischemia, even provoked by physiological stress such as exercise, activates vagal nerve resulting in cardioinhibitory reflex. Preserved basal vagal function seems to a prerequisite for the appearance of this phenomenon.

P3670 Post-exercise VO_2 "hump" phenomenon as an indicator for myocardial ischaemia in patients with anterior myocardial infarction

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In patients with exercise-induced myocardial ischemia, we occassionally observe abnormal post-exercise blood pressure responses (i.e. delayed recovery or paradoxical increase), presumably caused by transiently enhanced stroke volume following ischemia. Similar mechanisms may be operative in the genesis of abnormal transient VO_2 kinetics early after exercise, which may possibly serve as an indicator for inducible myocardial ischemia. Since the diagnostic accuracy of ischemia by exercise ECG is limited in patients with prior q-wave anterior infarction, we examined this hypothesis in those patients with (G-I) and without (G-N)inducible residual ischemia.

Methods: We examined 50 patients with recent anterior infarction who underwent cardiopulmonary exercise testing within 3 weeks after MI onset. The presence of residual ischemia was clinically defined as the necessity of revascularization within subsequent 3 months (n = 14). To quantify abnormal manifestation in early post-exercise VO_2 kinetics, we standardized the time-series of instantaneous post-exercise VO_2 up to 4 min for peak VO_2, and then exponentially fitted the curve with use of peak VO_2 and continuous data for a period of 90–240 sec. D curve obtained by subtraction of measured VO_2 curve by fitted VO_2 curve was compared between the 2 groups.

Results: Standardized VO_2 was greater in G-I than in G-N for a period of 36–198 sec ($p < 0.05$). In a further limited period of 48–72 sec, D curve in G-I was greater than that in G-N ($p < 0.05$). When "Hump" defined as (1) D curve peaked between 40–60 sec after exercise and (2) absolute peak value of D curve $\geq$ 100 ml/min, it was found only in G-I (n = 6/14, 38%), but not observed in G-N (n = 0/36.0%).

Conclusions: Although not highly sensitive, post-exercise VO_2 "Hump" phenomenon, with its peak occurring around 50 sec after exercise, seems to be a specific marker for inducible myocardial ischemia. The identification of this phenomenon may be useful, particular in patients with limited diagnostic accuracy of exercise ECG such as those with anterior myocardial infarction.

P3671 Use of myocardial perfusion imaging (MPI) with exercise testing (ET) in patients with low likelihood of coronary disease: physician adherence to published guidelines

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MPI is not recommended in patients with low CAD likelihood because of its low positive predictive value (AHA/ACC '95). Our objectives were to assess physician use of MPI as an adjunct to ET in low-risk patients; differences between cardiologists and noncardiologists in ET-MPI use; and incremental value and economic impact of concurrent ET-MPI. We conducted a longitudinal review of ET with or without Tc-99 sestamibi SPECT in patients with normal rest ECGs performed at the Hospital of the University of Pennsylvania (1/96–4/98) and identified a subset with low (<10%) likelihood of CAD (based on Diamond and Forrester data). 122/5170 ETs (2.4%) were done in low-risk patients. 77/122 (63%) had adjunctive MPI. MPI use among cardiologists and noncardiologists was similar, 19/31 (59%) vs 59/91 (65%)[p = 0.29] 71/77 (92%) patients who underwent ET-MPI had negative ETs and normal MPI. 4/77 patients had negative maximal ETs with abnormal MPI (all small isolated defects), while 2/77 patients had positive maximal ETs with normal MPI. Only the latter would merit MPI retesting had they been originally referred for routine ET. All 45 routine ETs were negative and none required MPI retesting. No patient was referred for catheterization. Using 1996 medicare fees, a sequential strategy with MPI retesting of positive ETs cost $15,600, while the observed approach favoring ET-MPI by 1.7:1 cost 3.5-fold or $53,830. Although results from this referral center underestimate the proportion of low-risk patients nationwide, extrapolation to the estimated >1,000,000 annual ET-MPI in the US yields substantial savings. We conclude that despite national guidelines, MPI continues to be used frequently – and in similar proportions among cardiologists and noncardiologists – for low-risk patients; MPI adds little information in this patient subset; significant cost savings could occur by restricitng MPI use in these patients; additional interventions are necessary to improve adherence to national guidelines.

P3672 Evaluation of exercise-induced changes in Q, R and S-waves during exercise stress testing in patients with ischaemic heart disease

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Exercise-induced ST-segment displacement is the most frequently used parameter in detecting ischemic heart disease, however, the value of this marker was proven to be limited with varying sensitivity and specificity. Therefore, several new parameters emerged to improve the efficacy of exercise testing. Our study aimed at evaluating the recently described QRS score based on the exercise induced changes in Q, R and S waves in the diagnosis of ischemic heart disease.

Methods: Data of 212 subjects performing treadmill exercise test were analyzed. 197 of them underwent stress myocardial perfusion SPECT and 54 of them were examined by coronary angiography. The extent of perfusion defect and the severity of coronary artery disease were characterized by simple scores. QRS score and cumulative ST depression were calculated at each subject and the values were correlated to the results of the myocardial SPECT and coronary angiography. Sensitivity, specificity and validity of QRS score and cumulative ST depression were also calculated.

Results: A significant, inverse correlation was found between the QRS score and the results of stress myocardial perfusion SPECT and coronary angiography in the whole population, especially in males, while females did not show significant relationship. The sensitivity, specificity and validity of the QRS score at the cut-off point of 3.5 mm were 73.5, 71.3 and 72.6%, respectively. These values surpassed those of the cumulative ST depression at the cut-off point of 6 mm. QRS score in patients with conclusive tests (achieving 85% of the maximal predicted heart rate) correlated significantly with stress myocardial perfusion SPECT and coronary angiography; nevertheless, in cases of inconclusive tests this issue could not be proven. The specificity of the QRS score in the group of inconclusive tests was lower than that of patients with conclusive tests and of the whole population in relation with stress SPECT; otherwise the diagnostic values of the QRS score concerning the coronary angiography in patients with inconclusive exercise were not markedly different from those of patients with conclusive tests. Similar correlation values between the QRS score and the severity of myocardial ischemia were obtained in subjects with and without antiischemic medication.

Conclusions: QRS score was significantly related to the extent of myocardial ischemia and the severity of coronary heart disease, thus along with the analysis of ST-segment displacement may contribute to the more precise evaluation of exercise stress testing.

P3673 Ergonovine and serotonin-induced coronary microvascular responses in subjects with false positive exercise ST-segment depression and normal coronary artery

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The mechanism of exercise ECG ST depression in subjects with normal coronary artery still remains unclear. We have reported that ergonovine (EM)-induced coronary microvascular dilatation was significantly greater in these subjects, suggesting enhanced serotonin (5HT) receptor mediated vasodilation.

Methods: In 52 subjects with atypical chest pain and normal coronary artery, we studied coronary flow responses using a Doppler-tipped guide wire (FloWire) and quantitative coronary angiography. 24 subjects had exercise-induced ST-depression (ExP group) and 28 subjects did not (Control group). After an administration of nitroglycerin (0.2 mg) to eliminate vasomotion of coronary conduit arteries, acetylcholine (ACh, 50 μg), papaverine (PAP, 10 mg), ergonovine (EM, 20 μg) and serotonin (5HT, 10 μg) were separately injected into the left main coronary artery in this order. Coronary blood flow (CBF) was estimated from average peak velocity and coronary arterial cross-sectional area.

Results: Baseline CBFs were not different in two groups. ACh, PAP and 5HT increased CBF similarly in both groups. EM did not change CBF in normal group (154 ± 9%, mean ± SEM), however, significantly increased CBF in ExP group (287 ± 34%, $P < 0.001$). The calculated maximum CBF (ml/min) in each intervention was as follows ($^*p < 0.01$ vs control),

	Baseline	ACh	PAP	EM	5HT
ExP (N = 24)	50 ± 5	153 ± 20	185 ± 15	121 ± 10*	116 ± 18
Control (N = 28)	52 ± 4	155 ± 12	194 ± 19	80 ± 8	101 ± 30

In conclusion, there was not abnormal vasoconstrictive response but vasodilatory response induced by EM in microvascular beds in ExP subjects, presumably leading to steal phenomenon. This vasodilatory response would not be caused by enhanced 5HT receptor pathway but might be related to attenuated alpha adrenergic vasoconstrictor pathway.

P3674 Comparison of multichannel magnetocardiography and body surface potential mapping in detection of exercise induced myocardial ischaemia

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Introduction: The aim of the study was to compare multichannel magnetocardiography (MCG) and 128-lead body surface potential mapping (BSPM) in detection of myocardial ischemia.

Methods: We studied coronary artery disease patients; 10 with left anterior descending (LAD) and 7 with right coronary artery (RCA) stenosis, and 12 age matched healthy controls during supine bicycle exercise testing. MCG and BSPM were registered in two separate similar stress tests in random order. Magnetic isofield and electrical isopotential maps were formed using averaged QRST signals in the ST-segment at rest and at cessation of exercise and at the T-wave apex at rest and 4 minutes postexercise. Changes from the rest state in the isofield and isopotential maps were quantified as rotations of the line connecting magnetic field and electric field maximum and minimum over the torso model.

Results: The rotation of the MCG isofield maps during ST-segment at cessation of exercise separated LAD patients from controls ($97 \pm 44°$ vs $37 \pm 35°$, $p < 0.005$), but not RCA patients from controls. On the contrary, the rotation of the BSPM isopotential maps during ST-segment did not differ between LAD and RCA patients and controls. At T-wave apex 4 minutes postexercise the rotation of the MCG isofield maps ($49 \pm 34°$ vs $10 \pm 16°$, $p < 0.005$) and BSPM isopotential maps ($71 \pm 43°$ vs $18 \pm 21°$, $p < 0.005$) separated RCA patients from controls. Same parameters separated RCA patients also from LAD patients (both $p < 0.05$). Only 6/17 patients fulfilled the standard ischemia criterion of >0.1 mV ST-segment depression in BSPM. Better performance of MCG may be due to its higher sensitivity to tangential injury currents produced by subendocardial myocardial ischemia.

Conclusion: Magnetocardiographic isofield maps seem superior to BSPM isopotential maps in detecting myocardial ischemia. Both isofield and isopotential maps during repolarization phase, at the T-wave apex, may have application in identifying the stenosed coronary vessel.

P3675 Echocardiography in systemic lupus erythematosus

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Aims: use of trans-thoracic-echocardiography (TTE) to study the frequency and the type of heart 1 lesions in a cohorte of 125 SLE Algerian patients

Methods: during a 6 years periode we have prosprectively studied 125 SLA patients diagnosed according to at least 4 ARA criterias. All patients were screened according to the ASE recommandations with the 1500 HP or with the ULTRAMARK 9 echocardiograph.

Results: 72 patients (57.6%) presented cardiac abdominalities. 50 patients (40%) had pericardial involvement. In 28 cases there xas pericardial effusion, 21 cases had a thikneed pericardium and 8 of them showed a moderate pericardial effusion. In one case there was a constrictive pericarditis., 43 patients (34.4%) had valcular abnormalities. There was a valcular thikning in 36 patients. The mitral valve was the most frequently involved (29 cases). In 2 cases there was also a mitral stnosis and mitral regurgitation grade 2 or 3 was found in 7 other cases. In 3 patients there was vegetations involving the mitral valve in 2 cases and the aorta in one case, 33 patients (26.4%) had myocardial abdnormalities. 3 patients had left atrial (LA) dilatation with normal sinus rrhythm. In 4 other patients the left ventricular (LV) was dilated and in 19 patients there was left cventicular hypertrophy (LVH). The LV revealed meanly a distolic relaxation abnormality in 14 cases and systolic contraction abdnormality in 6 cases. There was aloso a dysfunction regarding the segmental contractility in 5 cases including 2 patients with myocardial infarction. In 16 cases the SPAP was higher than 30 mmHg.

Conclusion: The heart involvelment in SLE Algerian population ins very high (56%). TTE appeared to be the best non agressive and the cheapest investigation tool in SLE patients.

P3676 Right ventricular ejection fraction in patients with left ventricular dysfunction

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Several studies are proposing normal range for right ventricle ejection fraction (RVEF) with radionuclide angiography (RA). But can we apply this values to the patients with left ventricle (LV) dysfunction?

Inter-relation between right and left ventricle (Berheim effect) may lead to a significant dependence of RVEF on left ventricle ejection fraction (LVEF).

In order to assess RVEF in pts with LV dysfunction, we studied 245 cases of RA.

Methods: 245 patients underwent equilibrium RA with measures of RVEF, right ventricle end diastolic volume (RVEDV), LVEF, and left ventricle end diastolic volume (LVEDV). We divided this population into 2 groups: group A with LVEF $\geq$ 40% (n = 119) and group B with LVEF < 40% (n = 126).

Results: in the entire group of 245 patients, RVEF was 33%, LVEF 39%. There was a significant difference between RVEF in group A (36%) and RVEF in group B (30%), $p < 0.001$. In both groups there was no correlation between RVEF and LVEF (group A: r = 0.14 and group B: r = 0.28).

In conclusion, RVEF decreases significantly in presence of left ventricle dysfunction. The absence of correlation between RVEF and LVEF is probably due to the numerous causes affecting RVEF.

P3677 Evaluation of T-wave pseudonormalisation on surface electrocardiogram as a marker of reversible myocardial ischaemia due to epicardial coronary artery disease

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Pseudonormalisation of T wave on surface electrocardiogram (ECG) during cardiac exercise testing is suggested to be one of the criteria for the positivity of the test. We performed stress thallium isotope scan and coronary angiography in patients exhibiting exercise induced T wave pseudonormalisation to assess its strength as an independent marker of reversible myocardial ischaemia.

Methods: 22 patients showing treadmill exercise induced pseudonormalisation in the surface ECG underwent coronary angiography. Presence of ST segment depression on ECG during exercise test associated with pseudonormalisation was also recorded.

Results: Of the 22 patients, 12 had angiographically demonstrated coronary artery disease. These 12 patients also had ST segment depression on exercise ECG. Remaining 10 patients neither had demonstrable coronary obstruction nor did they exhibit exercise induced ST segment depression. Thus in about one half of the patients with T wave pseudonormalisation, there was no demonstrable coronary artery obstruction on angiography.

In conclusion, exercise induced T wave pseudonormalisation, without ST segment depression does not appear to be an independent marker of reversible myocardial ischaemia due to disease in epicardial coronary arteries or its large branches. Its significance in identifying small vessel disease would need further evaluation.

P3678 Implantation of permanent pacemakers guided by transthoracic echocardiography

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The objective of this study is to demonstrate the usefulness, efficiency and safeness of transthoracic echocardiography (TTE) as a guide in the implantation of permanent pacemakers (PM).

Methods: We implanted PM (type VVI) in 42 patients, 28 (67%) male; the age was 22 to 91 years. 30 (74%) were diagnosed with complete AV block, 8 (19%) with second degree AV block and 4 (10%) with others. 32 (76%) presented Stoke Adams crisis. Pacemakers of different brand names were used; we also used 2.25 and 3 MHz transducers. The initial TTE, subcostal and apical views, evaluated the proximal cava veins and the right chambers. Special attention were given to measurements morphology, moderator band, apex and tricuspid valve. Vascular access was gained through the right subclavian vein in 32 (76%), right internal yugular vein in 4 (10%) and left subclavian vein in 6 (14%) cases. X-ray, ECG and TTE follow ups were done at 3 and 10 days.

Results: TTE showed an appropiate or optimal visibility of the cardiac chambers, the advancing catheter and the implant zone. The technique proved successful and had no complications in any case. Follow up evaluations verified proper PM catheter position and PM impulse capture.

Conclusions: TTE is efficient, safe and very useful in guiding the implantation of permanent pacemakers; fluoroscopy would not be needed. TTE makes the procedure easier and cheaper. As oppossed to fluoroscopy, TTE implies no ionizing radiation to the patient. This new technique is simple, lowers costs and could be performed in more medical facilities without fluoroscopy. Fluoroscopy is needed in cases of deficient echocardiographic windows.

P3679 Comparison of myocardial contrast echocardiography with Tc-99m SPECT in the assessment of segmental myocardial perfusion in patients with Chagas cardiomyopathy

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Nuclear agents proved to be useful for the evaluation of tissue perfusion in patients with Chagas disease. It has been reported that second generation contrast agents (Levovist, Shering,AG) leads to improve endocardial visualization and to the possible use of these agents for the determination of tissue perfusion.

Methods: We studied 50 myocardial segments in ten patients at rest after the injection of Levovist followed 24 hour latter by the injection of Tc sestamibi. All the patients had normal coronary arteries.

Results: 100% of the patients demonstrated abnormalities in tissue perfusion. All the patients demonstrated apical defects by both techniques. Contrast echocardiography was not able to identify two patients with lateral wall defects. Septal abnormalities were present in 80% of the patients. Inferior wall abnormalities were present in four patients. The anterior wall was spared in all the ten patients.

Conclusion: These findings coincide very well with the pathology in this disease entity. Myocardial contrast echocardiography provides a reliable tool for the diagnosis of wall motion and tissue perfusion in Chagas disease.