Day 3

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CLINICAL ASPECTS OF ENDOTHELIAL DYSFUNCTION: A HALLMARK IN VASCULAR DISEASE

1267 The impact of intermittent intravenous dobutamine therapy on endothelial function in patients with severe chronic heart failure

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Background: Intermittent intravenous dobutamine therapy is used to treat decompensated end-stage heart failure patients. However, its use has not been adequately documented in controlled trails and its prognostic effects are not well delineated. Vascular endothelium plays a key role in circulatory homeostasis. In CHF the vascular endothelium is usually impaired, and it has been suggested that modification or reversal of endothelial dysfunction may be of significant therapeutic benefit in the treatment of CHF patients.
Objectives: To investigate the impact of short-term intermittent intravenous dobutamine therapy on flow-mediated dilation (FMD) in patients with severe chronic heart failure (CHF).
Methods: We prospectively assessed intermittent intravenous low-dose dobutamine therapy (mean infusion rate of 3.5±1.5 μg/kg/min), endothelium-dependent brachial artery FMD and endothelium-independent nitroglycerin-mediated vasodilation (NTG) using high resolution (15 MHz) ultrasound in 15 consecutive severe CHF male patients with ischemic cardiomyopathy (New York Heart Association functional class IV) (mean age 57±11 years, mean left ventricular ejection fraction 22±8%), at baseline and after 4 months. Cardiac index (CI), stroke index (SI), and systemic vascular resistance (SVR) were assessed non-invasively by thoracic electrical bio-impedance device before and after intravenous dobutamine therapy.
Results: (see Table).

	%FMD	%NTG	SVR (dyne sec/cm5)	CI (l/min/m^2)	I (ml/m^2)
Baseline	1.1 ± 5.3	7.5 ± 8.8	2172 ± 1133	1.9 ± 0.6	27.2 ± 12.4
Post therapy	7.7 ± 4.6	7.6 ± 5.5	1797 ± 926	2.4 ± 0.6	33.5 ± 11.7
p-value	0.001	0.979	0.05	0.016	0.024

Values are expressed as mean±SD; %FMD, %NTG=% change from baseline in brachial artery diameter caused by FMD and NTG, respectively.

Conclusions: Severe CHF patients suffer from impaired endothelium-dependent and-independent vasodilation, suggesting the presence of both endothelial and smooth muscle dysfunction. Short-term intermittent intravenous low-dose dobutamine therapy, however, can significantly improve vascular endothelial function, perhaps demonstrating an additional mechanism whereby SVR, CI and SI are improved in severe CHF patients treated by intravenous dobutamine.

1268 HLA-DRB1 status influences endothelial dysfunction in long-term treated patients with rheumatoid arthritis

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Cardiovascular disease is the commonest cause of premature mortality in rheumatoid arthritis patients.
Aim: To examine the endothelial function in a series of long-term treated rheumatoid arthritis patients and assess whether clinical or genetic factors may be implicated in the development of endothelial dysfunction.
Methods: Fifty-five patients fulfilling the 1987 American College of Rheumatology classification criteria for rheumatoid arthritis were recruited from a single reference hospital in northwestern Spain. Patients were required to have been treated for at least 5 years and to be on treatment with one or more disease modifying anti-rheumatic drugs at the time of this study. Patients with diabetes mellitus, renal insufficiency, cardiovascular or cerebrovascular events were excluded. Thirty-one age, sex and ethnically matched controls were also studied. Endothelial dependent and independent vasodilatation were measured by brachial ultrasonography. Patients were HLA-DRB1 genotyped using molecular based methods.
Results: Patients had decreased endothelial dependent vasodilatation (3.8 ± 4.9%) compared with controls (8.0 ± 4.5%); P<0.001. There were no differences in endothelial independent vasodilatation. Clinical features were not associated with endothelial dysfunction. The mean value of endothelial dependent vasodilatation was decreased in the 30 rheumatoid arthritis patients carrying HLA-DRB1*04 shared epitope alleles (2.4 ± 4.1%) compared with the remaining rheumatoid arthritis patients (5.5 ± 5.3%); P=0.01. This was also the case when patients who carried the HLA-DRB1*0404 shared epitope allele were compared (-0.4 ± 2.5%) with the rest of rheumatoid arthritis patients (4.4 ± 4.9); P=0.01.
Conclusion: Endothelial dysfunction is present in long-term actively treated rheumatoid arthritis patients. Our results suggest a possible role for HLA-DRB1 status as a predictor of cardiovascular risk.

1269 Migraine is associated with peripheral vascular dysfunction

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Several studies have postulated an association between migraine and an increased risk of cardiovascular events, such as stroke and coronary artery disease. Recently, it has been hypothesized that endothelial dysfunction may play a role in increasing the risk of cardiovascular diseases in several conditions. However, few and inconsistent data are available with regard to the relation between migraine and vascular function. Thus, it remains unknown whether the endothelium plays a role in the increased risk of cardiovascular disease in patients with migraine. To clarify this issue, we studied 11 patients with migraine (M) during the interval between the attacks and compared them with 11 healthy controls (C). We measured forearm blood flow (FBF) by strain-gauge plethismography during intra-brachial, graded infusion of: acethylcoline (ACh, 15 to 60 ug/liter of forearm/min), sodium nitroprusside (NP, 1 to 9 ug/l/min), norepinephrine (NE,140 to 560 ng/l/min) and L-NMMA (1 mg/l/min). Diastolic blood pressure was higher in M than in C (66.4±2.6 and 57.4±1.52, respectively, p<0.01). Basal FBF was similar in M and in C. During ACh infusion, FBF reached 19.8±3.9 ml/dl/min in C and 9.2±2.4 in M (p<0.05 vs C). The slope of the dose response curve to Ach was steeper in C that in M (0.32±0.07 and 0.12±0.05 ml/dl/min/μg, respectively; p<0.05). During NP infusion, FBF rose to 22.9±1.9 ml/dl/min in C and 12.0±2.15 in M (p<0.001 vs C). Accordingly, the slope of the dose response curve to NP was steeper in C that in M (2.09±0.19 and 0.97±0.21 ml/dl/min/μg, respectively; p<0.001). During NE infusion, FBF decreased similarly in both groups. L-NMMA infusion decreased FBF by 0.52±0.6 ml/dl/min and 0.9±0.4 in C and M, respectively (p=NS). In conclusion: in patients with migraine studied in the interval between the attacks, vascular reactivity is abnormally reduced due to the contribution of both endothelium- and non-endothelium-dependent mechanisms; and 2) the vasoconstrictory response to norepinephrine is preserved. The abnormalities detected in vascular reactivity in patients with migraine may explain the increased risk of cardiovascular diseases observed in these patients.

1270 Endothelial function is transiently impaired by acute inflammation: evaluation in patients subjected to percutaneous coronary interventions

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Purpose: There has been a lot of interest on the relationship between inflammatory response and endothelial dysfunction. In fact, several studies have shown that endothelial function is impaired in patients showing an enhanced inflammatory response. However, there have been only a few studies on the changes in endothelial function during acute inflammation. Therefore, we performed the present study to examine endothelial function after percutaneous coronary interventions (PCI), which is considered as a model of acute inflammation of the coronary artery, in patients with coronary artery disease (CAD). Methods: Twenty-three patients (mean age 67yrs, 20 men) who underwent PCI (Group I), 23 patients (mean age 66 yrs, 20 men) with CAD subjected only to coronary angiography (Group II) were enrolled for the study. In each patient, changes in the diameter of the brachial artery on the non-punctured side in response to hyperemic flow (flow-mediated dilatation: FMD) and nitroglycerin spray (NTG) were measured using high resolution ultrasonography before, and 2 days and 5 days after PCI or coronary angiography. Results: Data were expressed as the mean"bSEM. The patients characteristics such as age, gender differences, angiographic findings, and high-sensitive C-reactive protein (hs-CRP) concentrations at baseline did not differ between the two groups. FMD and NTG-induced dilation at baseline were also similar between the two groups. In Group I, FMD decreased from 4.6"b0.3% before PCI to 0.7"b0.3% 2 days after PCI, and returned to 3.8"b0.4% 5 days after PCI (p = 0.0001); whereas FMD did not significantly change in Group II (4.6"b0.6% before coronary angiography, 4.2"b0.6% on Day 2, and 4.2"b0.5% on Day 5). NTG-induced dilation did not change after PCI in Group I (13.7"b1.2% before PCI, 12.3"b1.5% on Day 2, and 13.7"b1.4% on Day 5) or after coronary angiography (15.5"b1.6% before coronary angiogprahy, 13.9"b1.2% on Day 2, and 15.6"b1.0% on Day 5) in Group II. The increase in hs-CRP concentration on Day 2 correlated negatively with the decrease in FMD on Day 2 (r = -0.373, p = 0.0101). Conclusions: These results suggest that FMD of the brachial artery was impaired after PCI, which is a model of acute inflammation, but returned to the original level after the improvement of the inflammatory response. Endothelial dysfunction may be caused by acute inflammation but may be transient.

1271 Endothelium dependent flow mediated vasodilatation of systemic arteries is impaired in patients with myocardial virus persistence

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Objective: Endothelial dysfunction in patients with myocarditis has been associated with inflammatory immune responses in myocardial biopsies, as demonstrated by immunohistology. In some patients, this myocardial inflammatory process in induced by myocardial virus persistence. Myocardial inflammation has been associated with endothelial dysfunction of systemic arteries. The aim of this study is to investigate the impact of myocardial virus persistence on endothelial function in these patients.
Methods: In 115 patients with suspected cardiomyopathy, myocardial biopsies were examined for myocardial virus persistence (by polymerase chain reaction) and myocardial inflammation (by immunohistology). Endothelial function of the radial artery was examined by high resolution ultrasound. Diameter changes of the radial artery in response to reactive hyperemia (FMD), as compared to glyceroltrinitrate (GTN-MD), were measured. FMD represents endothelium dependent vasodilation, GTN-MD represents smooth muscle cell reactivity/endothelium independent vasodilation.
Results: Mean age of the 51 male and 64 female patients was 45±13 years, mean left ventricular ejection fraction was 56±17%. In 65 patients, adeno-, entero-, parvo- or HHV6-virus was detected via PCR, in 50 patients, no virus was detected. Flow mediated vasodilation was significantly impaired in patients with myocardial virus persistence, as compared to controls: FMD-V 4.42±4.94%, FMD-Co 5.74±3.54 (p=0.004). In 82 patients, myocardial inflammation was detected by immunohistology (MC), of those, 49 had myocardial virus persistence and in 33 no virus was detected. FMD was significantly impaired in patients with myocardial virus persistence, as compared to controls: FMD-MC-V 4.29±5.39%, FMD-MC-Co 5.29±3.25 (p=0.006). In 33 patients, immunohistology of the myocardial biopsies were normal (Co), of those, 16 had myocardial virus persistence and in 17 no virus was detected. FMD was impaired in patients with myocardial virus persistence, as compared to controls: FMD-Co-V 4.81±3.32%, FMD-Co-Co 5.51±4.01 (p=0.191). Endothelium independent vasodilation (GTN-MD) was not affected.
Conclusions: Endothelial function is impaired in patients with myocardial virus persistence. It can occur in patients with and without myocardial inflammation. Endothelial dysfunction is more pronounced in patients with myocardial virus persistence and myocardial inflammation.

1272 Endothelial dysfunction in young women with premature ovarian failure and reversal following cyclic oestrogen/progestin therapy

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Purposes. Premature ovarian failure (POF) or premature menopause is a condition characterized by amenorrhea, infertility, and sex steroid deficiency in women <40 years of age. Young women with POF are at increased risk for cardiovascular disease (CVD) and have a nearly two-fold age-specific increase in mortality rate. Although it is well known that normal menopause is associated with endothelial dysfunction, endothelial function in women with POF has not been studied. We studied whether endothelial function is impaired in young women with POF compared to age-matched healthy women and whether this may improve following cyclic oestrogen/progestin therapy.
Methods: Fifteen women with POF (diagnosis established at an age <40 years) aged 37.5±6.3 (25-43) years [mean±SD (range)] were studied prior to and after a 6-month period of cyclic oestrogen/progestin therapy. Nineteen age-matched healthy women with normal ovarian function (35.2±4.8, 29-48 years) were also studied. No women were receiving any medications apart from those used for the purposes of the study. Endothelium-dependent flow-mediated dilation (FMD) and nitroglycerin-mediated, endothelium-independent dilation (EID) was assessed in all women using high resolution (10 MHz) linear array ultrasound in the brachial artery.
Results: The 2 groups did not differ in body mass index, smoking habits, blood pressure, diabetes or family history of coronary artery disease. Total and LDL cholesterol were higher in POF compared to age-matched healthy women at baseline [223±46 vs 195±36 (p=0.05) and 150±38 vs 120±28 mg/dl (p=0.03) respectively] and did not change significantly in POF women post-treatment (208±25 and 131±19 mg/dl respectively, p=ns cf. pre-treatment). Endothelium-dependent FMD was impaired in women with POF prior to treatment compared to women with normal ovarian function; mean±SD percent change of brachial artery diameter to baseline 2.3±5.2% vs 9.0±2.2%, p<0.00001 (unpaired t-test). FMD improved in women with POF following treatment; FMD increased to 7.52±3.86%, p<0.005 cf. pre-treatment, p=ns cf. normal women. EID was similar between the 2 groups at baseline (19.5±4.8% in POF vs 22.4±6.1% in normal women, p=ns) and did not change post-treatment in POF women (21.0±5.6%, p=ns).
Conclusions: Premature ovarian failure is characterized by arterial endothelial dysfunction. Cyclic oestrogen/progestin therapy reverses endothelial dysfunction in women with POF.

GEOGRAPHIC VARIABILITY OF CARDIOVASCULAR RISK

1273 Differential hypertension control among patients with established coronary heart disease. Results from the EUROASPIRE II study

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Background: There is a wealth of evidence that blood pressure control among treated hypertensives is unsatisfactory. Recently, attention has been payed to the distinction of systolic (SBP) and diastolic (DBP) blood pressure control. This study aims to investigate patterns of differential SBP and DBP control in coronary patients.
Methods: The EUROASPIRE II survey was conducted between 1999-2000 in 15 countries. 5556 patients with established coronary heart disease (CHD) were interviewed and examined on average 1.4 years after their initial coronary event. Blood pressure was measured with standardised devices twice in a sitting position and the mean of the two measurements was used in the analyses. We assessed the prevalence of isolated systolic, isolated diastolic, and combined hypertension and determined proportions of control according to SBP (< 140 mmHg) and DBP goal (< 90 mmHg). Factors related to poor SBP and DBP control were identified using multivariate analyses.
Results: In total, 2579 patients reported antihypertensive treatment and diagnosis of hypertension at interview and were considered for further analyses. Only 36% of treated hypertensives were controlled to both SBP and DBP. Isolated systolic (49.6%) and combined systolic/diastolic hypertension (43.2%) were frequent types of uncontrolled hypertension, whereas isolated diastolic hypertension was rather rare (7.3%). SBP control decreased significantly from age < 50 years (58.6%) to age 61-74 years (32.1%, p<0.0001). In contrast, DBP control increased across these age groups (60.9% vs 70.3%, respectively, p=0.0004). We observed no major differences in overall blood pressure control between men and women. Age was most strongly related to poor SBP control (OR 2.7; 95% CI 2.1-3.5 for age <50 years vs age 61-74 years) and inversely associated with poor DBP control (OR 0.6; 0.4-0.7) in multivariate analyses. Elevated total cholesterol was associated with both poor SBP (OR 1.3; 1.1-1.6) and poor DBP control (OR 1.4; 1.2-1.7). Males were more likely to have elevated DBP than females (OR 1.5; 1.2-1.8).
Conclusions: This study shows a clear age-related pattern of hypertension control. Poor SBP control increased with age and constituted the bigger part of poor overall blood pressure control. Trial data suggest that DBP < 90 mmHg is achievable in 70-90% but only 30-50% of hypertensives may reach SBP < 140 mmHg. Though hypertension control is particularly important in secondary prevention of CHD, a SBP goal < 140 mmHg might be unrealistic in older patients.

1274 A comparison of diabetic multivessel coronary disease in Indian Asians versus white Europeans: results from a prospective registry 1998 to 2001

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Background West London is an area with a diverse ethnic mix and a significant minority of people who originate from the Indian subcontinent.
Purpose To compare the outcomes of White European and Indian Asian diabetics known to have multivessel coronary artery disease.
Methods From January 1998 to December 2001 we identified all diabetic patients with multivessel coronary artery disease, defined as narrowings of at least 50% in two or more major epicardial vessels and compared outcomes between White Europeans and Indian Asians whose ethnic origin is in the Indian subcontinent, but who are now living in the United Kingdom.
Results Of 9586 patients 1714 were found to be diabetic and 970 (56.6%) to have multivessel disease. The proportion of patients in the community in West london which refer to our hospital who are Indian Asian is known to be 12% in the 30 to 85 year age range. However over the course of the 4 years of the study 28% of the patients undergoing coronary angiography were Indian Asians compared to 58% who were White Europeans. The rate of diagnosis of coronary artery disease at coronary angiography is similar but significantly Indian Asians accounted for a disproportionately large number of the diabetics undergoing coronary angiography 41.0% versus 46.7%. Furthermore Indian Asians who were diabetic were then more likely to have multivessel disease. Of the 970 patients with this condition Indian Asians accounted for 49.0% versus 39.3% in White Europeans. However these two groups were equally likely to receive the same mode of therapy ie PCI, CABG or medical therapy. Follow up data is complete in 98.1% of patients in this study and preliminary analysis indicates that outcomes do not differ significantly between Indian Asians and White Europeans with diabetic multivessel disease.
Conclusion Our registry data suggest that Indian Asians in the United Kingdom have a higher risk of developing coronary artery disease than White Europeans and that they account for a disproportionately large number of patients who have diabetes, in particular diabetic multivessel disease.

1275 Prevalence of arterial hypertension in Poland in 2002, and its influence on risk of myocardial infarction

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Objectives: to assess prevalence of arterial hypertension (HT) in Poland in 2002 and its influence on the number of myocardial infarction (MI) events.
Design and Methods: In 2002, a representative sample of adults in Poland (n=3051) was examined in the NATPOL III PLUS study. The respondents were recruited from 300 geographical locations using a multistage sample selection method. The main aim of this nationwide survey was to assess the prevalence and control of all major cardiovascular risk factors. Blood pressure and anthropometric measurements were performed in all randomly selected subjects (age range 18-94 years); of which 78% completed laboratory tests (fasting lipids and glycaemia). According to JNC VI and WHO/ISH 1999 guidelines the diagnosis of hypertension (HT) was based on three separate visits (BP>=140/90 mmHg or on medication). The risk of myocardial infarction for the group of respondents aged 30-70 years (n=1549), was evaluated using the PRECARD risk management system.
Results: Prevalence of HT in the sample population was 29%. Optimal blood pressure was found in 21%, normal in 20% and high normal in 30% of subjects. One third of all hypertensives were newly detected and HT was well controlled (BP<140/90 mmHg) in 12% of all hypertensive subjects.
In subjects aged 30-70 years, the prevalence of HT was 33%. By using the PRECARD algorithms, this could imply that the number of expected MI's in Poland in the respective age group during the next 10 years will be 740.000 events (W: 246.000; M: 494.000). Presuming 100% control of systolic arterial pressure (<140 mmHg), the number of MI's would then be reduced by 22,6% in women (56.000 cases) and by 18,4% in men (91.000 cases).
Conclusions: 1. The NATPOL III PLUS study, conducted on a representative sample of adults in Poland, proved to be effective, relatively cheap, and accurate (SE<2,0%) tool to assess prevalence of arterial hypertension and other cardiovascular risk factors in the country. 2. Prevalence of hypertension and high normal blood pressure in Poland reaches 59% of adult population and indicates urgent needs for intensive and effective preventive measures. 3. Potential reduction of systolic blood pressure to at least 139 mmHg in subjects aged 30-70 years would prevent one fifth of MI's during coming 10 years.

1276 Worksite hypertension prevalence and control in three Central European countries

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Purpose: The primary objective of this study was to establish the prevalence of hypertension and treatment status in worksites in Austria, Hungary and Slovakia. The secondary objectives were to assess the awareness and level of control of hypertension. Compared to Austria, cerebrovascular stroke (CVS) mortality is three times higher in Hungary, and twice as high in Slovakia. Our hypothesis was that the relatively low (CVS) mortality in Austria is a result of better awareness and treatment of hypertension in Austria.
Methods: A cross-sectional survey of 'blue collar' employees on work sites in each of these countries, using blood pressure screening at 3 work sites in Austria, 1 in Hungary, and 1 in Slovakia. A standardized protocol was followed in each of these countries. The Bp-TRU(TM) measuring instrument was used to provide accurate reproducible readings and eliminate inter-observer error. Hypertensives were classified as those respondents who had a SBP >/=140 mmHg and/or DBP >/=90 mmHg or those who were taking antihypertensive medication, regardless of their blood pressure level. 'Controlled' hypertensives were classified as those with SBP <140 mmHg and DBP <90 mmHg.
Results: After exclusion of missing data, the study population included 323 males screened in Austria, 600 in Hungary, and 751 in Slovakia. The age range of the respondents in all three countries was 16-79 years. The prevalence of hypertension was 29% in Austria, 28% in Hungary and 40% in Slovakia. Of those identified as hypertensive, 73% in Austria, 45% in Hungary and 67% in Slovakia were newly diagnosed as a result of this screening. Of those treated for hypertension, 10% in Austria, 15% in Hungary and 5% in Slovakia were controlled (see Table).

Control of hypertension

Country	Total participants identified with hypertension (HT)	Total participants treated for HT	Total participants with HT controlled
Austria	93	26 (28%)	9 (10%)
Hungary	168	53 (32%)	25 (15%)
Slovakia	303	100 (33%)	16 (5%)

Percentage of control in participants identified with hypertension.

Conclusions: Despite dramatic differences in CVS mortality between Austria, Hungary and Slovakia, our study establishes that this gradient is not due to better treatment and control of hypertension in Austria, and highlights the need for further research to determine the cause of this mortality gradient in Eastern Europe.

1277 Status and management of hypertension, in Greece; the role of the adoption of Mediterranean diet: the ATTICA study

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Aim: The aim of this work is to evaluate the prevalence, awareness, treatment and control of hypertension, in a random sample of cardiovascular disease free adults, in Greece. Secondary goal is to evaluate the association between hypertension status and adoption of Mediterranean diet.
Methods: The ATTICA study is a cross sectional survey. Based on a multistage sampling, 1128 men and 1154 women (>18 years old) were enrolled. The survey included a detailed interview and, among other clinical measurements, status and management of blood pressure levels, was recorded. The consumption of red meat, chicken, fishes, vegetables, legumes, pasta, salads, cereals, diary products, sweets and fruits was investigated as an average per week, during the past year, using a special nutritional questionnaire, developed by the National School of Public Health. We defined subjects who adopt Mediterranean type of diet using as cut-off points the median values of the monthly food consumption score.
Results: The prevalence of hypertension was 38.2% in men and 23.9% in women (P < 0.05). The majority of men (65%) and women (38%) were untreated, and of those who were treated, only, 15% were adequately controlled. Multivariate logistic regression analysis revealed that the adoption of Mediterranean diet was associated with 26% (odds ratio = 0.74, P = 0.008) lower risk of being hypertensive, and with 36% (odds ratio = 1.36, P = 0.021) higher probabilities of being controlled.
Conclusions: A considerable proportion of the general population is still not well controlled or is unaware of their hypertension. However, adoption of Mediterranean type of diet seems to reduce population rates, and may assist the control of hypertension, at population level.

1278 Lipid levels and treatment in England and Scotland

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Preventing cardiovascular events with lipid-lowering drugs has been established in several trials reported since 1994. Consequently national guidelines recommend statins for those with established cardiovascular disease (CVD) and those at high risk of developing CVD.

Methods We investigated blood lipid levels and the prevalence and efficacy of the use of lipid-lowering agents in nationally-representative samples of English and Scottish adults and in subgroups of high risk subjects surveyed in 1998 by means of cross-sectional studies: the Health Survey for England and the Scottish Health Survey. These surveys included 15696 adults aged 16-74 with valid cholesterol results. The main outcome measures were mean blood levels of total cholesterol, HDL-cholesterol, total:HDL-cholesterol ratio by age and sex; prevalence of elevated total cholesterol levels, and total:HDL- cholesterol ratios; prevalence of lipid-lowering agent use and lipid levels of those on treatment.

Results Levels of dyslipidaemia, treatment and control were not significantly different between Scotland and England. Combining these data, mean total cholesterol levels were 5.43 and 5.48 mmol/l in men and women respectively, and mean HDL-cholesterol levels were 1.29 and 1.56 mmol/l. Overall 64.6% of adults had a total cholesterol $\geq$5mmol/l, 24.6% had a total:HDL ratio $\geq$5 and only 2.3% reported taking lipid-lowering drugs. Of 175 adults with no history of cardiovascular disease but an estimated 10-year risk of coronary heart disease $\geq$30%, and a total cholesterol $\geq$5mmol/l, 6 (3.4%) were taking lipid-lowering drugs. Treatment rates with lipid lowering agents among those with a total cholesterol $>$5mol/l and a history of coronary heart disease or stroke, hypertension, or diabetes, were 27.3%, 15.4% and 17.8% respectively, and control rates (total cholesterol $<$5mmol/l) among those treated were 45.3%, 38.5% and 32.7%.

Conclusions Despite the high prevalence of dyslipidaemia, the proportion of adults taking lipid-lowering drugs in Scotland and England in 1998 was only 2.3%. In addition, treatment rates were low among high-risk patients suitable for primary prevention, and were less than 33% in those with established CVD. Dyslipidaemia is under-treated in England and Scotland and is a target whereby the currently high rates of cardiovascular events could be greatly reduced.

DOPPLER MYOCARDIAL IMAGING IN MYOCARDIAL ISCHAEMIA

1279 Regional left-ventricular wall thickness and strain: new reperfusion and viability markers

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Introduction: There is need for better reperfusion markers in acute myocardial infarction. This study investigates if strain Doppler echocardiography (SDE) in combination with grey scale imaging may identify reperfused myocardium.

Methods: In 15 anaesthetized dogs we measured LV pressure, end-diastolic wall thickness (EDWT) by echocardiography, myocardial long axis strain by SDE, and segment lengths by sonomicrometry. The LAD was occluded for 15 minutes (n=5) and 4 hours (n=5), respectively, and then reperfused for 3 hours. In 5 dogs the LAD was occluded for 4 hours with no reperfusion. Necrosis was identified by TTC-staining and myocardial oedema by measuring water fraction. Myocardial compliance was calculated as systolic lengthening by sonomicrometry divided by systolic pressure rise.

Results: Reperfusion after 4 hours of ischaemia reduced myocardial compliance by 44$\pm$17%* (Fig. 1), reduced systolic lengthening by 44$\pm$14%* and postsystolic shortening (PSS) by 48$\pm$13%* (Fig. 2), and increased EDWT by 44$\pm$8% ($p<0.01$). These changes occurred rapidly and were near maximal after 5 minutes with reperfusion. Reperfusion caused a 4$\pm$0.7%* increase in water fraction (Fig. 3), indicating myocardial oedema. In each animal with 4 hours ischaemia TTC-staining showed necrosis. Reperfusion after 15 minutes of ischaemia caused partial recovery of systolic function, with no change in EDWT and water fraction.

Conclusions: Reperfusion of irreversibly injured myocardium caused rapid and marked increase in EDWT and reductions in systolic lengthening and PSS. These changes were attributed to reperfusion-induced myocardial oedema that caused a decrease in myocardial compliance. Thus, SDE in combination with wall thickness measurement may serve as markers of reperfusion and viability.

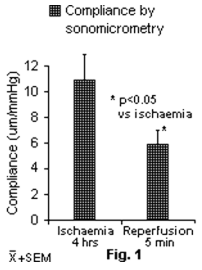


Fig. 1

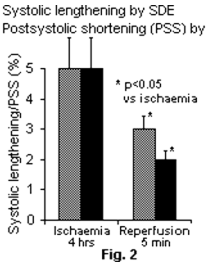


Fig. 2

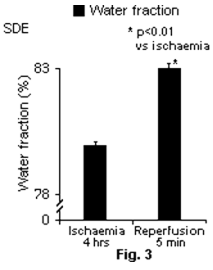
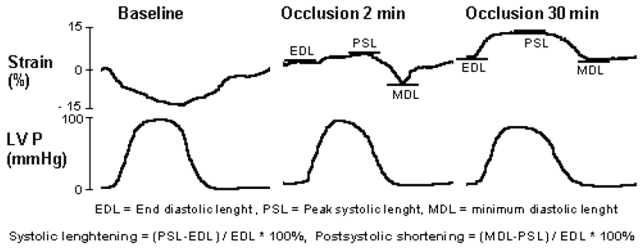


Fig. 3

Background: We investigated if strain Doppler echocardiography (SDE), as opposed to conventional echocardiography, can identify viable segments generating active wall tension. Our hypothesis was that active tension would limit systolic lengthening and enhance postsystolic shortening (PSS).

Methods: Nine anaesthetized dogs were instrumented with LV micromanometers and longitudinal segment length (SL) crystals in the LV anterior wall. Strain was measured by SDE. The LAD was occluded and measurements were done after 2 and 30 min. PSS was defined by a simplified approach without exact timing of end systole (Figure). From the regional LV pressure (LVP)-SL loops we defined active contraction as an upward-shift of the early diastolic portion (mid-IVR) of the loop relative to the fully relaxed loop in late diastole.

Results: After 2 min of occlusion there was 6$\pm$2% (mean$\pm$SD) systolic lengthening and 19$\pm$5% PSS. The ratio of systolic lengthening to PSS was 0.3$\pm$0.1. The LVP-SL analysis showed a 15$\pm$8 mmHg upward shift, indicating a component of active contraction. After 30 min of occlusion there was 8$\pm$3% systolic lengthening and 9$\pm$2% PSS ($p<0.05$), and the ratio was 0.8$\pm$0.1 ($p<0.05$). The LVP-SL analysis showed a 2$\pm$3 mmHg downward-shift ($p<0.05$), indicating absence of active contraction. The strain Doppler data were consistent with the sonomicrometry data.



Conclusions: Strain patterns discriminated between dyskinetic segments that were actively contracting, and therefore viable, and segments that were entirely passive. In active segments PSS markedly exceeded systolic lengthening, while in entirely passive segments PSS approximated systolic lengthening. This ratio can be easily measured in a clinical setting by SDE, and may offer a simple method to identify viable myocardium.

1281 Correlation between tissue Doppler, strain rate, strain imaging during dobutamine infusion and coronary fractional flow reserve during catheterization: a comparative study

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Coronary fractional flow reserve (FFR) as an invazive and dobutamin stress echocardiography as a noninvazive technique were used to detect critical coronary stenosis. This study was undertaken to correlation between these two technique by using tissue Doppler, strain rate (SR), strain imaging (S). Methods: In 17 patients (aged 53.0±12.5, 5 F), totally 22 vessel were studied. On dobutamin stress echocardiography, baseline and peak systolic(Sm),early (Em) and late (Am) diastolic myocardial velocities, SR and S were recorded from parasternal view (mid-posterior segment) for radial and apical view (mid-septum) for longitudinal deformation. And then coronary FFR was performed by using intracoronary adenosine infusion, and the value of $\leq$0.75 was accepted as critical coronary stenosis. Results: FFR was found significant in 10 vessel (FFR critical). Baseline Sm, Em/Am, SR, S values, and peak Em/Am, SR, S values were similar between critical or noncritical FFR groups. Baseline Sm and Em, and change between baseline and peak Sm and S were significantly higher in noncritical FFR group ($p<0.01$, <0.05, <0.001, <0.001 respectively). In critical FFR group, baseline Sm, Em/Am, SR and S significantly decreased when compared the same values of peak dobutamin stress test ($p<0.05$ for all). In all vessel, baseline FF was shown a poor correlation with baseline Sm and chance in S parameters, and a good correlation with change in Sm (r:0.32, 0.32, 0.69 respectively). In critical vessel, FFR after adenosine was shown a poor correlation with baseline and peak SR, S, and chance in Em/Am parameters(r:0.48, 0.36, 0.46, 0.48, -0.32 respectively), and a good correlation with change in Sm and SR (r:0.65, 0.65 respectively). Conclusion: The quantitation of regional myocardial deformation by using Dobutamin stress echocardiography rather than motion would to be more appropriate in detecting ischemic dysfunctional segment which supplied by critical coronary sternosis. And strain measurement during dobutamin infusion may estimate FFR of the culprit vessel.

1282 Tissue Doppler versus strain rate imaging for detecting regional myocardial ischaemia during dobutamine stress echocardiography

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The interpretation of Dobutamine Stress Echos (DSE) is subjective. Tissue Doppler (TDI) and Strain Rate Imaging (SRI) provide the possibility of measuring regional myocardial velocity and deformation. We compared the performances of both methods in recognizing stress induced ischemia (ISCH) during DSE.

Methods: TDI loops in apical views were recorded digitally in 44 patients at all DSE levels using a Vivid Five Ultrasound Machine (GE Vingmed, Norway). Velocity (V), motion (M), strain rate (SR) and strain (S) curves were derived from all myocardial segments (SEG). SEG with ISCH were defined by simultaneous SPECT perfusion imaging. Area under the receiver-operating curve (AUC) was used to compare the diagnostic accuracy of the following parameters: V and SR (Vsys, SRsys), total M and S during a cardiac cycle (Mtot, Stot) and during ejection time (Met, Set), velocity (Vps) and S (Sps) of postsystolic shortening (PSS) as well as its percentage of Stot (Sps/Stot).

Results: During DSE, in SEG without ISCH SRsys increased from -1.6/s to -3.4/s ($p<0.01$), while Stot, Set and Sps/Stot remained unchanged. SEG with ISCH showed a significantly reduced ($p<0.01$) SRsys increase (-1.6 vs. -2.0, $p<0.05$), Set decreased (-16% vs. -10%, $p<0.05$) and marked PSS occurred (Sps: +1% vs. -7%, $p<0.01$). TDI parameters of apical, middle and basal SEG differed significantly. In SEG without ISCH, apical Vsys increased from 1 to 2 (n.s.), middle from 3 to 5 (59%, $p<0.05$) and basal from 4 to 7 cm/s (69%, $p<0.01$). In SEG with ISCH the increase in Vsys was not significant. In the presence of apical ISCH the non-ischemic basal SEG showed no Vsys increase too (-8%, $p<0.05$). The other TDI parameters behaved similarly. The best marker of ISCH during DSE on TDI was Vps (AUC=0.62), on SRI it was Sps/Stot (AUC=0.90, $p<0.05$).

Conclusions: Compared to TDI, SRI parameters showed no difference from basis to apex, had significantly higher diagnostic accuracy and measurements in basal SEG were not influenced by apical ISCH. SRI thus appears superior to TDI for the detection of stress inducible ischemia.

1283 Delay in start of local relaxation velocity – contra the global event – corresponds to maximal tissue velocities and visual assessment in the acute coronary syndrome

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Purpose This study aimed to determine the time relationship between the onset of mitral left ventricular inflow and the start of the local relaxation tissue velocity of different walls in the acute coronary syndrome.

Methods Patients with an acute coronary syndrome (n=161) and age-and sex-matched healthy controls (n=50) were echocardiographically examined; pulsed Doppler Tissue Imaging, DTI, was applied to the basal septal, lateral, inferior and anterior left ventricular wall. Each wall was also assessed for number of visually pathological segments. All DTI-curves were digitized for off-line analyses in a computor program designed for this purpose. Maximal velocities of the systolic (s)-, and early diastolic (e)- waves were measured as was the temporal relationship between the initiation of the local relaxation velocity (e-start) and the onset of the mitral inflow (E-start), derived from pulsed mitral Doppler. Both e- and E-start were normalized to the ECG R-wave. Furthermore we calculated the time range of all e-starts per person. Values are means±SD.

Results Both systolic and diastolic maximal velocities were lower for patients than for controls and the time difference between E- and e- start was more negative. All three variables corresponded well to the number of visually affected segments (see table). In addition the time range of all e- initiations for one individual was broader for patients (43±27 vs 30±18 ms, $p< 0,0001$).

	c	p0	p1	p2	p3
smax (cm/s)	7,9**	6,6	6,2*	5,6**	4,8**
emax (cm/s)	-10,1**	-7,6	-6,7**	-6,1**	-5,6**
E-e (ms)	-2,0	-4,2	-12,7*	-20,3**	-32,7**

Values for healthy controls (c) and patients (p) with an acute coronary syndrome with 0, 1, 2, or 3 visually patholgical segments per wall (p0, p1, p2, p3). Values are means. * $P<0.01$ and ** $P<0.0001$ versus p0.

Conclusions Our results suggest that the local start of relaxation velocity occurs later - in relation to the onset of mitral inflow - for patients with an acute coronary syndrome than for healthy individuals, and with greater asyncrony. This finding was compatible with two established methods; traditional visual judgement and measurement of maximal tissue velocities. We believe this new approach of tissue doppler could increase patophysiological understanding.

GENETICS AND ARRHYTHMIAS

1289 Ventricular tachyarrhythmias caused by reduced connexin 43 expression

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Background: Connexin 43 (Cx43) is a major gap junction protein in the ventricular working myocardium of mammals. The role of a reduced Cx43 expression for ventricular arrhythmias was studied using inducible Cx43 deficient mice.

Methods: One coding region of the Cx43 gene was replaced by CreER(T), an inactive form of Cre-recombinase. The second Cx43 coding region was replaced by a floxed Cx43 construct. Administration of 4-hydroxytamoxifen activates Cre, which deletes the Cx43 allele. Twenty mice were studied; 10 control mice (group 1, no tamoxifen), 10 mice at day 13 after administration of tamoxifen (group 2). Hearts were removed and Langendorff-perfused. Epicardial electrical activity was recorded from the right (RV) and left ventricle (LV) using a 13x19 multi-terminal electrode grid (300μm spacing). Programmed stimulation was applied to determine electrophysiological characteristics and to induce arrhythmias.

Results: Cx43 protein was decreased by ~90% in group 2 animals. Stimulation in the center of the grid electrode revealed reduced conduction velocity in group 2 on both RV and LV (25% and 15% reduction, respectively). In group 2 mice dispersion of conduction in RV(LV) increased by 91%(38%). The anisotropic ratio increased by a factor of 2.0 (RV) and 1.4 (LV). Premature stimulation resulted in short runs of ectopic ventricular beats or sustained ventricular tachycardias in group 2 mice only (7 of 10 mice). Three out of 4 hearts that exhibited sustained tachycardias revealed a stable reentry circuit on the RV and multiple wavefronts meandering on the LV. One heart showed fibrillatory activation on both RV and LV.

Conclusions: Reduction of Cx43 up to 90% decreased conduction velocity by 15-25%, increased dispersion of conduction and propensity for ventricular arrhythmias. Activation patterns suggested that sustained arrhythmias were based on anisotropic reentry on RV and fibrillatory conduction on LV.

1290 Gene dose-dependent atrial arrhythmias, heart block and atrial cardiomyopathy in mice overexpressing the A3 adenosine receptor

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Objective: Enhanced function of adenosine receptors could contribute to both sinus nodal and AV nodal dysfunction. Both A1 and A3 adenosine receptors are present in the human atrium. We studied whether overexpression of A3AR alters sinus and AV nodal function.
Methods and Results: Mice with heart-directed overexpression of A3AR at high (A3high) or low (A3low) levels were instrumented with a telemetric ECG transmitter, and the ECG was recorded in freely moving animals during periods of normal activity and swimming exercise (n=7 per group). During normal activity, A3high mice had profound sinus bradycardia (A3high 217±25; WT 406±21 b/min*, all values as mean±SEM, * denotes p below 0.05), resulting in either ventricular escape rhythms or incessant tachycardia-bradycardia syndrome at 3 and 18 weeks of age. During exercise, bradycardia was less pronounced (maximal heart rate A3high 650±13; WT 796±13 b/min*) and first degree AV nodal block was present (PQ interval A3high 36±4; WT 23±5ms*) in 18 weeks old A3high mice. Bradyarrhythmias documented before 3 weeks of age in A3high preceded atrial dilatation: At 12 and 21, but not at 8 weeks of age, atrial size as determined by echocardiography was enlarged (A3high 2.30±0.14; WT 1.77±0.08 mm*). Sirius red staining showed atrial fibrosis and focal necrosis at the age of 21 weeks in A3high. Both left and right atrial weight was doubled compared to WT in A3high at 21 weeks of age. A3low mice had slower AV nodal conduction at low heart rates only (PQ interval A3low 37.9±1.0 ms at heart rates of 467±12b/min, WT 34.9±0.7ms at 460±7b/min) with otherwise normal morphology and function. Basal and β-adrenergic stimulated contractiliy was attenuated in A3high isolated atria. Atrial action potentials as measured in Langendorff perfused isolated hearts were prolonged in A3high mice (e.g. at 180ms cycle length A3high (n=4) 59.0±5.7; WT (n=17) 25.9±1.7 ms*) and complete heart block was present (A3high 10/17; WT 1/17*).
Conclusions: Overexpression of A3AR results in a gene-dose dependent AV nodal block and profound sinus nodal dysfunction. These changes precede, and may cause, atrial cardiomyopathy. In contrast to A1 overexpression, the effects of A3 overexpression are attenuated during exercise. A3 adenosine receptors regulate AV nodal and sinus nodal function, predominantly at rest.

1291 The QTc interval duration is correlated to KCNQ1 polymorphisms in a population based MONICA survey

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Prolongation of the QTc interval is known to be a risk factor for ventricular arrhythmias. The influence of polymorphisms in genes encoding for ion channels on QTc duration in the regular population without structural heart disease or inherited long QT syndrome is not known. Digitized ECG's of 1516 probands from the MONICA-Augsburg survey were used to calculate QTc interval duration. Furthermore, the results were correlated with echocardiographic and electrocardiographic parameters as well as with age, gender, and drug medication. The complete coding region of the KCNQ1 gene was screened for genetic variants using single strand conformation polymorphism (SSCP) analysis in all probands with a QTc below (group 1, n=38) and above (group 2, n=44) the second standard deviation as well as in probands with a median QTc interval (group 3, n=44). The table summarizes the significant differences between the three groups, while ejection fraction, left ventricular diameters and blood pressure were not different.

	Group 1	Group 2	Group 3	p-value
n	38	44	55	
Age	42±14	60±13	54±12	0.01
Heart rate	57±8	76±18	67±9	0.01
QT interval	367±25	397±43	377±26	0.01
QTc interval	345±9	444±17	397±1	0.001

Next to nine known polymorphisms we identified four new intronic polymorphisms in KCNQ1 (IVS 10 +46A->T; IVS 11 +14T->C; IVS 12 +36G->A; IVS 14 +32G->T). Three main haplotypes with different frequencies in the three groups were identified, resulting in a significant correlation with QTc and heart rate (0.58 and 0.57, $p<0.01$).
The QTc interval duration as well as resting heart rate are modified by polymorphisms in the KCNQ1 gene in the general population. These results provide evidence for a genetic influence on QTc duration independent of gender and age.

1292 Genotype-phenotype correlation in arrhythmogenic right-ventricular cardiomyopathy linked to desmoplakin mutation (ARVD8)

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Background: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetically heterogeneous disease characterized by cardiac electrical instability and increased risk of sudden death. Recently a mutation in desmoplakin (DSP) gene was found to cause a dominant form of ARVC, that has been called ARVD8. Desmoplakin, together with plakoglobin, are major components of desmosomal plaque. **Purpose:** genotype-phenotype correlation in Arrhythmogenic Right Ventricular Cardiomyopathy linked to desmoplakin mutation.
Methods: the family consisted of 32 members, spanning four generations. The proband was a boy who had an aborted sudden death at the age of 18 years and was diagnosed as having ARVC. The study protocol included: 12-lead ECG, signal averaged ECG, 24-hour Holter ECG, 2D-echocardiogram. Angiographic study was performed in three subjects; in one endomyocardial biopsy was also carried out. All family members underwent genetic study (linkage analysis and screening for mutations).
Results: 16 subjects resulted to carry the desmoplakin mutation. Three had a severe form of ARVC, 2 a moderate and 5 a mild form. Two subjects who had been previously classified as not affected, died suddenly at the age of 65 and 15 years respectively. The remaining four subjects did not fulfilled the ESC-ISFC major and minor criteria for the diagnosis. Ventricular arrhythmias with left bundle branch block (LBBB) morphology were present in 8 subjects: 2 sustained ventricular tachycardia (VT), 2 non-sustained VT and 4 isolated premature ventricular beats. The ECG had the typical ARVC features in 7 subjects and late potentials were present in 8 cases. Imaging techniques showed right ventricular kinetic alterations in 10 subjects; in 3 left ventricular involvement was also present. During follow-up 6 subjects were diagnosed with ARVC, while in 3 affected patients the disease showed a great progression.
Conclusions: desmoplakin mutation has been demonstrated to be linked to ARVC, with various clinical expressions. The pathologic process can cause the onset of ventricular arrhythmias with LBBB morphology and sudden death. The involvement of desmosomal proteins in ARVD8 and Naxos disease suggests that some forms of ARVC might result from defects in intercellular connections.

1293 Further evidence for prolonged atrial action potential durations and polymorphic atrial tachyarrhythmias in patients with long QT syndrome

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Objective: LQT causes ventricular action potential prolongation and torsade de pointes tachycardias due to altered expression or function of repolarizing ion channels. Although it is genereally accepted that the mutations responsible for LQT may also affect atrial repolarization, and despite the fact that a KVLQT1 mutation was recently identified in a family with familial atrial fibrillation, there is no systematic study of how atrial repolarization is altered in LQT patients. We therefore measured atrial action potential durations and assessed atrial arrhythmias in LQT patients.
Methods: We simultaneously measured monophasic action potentials from the right atrial appendage and the infero-lateral right atrium in 10 patients with newly diagnosed LQT and syncope and and compared them to 7 control patients with normal QT intervals and syncope. In addition, atrial arrhythmias were compared to control groups of patients with persistent (n=10) and patients without a history of atrial fibrillation in whom atrial fibrillation induced during an eleectropyhsiological study (n=4).
Results: Steady-state action potential durations (APD) and effective refractory periods (ERP) were longer in LQT patients than in control subjects during pacing at cycle lengths of 300-500 (APD prolongation 30-41ms; ERP prolongation 26-52ms; all $p<0.05$). Short episodes of polymorphic atrial tachyarrhythmias (polyAT) of 4-175s duration (cycle length=230±20ms) occurred during pauses after pacing (5 patients), during atrial stimulation (3 patients), or spontaneously (2 patients) in 5/10 LQT patients, but not in controls ($p<0.05$). P wave axis undulated in the surface ECG during polyAT. Cycle lengths of polyAT were markedly longer than during persistent atrial fibrillation (n=10 patients, $p<0.05$) and induced atrial fibrillation (n=4 patients, $p<0.05$). Afterdepolarizations were observed prior to polyAT in 2/5 patients. The electrical restitution curve was shifted to longer APD in LQT patients, and to even longer APD in LQT patients with polyAT.
Conclusions: Prolonged atrial action potentials, EADs during or after pacing and a vulnerability to polyAT demonstrate that LQT patients have an altered atrial electrophysiology. polyAT in LQT patients appears to be a specific arrhythmia of LQT reminiscent of an atrial form of "Torsade de pointes".

1294 Atrial fibrillation and ventricular tachycardia in Annexin A7-deficient mice

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Background: Annexin A7 (Anxa7) is supposed to be involved in Ca^{2+}/GTP-dependent secretory events. In isolated cardiomyocytes of Anxa7-deficient mice, altered cell shortening frequency relation has been detected and attributed to Anxa7 related changes of Ca^{2+} homeostasis. The aim of the present investigation was to evaluate cardiac electrophysiologic properties in Anxa7-deficient mice in vivo. Methods: 17 male mice (10.1±1.2 weeks, 8 Anxa7 +/+, 9 Anxa7-/-) were examined in inhalative anaesthesia (1.5 vol% isoflurane in 70% N2O and 30% O2) by transvenous intracardiac atrial and ventricular stimulation. Baseline ECG and electrophysiologic parameters as well as incidence and inducibility of atrial/ventricular arrhythmias were evaluated using programmed (up to 3 extra-beats) and burst stimulation protocols. Atrial fibrillation (AF) lasting >1 sec was evaluated, ventricular tachycardia (VT) was defined as >4 ectopic ventricular beats. Results: The surface ECG of Anxa7 -/- mice showed a significantly shorter P-wave (17.4±2.7ms vs. 20.8±2.4ms, $P<0.05$), PQ- (41.7±7.2ms vs. 52.7±8.5ms, $P<0.01$) and QRS-interval (13.9±2.0ms vs. 16.9±3.3ms, $P<0.05$) as compared to Anxa7 +/+. Sinus nodal recovery time, Wenckebach periodicity and atrial or ventricular refractory period were not different among the groups. After rapid atrial burst stimulation AF could be induced in both gentypes equally frequent (4.4±1.4 vs 3.7±2.5 episodes in wildtype (WT), $p>0.55$). However, 4 Anxa7 -/- showed sustained AF >30 min, whereas the longest episode in WT lasted only 480.1 sec in one single animal. Incidence of VT was significantly higher in Anxa7-deficient mice after ventricular extrastimulus pacing (4.4±3.1 vs 0.7±1.6 episodes, $p>0.03$), but not after ventricular burst (4.3±5.1 vs 1.0±1.3 episodes, P=0.14). Conclusion: Anxa7 deficiency elevates susceptibility to induction of VT by programmed ventricular stimulation, aside of effects on myocardial and AV-nodal conduction velocity. AF inducibility is not significantly altered, but sustained AF is inducable only in Anxa7 -/-. These observations might be attributable to alterations of Ca^{2+} homoeostasis in murine cardiomyocytes. Anxa7 may thus be a factor of pathophysiologic relevance in the genesis of human atrial and ventricular arrhythmia.

IS CARDIOVASCULAR THERAPY COST-EFFECTIVE?

1299 NATURAL project: multinational comparison of clinical management and treatment costs in patients with acute coronary syndrome undergoing invasive evaluation

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Background: Treatment of patients (pts) with acute coronary syndrome (ACS) might vary in different health care systems. The aim of the multinational (Switzerland, Germany, United Kingdom) NATURAL project was to assess prospectively clinical management patterns and their impact on costs and outcome in pts with ACS undergoing invasive evaluation.

Methods and Results: A total of 2182 consecutive, mainly high risk (65% troponin positive) ACS pts (57% without ST-elevation, 29% with ST-elevation and 14% with post infarct angina) were enrolled in four centers and followed for 6 months. Process mapping with detailed cost analysis was performed.

Swiss and German centers had a higher rate of primary PCI for ST-elevation myocardial infarction compared to the UK center (29-47% vs. 6%, $p< 0.05$). This contributed to differences in treatment strategies for all ACS pts. (table). A high rate (94%) of procedural success in PCI was achieved in all centers.

Differences in total treatment costs resulted from widely varying length of hospital stay and material costs. Clinical outcome at 6 months will be presented.

Acute treatment strategies

	Acute PCI, %	Acute CABG, %	Elective CABG, %	Conservative, %
Bern, n=767	67	3	21	9
Magdeburg,n=421	59	3	24	15
Villingen, n=258	68	4	20	9
Bristol, n=736	28	0	21	51

Conclusions: Treatment strategies in ACS are dependent on health care system and infrastructure. True costs can reliably be assessed by process mapping and vary with the treatment strategy and material chosen. Analysis of cost-effectiveness, as assessed by the 6 months follow-up, will be presented.

1300 Cost-effectiveness analysis of clopidogrel in patients with unstable coronary artery disease undergoing percutaneous coronary interventions: a five European countries analysis

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Background: The PCI-CURE study demonstrated that clopidogrel on top of standard therapy (including aspirin alone) reduces the risk of major cardiovascular events compared to standard therapy (including aspirin alone) in patients with acute coronary syndrome undergoing PCI. The purpose of this analysis was to evaluate the cost per event avoided in Belgium, Italy, Netherlands, Spain, and Switzerland during the clinical trial.

Methods: The outcome used for the cost-effectiveness analysis was the difference in all occurrences of cardiovascular death, myocardial infarction and stroke. Costs of hospitalization, procedures, medication and study drug were calculated based on resource utilization for all patients undergoing PCI in the CURE study. Hospitalization costs were evaluated through a Diagnosis Related Group approach in all countries, except for Netherlands, where a micro-costing approach was performed (taking into account length of stay, procedures and medications). Unit costs were developed in each country and applied to all patients of the CURE study. Cost-effectiveness was expressed as the cost per event avoided. The time horizon was the mean study duration of 8 months.

Results: The occurrence of the composite outcome was significantly lower in the clopidogrel arm on top of standard therapy 11.65% versus 15.17%. For every 1000 patients treated with clopidogrel on top of standard therapy, versus standard therapy (including aspirin alone), there were 38 less strokes, myocardial infarctions or cardio-vascular deaths (crude NNT=25). The cost of clopidogrel was partly offset by savings during the initial hospitalization: -85 Euros in Belgium, -93 Euros in Spain, -212 Euros in Italy, -277 Euros in Switzerland and -550 Euros in Netherlands per patient. Patients in the clopidogrel arm had on average slightly higher costs than patients treated with aspirin alone: Switzerland: +1.2% (13770 vs 13604 Euros), Italy: +2.9% (9830 vs 9551 Euros), Belgium: +4.5% (8107 vs 7761 Euros), Spain: +4.9% (8330 vs 7940 Euros), except for Netherlands where the average total cost is lower in the clopidogrel arm (-62 Euros). This lead to a cost per cardiovascular event avoided in the clopidogrel arm of 4,732 Euros in Switzerland, 7,931 Euros in Italy, 9,851 Euros in Belgium and 11,065 Euros in Spain whereas clopidogrel on top of standard therapy is cost saving in Netherlands.

Conclusion: Clopidogrel on top of aspirin in patients undergoing a PCI is cost-effective as compared to other interventions in this area and even a dominant strategy in Netherlands which might be due to the micro-costing approach.

1301 High-risk acute coronary syndromes without ST-segment elevation: a cost-effective management strategy in the emergency department

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Background: Acute coronary syndromes without ST-segment elevation (NSTEACS), represent a common cause of hospital admission and their management involve very high costs. Non-conventional care of NSTEACS by chest pain units (CPU) is a potentially cost-effective alternative to conventional management by dedicated coronary care beds (CCU). However, the potential advantages of such approach in high-risk NSTEACS are still unresolved. **Aims:** To assess safety, efficacy and costs of CPU management of high-risk NSTEACS in a public welfare health care system. **Methods:** 210 patients (pts; mean age 71 years; male 61%,during 2000-2001 years) with definite NSTEACS and TIMI risk score $\geq$ 3 admitted to a large community based hospital were randomised to receive CPU or conventional management; 105 pts in each group. Baseline characteristics were similar in both groups. All pts received recommended anti-thrombotic and anti-ischemia treatment on presentation, including IIB/IIIa receptor blockers. **End points:** Use of resources and a triple composite end point including angina, non fatal myocardial infarction and cardiovascular death were compared between the two groups, during in-hospital stay and at 6-month follow-up. **Results:** Occurrence of the composite end point was similar in pts managed in CPU and conventional CCU, either during in-hospital stay (28% versus 26%, respectively; p=n.s.) and at 6 months (17% versus 16%, respectively; p=n.s.). The overall hospital stay was similar in both groups. CPU patients less frequently underwent revascularisation procedures (32% versus 57%; p=.002). Overall, CPU pts had a 22% reduction in full costs of hospitalisation as compared to conventional CCU management (9,913 Euro versus 12,056 Euro; p=0.01). This gain was particularly relevant (29%) when patients with TIMI risk score $\leq$ 4 were compared to patients with TIMI risk score $>$ 4 (10,599 Euro/patient versus 13,699 Euro; p=0.004). **Conclusions:** In a public welfare environment, CPU care of high-risk (TIMI risk score $\geq$ 3) NSTEACS: 1) is a safe and cost/effective alternative to conventional CCU management, particularly for patients presenting with TIMI risk score $\leq$ 4; 2) could represent an useful tool for optimising admissions to CCU by early selection of patients with higher TIMI risk score ($>$4) and/or effective clinical instability; 3) should allow an optimal use of cath lab resources and dedicated cardiologists.

1302 Fluvastatin for the prevention of cardiac events following successful first percutaneous coronary intervention: analysis of cost-effectiveness based on the lescol intervention prevention study (LIPS)

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Background: In the Lescol Intervention Prevention Study (LIPS), 1677 patients who underwent successful first percutaneous coronary intervention (PCI) for unstable or stable angina or silent ischemia were randomized to fluvastatin 80 mg/d or placebo for four years and followed for the occurrence of nonfatal MI, cardiac death, or reintervention procedures ("major coronary events" [MACE]). Eligibility criteria included total cholesterol 135-270 mg/dL (3.5-7.0 mmol/L) and fasting triglycerides $<$400 mg/dL (4.5 mmol/L). Fluvastatin patients experienced a 22% reduction in the risk of MACE (21.4% vs 26.7%, P=.01). In a prespecified analysis excluding reinterventions for restenosis, the risk reduction was 33% (P$<$.001). Although LIPS demonstrated the benefits of fluvastatin in post-PCI patients, the cost-effectiveness of such therapy is unknown.
Methods: We used a Markov model to estimate the expected lifetime outcomes and costs of two treatment strategies in post-PCI patients similar to those in LIPS: (1) initiate fluvastatin 80 mg/d immediately following PCI; (2) dietary and lifestyle counseling until nonfatal MACE and fluvastatin 80 mg/d thereafter. Cost-effectiveness was calculated as the ratio of the difference between strategies in expected lifetime costs to the difference in life expectancy (life-years) and quality-adjusted life years (QALYs). A US health-care system perspective was employed. Probabilities of MACE in patients not receiving fluvastatin were estimated using data from the placebo arm of LIPS. Fluvastatin 80 mg/d was assumed to reduce the risk of MACE excluding reinterventions for restenosis by 33%. Costs and utility weights were estimated using published sources. A 3% discount rate was used in the analysis.
Results: Treatment with fluvastatin 80 mg/d following successful first PCI is estimated to reduce the lifetime risk of MACE by approximately 10% (number needed to treat [NNT] $\sim$10) and to increase life expectancy by up to $\sim$1.5 years. Cost-effectiveness of fluvastatin is estimated to be $\leq$$30,000 per life-year and QALY saved. Findings were robust with respect to changes in key model parameters and assumptions.
Conclusions: Fluvastatin therapy is cost-effective compared with dietary and lifestyle counseling following successful first PCI for unstable or stable angina or silent ischemia.

1303 Economic consequences of a multidisciplinary intervention in heart failure patients in French medical practice. Results of a multicentre randomised trial

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The aim of this study was to evaluate the economic cost of a multidisciplinary intervention to prevent the readmission of elderly patients with congestive heart failure (CHF) in French medical practice.
Two hundred and two patients, mean age 77$\pm$7 years, admitted with Framingham criterion of CHF and at least 1 previous hospitalisation for CHF, were prospectively recruited and randomised in a control group (n=100), assigned to a post-hospitalisation conventional care by their cardiologist and general practitioner, and an intervention group (n=102) assigned to a 4 session education program with an individualised dietary assessment, specific advice regarding NaCl intake and physical activities, daily weight monitoring, a home visit from a nurse and a dietician and monthly telephone monitoring. One year follow up results are summarised. Mean age, sex ratio, self sufficiency, NYHA class repartition, proportion of preserved left ventricular function, diabetes, chronic renal failure, ACE inhibitors and betablockers prescriptions did not differ between the two groups. The medical expenses (i.e. hospitalisations, medications, medical and paramedical interventions, biology, transportation) related to CHF were lower in the intervention group (870 580 euros) than in the control group (1 195 153 euros); moreover total cost of care during the one year follow up was lower in the intervention group (1 141 647 euros vs 1 348 288 euros) mostly due to a significant decrease in the duration (8.4$\pm$15.6 vs 15.7$\pm$25.9 days, p$<$0.05) and number of hospital readmissions for CHF (O.6$\pm$8.9/patient vs 1.3$\pm$2.3/patient, p$<$0.05). In conclusion, this study demonstrates that in French medical practice a one year multidisciplinary intervention to manage elderly patients with congestive heart failure can reduce the economic cost of medical care.

1304 Cost-effectiveness of ezetimibe co-administration in coronary artery disease patients not at goal with current statin therapy in Sweden

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Background: While treatment guidelines recommend lowering cholesterol to target levels appropriate for CHD patients, many remain above goal even with use of statins. In a clinical trial, ezetimibe co-administered with existing statin therapy got 72% patients to NCEP II goal versus 19% among patients continuing statin monotherapy. The objective here is to assess cost-effectiveness of Ezetimibe 10mg (EZ10) co-administration in CHD patients not attaining goal (Total Cholesterol (TC) $\geq$ 5 mmol/L) with Atorvastatin 10mg (A10) alone.
Method: A decision-analytic model was developed to project lifetime costs and benefits of lipid therapy. Clinical trial data were used to estimate TC reductions for different treatment strategies. The effect of TC reductions on CHD event rates was estimated using Framingham equations and Swedish data on non-CHD-related mortality. Direct costs of CHD events in Sweden, Swedish prices for Atorvastatin and the established German EZ10 price were used to project lifetime costs. Estimates were obtained for incremental cost per life year saved (C/LY) and incremental cost per quality-adjusted life year gained (C/QALY) for EZ10 co-administered in CHD patients not at goal on A10 compared to two statin monotherapy strategies: remain on A10 or titrate A10 to attain TC goal. In base case, the model was run for a 60 year old man with TC=6 mmol/L and HDL=1.1 mmol/L after treatment with A10. C/LY estimates were also obtained for men and women aged 35 to 75 with TC from 5.5 to 8.0 mmol/L.
Results: For a 60 year old male CHD patient with TC=6 mmol/L, EZ10 co-administered with A10 is projected to increase life expectancy by 1.1 years compared to remaining on A10 and 0.3 years compared to Atorvastatin titration. C/LY estimates for EZ10 co-administered with A10 are 8,240 EURO and 5,095 EURO compared to the statin-only strategies of maintaining A10 dose and titrating to goal, respectively. The corresponding C/QALY estimates are 13,347 EURO and 8,260 EURO. Across the ages and cholesterol levels studied, C/LY for co-administration of EZ10 in CHD patients ranged from 6,500 EURO to 15,000 EURO compared to maintenance of A10. Compared to atorvastatin titration strategy, C/LY for EZ10 co-administration ranged from 4,500 EURO to 10,000 EURO.
Conclusion: For patient profiles studied, addition of Ezetimibe 10mg increased life expectancy at a cost of 6,500 EURO to 15,000 EURO per life year gained in CHD patients not currently at goal with Atorvastatin 10mg. Cost-effectiveness ratios are even lower for co-administration of Ezetimibe compared to Atorvastatin titration.

WHAT DOES GENE EXPRESSION TELL ABOUT MYOCARDIAL FUNCTION?

1305 Cardiac overexpression of alpha1A-adrenoceptors enhances ventricular function but does not modulate pressure-overload hypertrophy

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alpha1A-Adrenoceptors (a1A-AR) are believed to play a key role in mediating hypertrophy, but to have a limited effect on contractile function. Transgenic (TG) mice with cardiac a1A-AR overexpression do not develop hypertrophy but show enhanced contractility (Lin F et al: Circ Res 2001;89:343-50). Here we studied if cardiac overexpression of a1A-AR modulates the development of pressure-overload hypertrophy, and if the inotroic phenotype seen in the TG mice improve cardiac function under chronic pressure overload. TG mice (3-5 mo) with 66-fold more a1A-AR and non-transgenic littermates (NTG) were studied by constricting the transverse aorta (TAC) to 40% for 7 and 12 wks. Although there was no significant difference in the total mortality following TAC, TG mice were less likely to die of heart failure and had reduced lung wet weight (190±23 vs 278±25 mg, $P<0.05$) and incidence of thoracic pleural effusion than NTG (33% vs 80%, $P<0.05$). Echocardiography showed a higher left ventricle (LV) fractional shortening (FS) in sham-operated TG mice without hypertrophy. LV mass increased similarly in both genotypes with TAC during the early phase (data not shown) or 7 and 12 weeks after TAC (Table). At 12 wks, both NTG and TG mice with TAC had reduced FS versus respective Sham controls. However, FS was significantly higher in TG than in NTG groups ($P<0.01$, Table). Hypertrophied LVs from TG and NTG mice had similar contents of SERCA2a, phospholamban, desmin and collagens (data not shown).

Encho indices and LV/body weight ratio

n=8-11	LVDd, mm	LVDs, mm	FS, %	LVmass, mg	LV/BW, mg/g
Sham/NTG	3.6±.1	2.3±.1	37±2	91±7	3.2±.2
Sham/TG	3.3±.2	1.3±.1*	61±2*	89±6	3.0±.2
7wk TAC/NTG	3.6±.2	2.2±.1	39±2	124±6+	5.0±.3+
7wk TAC/TG	3.2±.1	1.3±.1*	57±3*	121±14+	4.7±.2+
12wk TAC/NTG	4.1±.1+	2.9±.1+	29±1+	141±5+	5.2±.2+
12wk TAC/TG	3.7±.1*+	2.1±.1*+	42±2*+	149±5+	5.3±.4+

LVDd/s: LV diastolic/systolic dimension. *$P<0.05$ vs NTG, +$P<0.05$ vs Sham.

Thus, the a1A-AR TG mice respond to pressure overload with a normal hypertrophy and maintain the inotropic phenotype under these conditions. Ourfindings suggest a major role of a1A-AR in regulating contractility, but question its role as a mediator or modulator of hypertrophy. Cardiac a1A-AR overexpression may become a useful approach for heart failure gene therapy.

1306 Beta2-adrenergic receptor polymorphisms influence the resting and exercise haemodynamics in the patients with chronic heart failure

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Beta2-adrenergic receptors (B2-AR) may comprise up to 40% of the total AR population of the failing heart and their function may vary between individuals depending on gene polymorphisms. Two common polymorphisms are the substitution of Arg with Gly at the position 16 and the substitution of Gln with Glu at the position 27. The Gly16 polymorphism is associated with an enhanced agonist-promoted B2-AR downregulation with a secondary decreased sensitivity to B2-AR drive while the Glu27 polymorphism is associated with a reduced agonist-induced downregulation causing a greater B2-AR sensitivity. Thus, the patients homozygotes for both the Gly16 and the "wild-type" Gln27 polymorphism have the lowest sensitivity to B2-AR stimulation while the Glu27 homozygotes have an enhanced sensitivity to B2-AR stimulation. We related these polymorphisms with the hemodynamic and functional capacity parameters in 124 HF patients who underwent MUGA and Swan-Ganz catheterization at rest and during CPX testing before and after 12-16 months of beta-blocker therapy (BB) (carvedilol, 39±19 mg/day, in 89 patients and metoprolol, 90±49 mg/day, in 35). We compared the 15 patients who showed the Gly16/Gln27 combination (lowest B2-AR sensitivity) with the 21 Glu27 homozygotes (high B2-AR sensitivity). These two groups had similar clinical characteristics (age, sex, cause and duration of HF, concomitant therapy). Before the initiation of BB, the Gly16/Gln27 homozygotes had, compared with the Glu27 homozygotes, a lower resting cardiac index (CI, 2.5±0.7 vs. 2.9±0.6 L/m/m^2; p=0.04) and stroke volume index (SVI, 29±8 vs. 33±10 ml/bt/m^2, p=0.03) with higher systemic vascular resistance (SVR, 1652±438 vs. 1261±304 d*s*cm-5, p=0.03). These differences persisted after BB: CI, 2.6±0.8 vs 3.2±0.7 L/m/m^2, p=0.04; SVI, 38±11 vs. 50±13 ml/bt/m^2 at rest, and 41±24 vs 57±18 ml/bt/m^2, at peak exercise; p=0.03. The LVEF was lower in the Gly16/Gln27 patients, compared to the Glu27 homozygotes, both before BB (17±4% vs. 22±7%, p=0.006) and after BB (28±16% vs. 37±14%, p=0.09). The patients with the Gly16/Gln27 genotype tended to have a lower exercise capacity both before BB(peak VO2, 50±12% of predicted values vs. 54±14%; VE/VCO2 slope, 43±16 vs. 38±9) and after BB (peak VO2 50±13% vs.60±18%; VE/VCO2 slope, 41±13 vs. 35±6). Similar data were found when the patients on carvedilol were analyzed separately.

Thus, the Gly16/Gln27 polymorphism, related with a lower B2-AR sensitivity, is associated with a greater impairment in the hemodynamic parameters both before and after beta-blockade.

1307 Distinct effects of pressure and volume acute cardiac overload on SERCA2a and phospholamban gene expression

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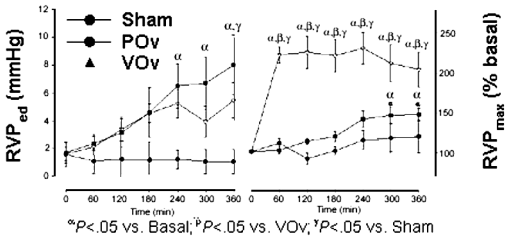
Introduction: The sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2a) and phospholamban (PLB) are critically involved in cardiomyocyte Ca^{2+} kinetics. Profound disturbances in the expression of these calcium regulatory proteins were implicated in heart failure progression. We investigated, in-vivo, the acute modulation of myocardial SERCA2a and PLB gene expression by pressure and volume overload.

Methods: Male Wistar rats (n=18) were instrumented with tip micromanometers to record right ventricular (RV) pressure and submitted to one of three protocols: (i) 6h sustained pressure overload (POv; n=6) induced by pulmonary trunk banding in order to double RV peak systolic pressures (RVPmax) from 24.8±1.1 mmHg to 49.9±4.9 mmHg; (ii) 6h volume overload (VOv; n=6) with dextran70 infusion (5 ml/h), in order to increase RV end-diastolic pressures (RVPed); (iii) sham group (n=6). RV free wall samples were collected for SERCA2a and PLB mRNA quantification by reverse transcription and quantitative polymerase chain reaction using calsequestrin (CSQ) as the housekeeping gene. Significant results are presented as mean±SEM; $p<0.05$.

Results: The hemodynamic data are presented in the Figure. In POv group SERCA2a and PLB gene expression were decreased by 57.6±11.9% and 42.1±1.8%, respectively. In VOv group SERCA2a mRNA levels were increased by 74.3±9.9% but PLB gene expression did not change significantly.



*$P<.05$ vs. Basal; ¨$P<.05$ vs. VOv; ¥$P<.05$ vs. Sham

Conclusions: In-vivo acute cardiac overload modulates SERCA2a and PLB myocardial gene expression. Pressure and volume overload induce opposite effects on myocardial SERCA2a gene expression and regulates PLB gene expression distinctly.

1308 Increased Rac-1 activity in heart failure is associated with increased oxidative stress and is reduced by HMG-COA reductase inhibtion

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Background: Reactive oxygen species (ROS) contribute to the pathophysiology of heart failure. A potential source of myocardial ROS is the NADPH oxidase, which is regulated by the small GTP-binding protein rac1. Isoprenylation of rac1 can be inhibited by statin therapy. Thus, we examined ROS and rac1 in human failing myocardium and tested their regulation by statins in vivo.
Methods and Results: In human left ventricular myocardium from patients with ischemic (ICM) or dilated cardiomyopathy (DCM), NADPH oxidase activity was 1.5-fold increased compared to nonfailing controls (NF; $p<0.05$, n=8). In failing myocardium, increased oxidative stress determined by aconitase activity assays correlated (r=0.69, $p<0.001$) with increased translocation of rac1 from the cytosol to the membrane (ICM, 142±16%; DCM, 193±19%; $p<0.05$ vs. NF). Pull-down assays revealed a 3-fold increase of rac1-GTPase activity in ICM and DCM compared to NF ($p<0.05$). In parallel, membrane expression of the NADPH oxidase subunit p47phox, but not p67phox, was upregulated in failing compared to nonfailing myocardium.
Patients undergoing cardiac surgery were prospectively treated with atorvastatin or pravastatin (40 mg/die) or no statin for 4 weeks. In the right atrial myocardium of atorvastatin and pravastatin treated patients rac1-GTPase activity was decreased to 67.9±12% and 65.6±13.8% compared to patients without statin ($p<0.05$, n=8). Both statins significantly reduced angiotensin II-stimulated NADPH oxidase activity.
Conclusions: Failing myocardium of patients with DCM and ICM is characterized by upregulation of NADPH oxidase mediated ROS release associated with increased rac1 activity. Oral statin treatment inhibits myocardial rac1 activity. These data suggest that extra-hepatic effects of statins can be observed in humans and may be beneficial for patients with chronic heart failure.

1309 Drosophila melanogaster: a powerful genetic model to identify members of a particular human genetic pathway related to cardiomyopathies

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The completion of both human and Drosophila genomes, ~30000 and ~14000 genes respectively, revealed that we are more similar to this simple organism than it was previously suspected. These two proteomes are 67% similar at the amino acid level and 75% of human genetic disease genes have clear homologues in the fly. Fly model has been essential for the understanding the determination of essential developmental and neurological pathways conserved from invertebrates to humans. The combination of heterologous transgenesis and transcriptome analysis of transgenic tissues in Drosophila allows characterizing rapidly members of the genetic pathways where the human gene is acting.
This approach was used to MYBPC3 gene that encodes the human cardiac myosin binding protein C (cMyBPC) associated with Familial Hypertrophic Cardiomyopathy (FHC). Transgenic flies were produced that can express wild type or mutated forms of cMyBPC in the Indirect Flight Muscles (IFMs) of the fly, a tissue whose the physiology resembles that of cardiac muscle. Our results shows that the human proteins are correctly expressed and incorporated in the I Band of the IFMs sarcomeres. The expression of truncated human cMyBPC in the IFM results in flightless flies with abnormal wing position. Electronic microscopy analysis of the IFMs of the flies expressing cMyBPC showed that the muscle fibers had their Z-line/I-band torn. Moreover, the sarcomere length was reduced of 10% compared to the wild type. These data suggest that human c-MyBPC may interact with yet unidentified sarcomeric proteins to produce hypercontraction of the muscle fibers. In order to gain insight in the molecular consequence of the transgene expression and to characterize the genetic network involved in the flightless phenotype, we have performed a transcriptome analysis using the nylon microarray technology with the help of Marseille Genopole. Preliminary result on 3700 genes shows that the expression of human cMyBPC in Drosophila sarcomeres modifies the transcription of 115 specific genes that will be described. Work is in progress to performed genetic tests on putative modifier genes identified by microarray analysis.

1310 Expression profiling of human hypertrophic cardiomyopathy progressed to dilated cardiomyopathy by DNA microarray analysis: insight into the pathogenesis of phenotypes

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Background: Hypertrophic cardiomyopathy (HCM) is characterized by myocyte disarray and a variable phenotypic expression. About 10% of cases of HCM develop a dilated cardiomyopathy (DCM). In order to investigate the altered gene expression implicated in the evolution of HCM in human, we compared myocardial RNA from 8 patients (pts) with HCM progressed to DCM to myocardial RNA from 7 pts with typical HCM, through DNA microarray analysis.
Methods: Endomyocardial biopsies were obtained from each pt from which we produced 2 RNA pools, one for each pts' phenotype, as targets for hybridizations: HCM evolved to DCM (pool A) and HCM with preserved systolic function (pool B). For each pool, equal amounts of total RNA extracted from each single biopsy were mixed and two round linear amplification of the pooled RNAs was performed. The platform used was a tissue-specific microarray containing 5000 among skeletal, cardiac muscles, and bone marrow clones.
Results: A total of 88 deregulated transcripts were identified, among which 76 were overexpressed and 12 underexpressed. Of note, 41 transcripts have still unknown function. Induction of fetal gene expression program, as shown by overexpression of alpha-actin, brain natriuretic peptide and atrial natriuretic peptide, is consistent with HCM phenotype. We suggest that while initially supporting compensatory hypertrophy, this program is augmented as the hearts progress to DCM. We observed the reduced expression of some ribosomal proteins and of mithocondrial COX7 gene, in contrast with the generally increased expression of these genes in the HCM spectrum. The abnormalities of energy production and/or abnormal protein synthesis may play an important role in the pathogenesis of the HCM/DCM evolution, consistent with the finding of several mitochondrial DNA mutations associated with this phenotype. Significant underexpressed genes were those of the immune response. Finally, an anti-apoptotic gene was underexpressed, supporting a mouse trangenic model in which increased levels of apoptosis are associated with the transition from compensated HCM to decompensated DCM.
Conclusion: We speculate that some of these transcripts could be related to the more severe clinical trait associated with pool A. However, their role together with that of deregulated transcripts whose functions are still unknown, has to be clarified. Finally, we are obtaining expression profiles from each affected individuals with different clinical traits to better clarify the individual relation between genotype and phenotype.

INFLAMMATORY HEART DISEASE

1311 Tenascin-C is a useful marker of disease activity in human myocarditis

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Objective: To determine whether disease activity and tenascin-C (TNC) expression are correlated in human myocarditis.
Background: In myosin-induced autoimmune myocarditis mouse models, it has been demonstrated that the level of TNC expression reflects disease activity.
Methods: Endomyocardial biopsies were performed in 32 cases in the acute phase of myocarditis, and a total of 109 biopsy samples obtained. Histological specimens were prepared by routine methods, and immunostaining was performed with anti-TNC antibody. Under a light microscope 109 specimens were classified according to the Dallas criteria as active myocarditis (AM): 51 specimens, borderline myocarditis (BM): 33 specimens, and no myocarditis (NM): 26 specimens. The degree of TNC expression was scored into 5 grades according to the proportion of TNC-expressing regions. As a control, 39 specimens obtained from 14 cases without any obvious cardiac lesions were also studied. TNC expression was compared in the 4 groups. In addition, serial biopsies were performed in 25 of the 32 cases, making it possible to investigate the changes in TNC expression associated with the passage of time.
Results: The TNC expression score was 3.5±0.7 in AM, 2.0±0.9 in BM, 0.9±1.0 in NM, and 0.4±0.5 in the Control, with the differences between the 4 groups all significant. TNC expression was found to gradually decrease with time after myocarditis onset.
Conclusion: In human myocarditis as well, the level of TNC expression reflects disease activity.

1312 Myocardial signal intensity analysis with magnetic resonance imaging (T2-weighted short time inversion recovery sequence-STIR) in patients with suspected or known myocarditis – a preliminary report

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Introduction: One of the most important features of inflammatory process is oedema. The visualization of oedematic tissue characteristics might be useful in diagnosis of inflamatory process.
Aim: We applied the oedema-sensitive MR sequence Spin Echo T2-weighted STIR to fast non-invasive detection of inflammatory process in myocardium.
Methods: The study covered 24 patients in two groups beetwen January 2001 to February 2003. Group I consisted of 12 subjects 7 women, 5 men mean age 36 years (15 – 46) with clinical and biochemical signs of myocarditis (atypical chest pain, history of previous infection, arrhythmia, moderately increased CRP, global impairment of contractility in echo, with normal angiography or no atherosclerotic plaques in MSCT), Group II consisted of 12 subjects (6 women, 6 men) mean age 48 years with stable angina (CCS II) pectoris without clinical and biochemical symptoms of myocarditis. The MR examinations were performed with Magnetom Vision Plus 1.5 T. Cardiac MR protocol consist of 1) T1-weighted Turbo Flash localization sequences - scouts 2) spoiled – gradient echo cine (GE) sequences: 4-chamber and 2-chamber long axis 2) series of spoiled cine-GE 2-chamber short axis images from base to apex (slice thickness 8 mm, 2 mm gap) 3) T2-weighted STIR Spin Echo (6 mm slice thickness) in basal and medial segment of LV measuring signal intensity at all segments and calculating it's average value. The measurements of signal intensity (SI) were performed simultaneously in myocardium and intercostal muscles (the same acquisition and image). The mean myocardial SI/skeletal muscle SI ratio was calculated. The left ventricular EF was measured and LV–contractility was assessed.
Results: On cardiac MR examination patients with clinical myocarditis had a significantly higher mean signal intensity ratio than patients who had no symptoms of myocarditis (2.9 vs 1.6, $p<0.05$). The mean EF was lower in group with myocarditis (40% vs 54% $p<0.05$). The global hypokinesis of LV was found only in 8 patients with suspected myocarditis, the regional contractility impairment were observed in 6 (50%) patients with coronary artery disease.
Conclusion: The application of MR STIR sequence in high quality visualization of oedematic tissue might be useful diagnostic and follow up evaluation tool in patients with myocarditis.

1313 Elevated serum cardiac troponin-T levels in murine coxsackieviral myocarditis was correlated with heart viral titer rather than degree of inflammation

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Background: Endomyocardial biopsy often fails to reveal myocardial injury and inflammation in clinically suspected myocarditis. Levels of serum cardiac troponin T (cTnT) are elevated in myocardial injury, even in the absence of histological signs of myocarditis. We measured serum cTnT levels, histology and viral titers in hearts at various stages of murine coxsackieviral B3 (CVB3) myocarditis, to investigate their correlation during the course of viral myocarditis. Methods: Balb/C female mice were infected intraperitoneally with 10,000 pfu of two different CVB3 variants, myocarditis strain (H3) and amyocarditic variant of CVB3-H3 (10A1). Serum and hearts were collected at various time points. To identify myocyte damage in the hearts, Evans blue dye was injected intraperitoneally at 12 hours before harvesting hearts. The degree of inflammation was analyzed by H&E staining. In the cryosection, CVB3 infected myocytes were immunostained with an anti-enteroviral VP1 antibody. Serum cTnT level was measured by ELISA. Results: Viable virus titers in H3 hearts were higher than in 10A1 hearts, peaked 3 days after infection, and decreased at day 7, and no viable virus at day 14, in the heart infected with both viruses. Myocardial inflammation was peaked at day 7, and decreased markedly at day 14 in H3 hearts. Scanty inflammation was observed in 10A1 hearts. Evans blue uptake under fluorescent microscopy was observed from day 3 and peaked at day 7, and it was co-localized with the infected myocytes. Individual serum cTnT levels were significantly increased on day 3 (7.37 ± 1.47, 1.15 ± 0.35 ng/ml), persisted to day 7 (0.73 ± 0.08, 0.47 ± 0.13), and normalized at day 14 in H3 and 10A1 hearts, respectively. Serum cTnT levels were positively correlated with viral titers in the heart ($r = 0.746$, $p < 0.01$), but not with the degrees of inflammation. Conclusions: The elevated serum cTnT level provides evidence of myocardial injury even in the absence of inflammation in the histology after viral infection, therefore, in clinical situations, the additional virus detection methods are needed for the accurate etiologic diagnosis of viral myocarditis in the clinically suspected myocarditis.

1314 The role of pericardioscopy and epicardial biopsy in determination of the etiological treatment for chronic pericardial effusions

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Assessment of the etiology of pericardial disease has important therapeutic implications. The aim of the study was to evaluate the clinical efficacy and safety of etiology-specific intrapericardial treatment with cisplatin or triamcinolone.
Methods: Out of the registry of 260 pts undergoing pericardiocentesis, 42 pts with cytologically verified neoplastic pericardial effusion (PE)(Group 1: 69% males, 58.8 ± 13.2 yrs) were selected for cisplatin treatment (30 mg/m^2/24h). Further 84 pts with autoreactive chronic PE were treated intrapericardially with two triamcinolone regimens (Group 2: 54 pts, 50% males, 48.9 ± 14.3 yrs, triamcinolone 600 mg/m^2/24h; Group 3: 30 pts, 46.7% males, 52.5 ± 12.7 yrs, triamcinolone 300 mg/m^2/24h). At the initial assessment all pts underwent clinical examination, echocardiography, pericardiocentesis, PE drainage, pericardioscopy, epicardial and pericardial biopsy. PE and pericardial/epicardial biopsy analyses included biochemistry, cytology, serology, microbiology, histology, immunohistology, and PCRs for microbial DNA/RNA.
Results: The following malignancies were established: lung cancer - 52.4%, breast cancer - 19.0%, Morbus Hodgkin - 4.8%, esophageal cancer - 2.4%, mesothelioma - 2.4%, colon cancer - 4.8%, and cancer of unknown origin - 14.3%. None of the pts intrapericardially treated with cisplatin died due to cardiac tamponade. Mortality due to non-cardiac tumor progression was 52.4% and 80.9%, after 3 and 6 months respectively. Cisplatin prevented recurrence of symptoms and a hemodynamically relevant PE during the first 3 months of the follow-up in 92.8% of the pts, and after 6-12 months in 83.3% of the pts. With exception of myocardial ischemia in one patient (2.4%) there were no major complications of the treatment. Triamcinolone treatment resulted in symptomatic improvement and prevented PE recurrence in 92.6% vs. 86.7% of the pts after 3 months and in 85.1% vs. 83.3% after 1 year in the Group 2 and Group 3 respectively ($p>0.05$). There were no treatment related acute complications. During the follow-up 29.6% of the pts developed transitory iatrogenic Cushing syndrome in the Group 1 vs. 13.3% in the Group 2 ($p<0.05$).
Conclusion: Intrapericardial treatment of neoplastic pericarditis with cisplatin significantly prevented recurrences of symptoms and PE during the follow-up of 12 months. Intrapericardial treatment of autoreactive chronic/recurrent PE with 300 mg/m^2/24h of triamcinolone prevented recurrences of symptoms and relapses of PE equally effective as the 600 mg/m^2/24h regimen, but with significantly lower incidence of side effects.

1315 Is colchicine the initial mode of treatment for acute pericarditis?

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Background: Recurrent pericarditis is the most troublesome complication of acute pericarditis, occurring from 15 to 30% of cases. Colchicine is effective and safe for the treatment of recurrent pericarditis as adjunct to the conventional treatment and may ultimately serve as the initial mode of treatment especially in idiopathic cases (Adler Y. et al.Circulation 1998;97:2183-5). To the best of our knowledge no prospective studies have been published to test this intriguing hypothesis. Aim of this work is to verify the safety and efficacy of colchicine as first choice therapy of the first episode of acute pericarditis and then to verify its efficacy in the prevention of recurrences.
Methods: A prospective, randomized, unblinded design was used. From June 2001 to June 2002 new cases of acute pericarditis were randomized to receive a conventional treatment with aspirin 800mg orally every 6 or 8 hours for 7-10 days with gradual tapering over 2-3 weeks (group I) or a treatment with aspirin at the same dose combined with colchicine 2mg for the first day and then 1mg daily for at least 3 months (group II). Exclusion criteria were: current serum creatinine above the upper normal limit, current transaminases >1.5 times the upper normal limit, known liver disease, myopathy or blood dyscrasias, pregnant or lactating women or women of childbearing potential not protected by a contraception method, known hypersensitivity to study treatments.
Results: 30 patients(mean age 51.4 $\pm$ 17.3, 14 males) were assigned to group I and 30 patients(mean age 52.7 $\pm$ 17.2, 13 males) were assigned to group II. There were no statistically significant differences in baseline clinical characteristics between the groups. Patients treated by colchicine had a higher frequence of remission of the first episode compared with patients in group I (respectively 100.0% vs 80.0%;p=0.03). In two cases(6.7%) colchicine treatment was interrupted because of gastrointestinal side effects while no treatment interruption was recorded in group I. No recurrencies were detected after a mean follow-up of 15.1 $\pm$ 4.2 months in patients who were able to complete the 3-month treatment with colchicine (recurrencies in group II vs group I: 0.0% vs 20.0%; p=0.03).
Conclusions: Colchicine combined with aspirin is safe and very effective in the treatment of the first episode of acute pericarditis and in recurrencies prevention. Gastrointestinal side effects(mainly nausea, diarrhea and abdominal pain) may limit its tolerability. A large, randomized, double blind, placebo controlled trial is warranted to confirm these promising results.

1316 Tissue Doppler analysis of mitral annulus motion in patients with severe diastolic heart failure

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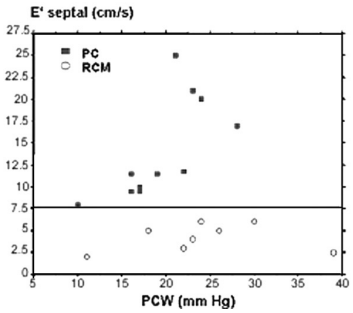
Background: It has been suggested that tissue Doppler (TD) analysis of mitral annulus (MA) motion might be helpful to further differentiate severe diastolic heart failure (D-HF) as demonstrated by a restrictive left ventricular (LV) filling pattern. We studied the relationship between the early transmitral flow velocity (E), the early component of MA motion by TD (E') and LV filling pressures in 20 consecutive patients (pts.) with D-HF of either proven myocardial origin (RCM) or from constrictive pericarditis (CP). All pts. underwent a complete echocardiographic and hemodynamic assessment.



Results: Out of the 20 pts. (mean age 60$\pm$13 years) 11 had CP, and 9 RCM. NYHA class III symptoms were reported by 12 pts (60%), 9 (45%) had atrial fibrillation (AF). Mean pulmonary wedge pressure (PCW) 21$\pm$7 mmHg. E was 92$\pm$22 cm/s, deceleration time of E 137$\pm$39 ms without a significant difference between RCM and CP. Systolic LV function was normal in all CP pts., slightly abnormal or moderately abnormal in 3 in RCM pts each. Mean pulmonary artery pressure (PAP) was 29$\pm$10 mmHg with a significant difference between RCM and CP (35$\pm$11 vs. 26$\pm$5 mm Hg; $p<0.01$). Pts. with CP showed a higher E' both on the septal and lateral side of the MA (14$\pm$6 cm/s vs. 4$\pm$2 cm/s, and 13$\pm$4 cm/s vs. 5$\pm$2 cm/s, resp.; $p<0.001$). E' was <8 cm/s in all RCM pts. and >8 cm/s in all CP pts. (see figure). Moreover, pts. with RCM showed a higher E/E'-ratio (26$\pm$10 vs. 7$\pm$3 cm/s; $p< 0.001$).
Conclusion: Among pts. with severe D-HF, those with RCM frequently also have slight to moderate impairment of systolic LV function, and a higher PAP. TD analysis of MA motion, however, seems to clearly differentiate pts. with RCM from CP independent of cardiac rhythm with a cut-off value of E' <8 cm/s.

MYOCARDIAL ISCHAEMIA – PATHOPHYSIOLOGY

1317 Protein kinase C-δ mediated the expression of heat shock protein 72 by geranylgeranylacetone in rat heart

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Purpose: Cardioprotection during ischemia and reperfusion is an important issue. Heat shock protein 70 has been revealed to exert cardioprotection during ischemia/reperfusion. Our laboratory recently demonstrated that oral administration of geranylgeranylacetone (GGA), an antiulcer agent, induces heat shock protein 72 (HSP72) in the rat heart and renders cardioprotection against ischemia/reperfusion injury. However, the signaling pathways remain to be elucidated. The present study tested the hypothesis that oral GGA would activate protein kinase C (PKC), leading to the phosphorylation and translocation of heat shock factor 1 (HSF1), and thus promote the expression of HSP72 protein. **Methods and Results:** Rats were classified into 4 groups: a control (CNT) group (vehicle administration), a GGA group (GGA 200 mg/kg administration), a CHE-CNT group (pretreated with intravenous injection of 5mg/kg chelerythrine (CHE) before vehicle administration), and a CHE-GGA group (pretreated with CHE before GGA administration). Twenty-four hours after administration, oral GGA induced overexpression of HSP72, increased amount of the phosphorylated form of HSF1 in the nucleus, and translocation of PKC delta, all of which were prevented by pretreatment with CHE. Isolated perfused heart experiments revealed that the better functional recovery observed in the GGA group during the reperfusion period following the 20 min of no-flow global ischemia compared with the CNT group was abolished by pretreatment with CHE. The effect of rottlerin, a specific PKC delta inhibitor, abolished HSP induction. Genistein did not antagonize the induction and cardioprotection afforded by GGA induced HSP 72, showing little contribution of tyrosine kinase signaling pathway. Thus the induction of HSP by GGA is assumed to be mediated by PKC delta. **Conclusions:** These results suggest that activation of PKC (translocation of PKC delta), which primes the phosphorylation of HSF1, plays an essential role in the cardiac overexpression of HSP72 by GGA that leads to cardioprotection.

1318 Increased resistance to ischaemia/reperfusion stress of cardiomyocytes in apolipoprotein E-deficient mice

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Objective: It has been shown that long-term high cholesterol diet reduces infarct size after LAD occlusion in LDL receptor-deficient mice [1]. However, these mice are also more vulnerable to microvascular ischemia/reperfusion (I/R) injury [2]. As the cellular response to I/R has not yet been elucidated, we investigated the effect of I/R stress on cardiomyocytes of severly hypercholesterolemic apolipoprotein (ApoE)-deficient and C57BL/6 wild type mice.
Methods: Before the study, mice were treated with a fat diet that increased cholesterol levels in ApoE but not in control animals. Ischemia was simulated by superfusing the cells with an acidic, deoxyglucose containing medium (pH 6.3) in a nitrogen athmosphere. After 30 min of ischemia, cells were perfused for 50 min with Tyrode's solution (pH 7.4 with glucose) under normoxia. Intracellular calcium and pH were monitored simultaneously with Fura-2 and BCECF, respectively. Diastolic cell length and the occurrence or absence of calcium transients unrelated to electrical stimulation were also recorded. Additionally, myocardial protein content of three calcium handling proteins (SERCA 2, PMCA 2, and Na/Ca exchanger) was quantified. **Results:** After ischemia, diastolic Fura-ratio increased from 0.41 $\pm$ 0.03 to 0.48 $\pm$ 0.03 (ApoE) and from 0.44 $\pm$ 0.05 to 0.47 $\pm$ 0.08 (control, n.s.). While it remained at that level in ApoE cells, it further increased to 0.83 $\pm$ 0.24 in controls after reperfusion ($p < 0.05$). After I/R, BCECF-ratio had dropped from 3.5 $\pm$ 0.3 (baseline) to 3.2 $\pm$ 0.2 (n.s.) in ApoE and from 3.8 $\pm$ 0.3 to 2.7 $\pm$ 0.3 in the control group ($p < 0.05$). Diastolic cell length decreased to 94% and 67% of initial length in ApoE and control cells, respectively ($p < 0.05$), indicating an increased incidence of hypercontracture in controls. The percentage of arrhythmic cells after ischemia was 71% and 77% in ApoE and control cells, respectively (n.s.). It further decreased to 25% in the ApoE group whereas it climbed to 88% in controls ($p < 0.05$). There was no group difference in the protein content of SERCA 2, PMCA 2, and Na/Ca exchanger. **Conclusion:** These results show that cardiomyocytes from ApoE-deficient mice have mechanisms that protect them from intracellular acidosis, calcium overload, hypercontracture and arrhythmias during I/R. Thus, myocytes from hyperlipemic mice are better prepared to sustain I/R stress.The lower calcium levels in ApoE cells cannot be explained by differences in the expression of the three calcium handling proteins.
References: [1] Arterioscler Thromb Vasc Biol 19, 2776, 1999; [2] Am J Physiol 276, H1647, 1999.

1319 Onset of cell-to-cell electrical uncoupling precedes rigor contracture and conduction blockade in isolated rat hearts

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Objective: Previous studies have demonstrated a close temporal relationship between the onset of rigor contracture and of cytosolic Ca^{2+} rise in ischemic myocytes, and in isolated rabbit papillary muscles rigor onset and Ca^{2+} rise have been shown to precede the onset of cell-to-cell electrical uncouling, supporting a determinant role of severe ATP depletion and Ca^{2+} overload in gap junction closure. In this study we correlated changes in tissue electrical impedance and cell-to-cell uncoupling and conduction blockade with rigor onset during myocardial ischemia and hypoxia in an isolated rat hearts.
Methods: Thirty three isolated open rat hearts were submitted to one hour of acute myocardial ischemia (n=14), hypoxia at pH 7.4 (n=10), or hypoxia at pH 6.4 (n=9), while paced at the cardiac base. Developed tension was monitored using force transducers, myocardial electrical impedance (resistivity and phase angle) by four-electrode probes, and conduction velocity by analysis of transmembrane action potential recordings. Rigor onset was determined as an abrupt increase in diastolic tension. Onset of cell-to-cell electrical uncoupling was determined as an abrupt increase in tissue resistivity and a sharp decrease in phase angle occurring after a first phase of slight changes.
Results: There was a strong correlation between the time of onset of electrical uncoupling and the time of onset of rigor ($r=0.82$, $p<0.001$), but cell-to-cell electrical uncoupling preceded both rigor onset and conduction blockade during ischemia (10.20 ± 0.43 min for electrical uncoupling vs. 15.54 ± 1.21 min for rigor onset and 14.24 ± 0.98 min for total conduction blockade, ANOVA, $p<0.001$), hypoxia at pH 6.4: (7.00 ± 0.88 min vs. 14.47 ± 0.98 and 18.27 ± 1.84 min, respectively, $p<0.001$), or hypoxia at pH 7.4 (4.93 ± 0.40 min vs. 5.89 ± 0.49 and 12.83 ± 1.29 min, respectively, $p<0.001$). Cell-to-cell electrical uncoupling, rigor onset and conduction blockade occurred earlier during hypoxia at pH 7.4 than during ischemia or hipoxia at 6.4 (ANOVA, $p<0.05$). However, changes in tissue impedance were much more pronounced during ischemia than during both types of hypoxia (the increase in tissue resistivity at 45 minutes was $113.37\pm10.99\%$ during ischemia, $31.11\pm3.70\%$ during hypoxia, and pH 7.4 and 19.56 ± 3.73 for hypoxia at pH 6.4, ANOVA, $p<0.001$).
Conclusion: In the intact rat heart cell-to-cell electrical uncoupling occurs clearly before the onset of detectable rigor contracture or conduction blockade independently of the presence or absence of catabolite accumulation or acidosis.

1320 Partial inhibition of myocardial fatty acid oxidation increases regional contractile power and efficiency during demand-induced ischaemia

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Clinical trials in patients with stable angina show that drugs that partially inhibit myocardial fatty acid oxidation reduce the symptoms of demand-induced ischemia (e.g. prolonged exercise time, fewer anginal attacks), presumably by reducing lactate production and improving regional systolic function. It is not known if partial inhibition of myocardial fatty acid oxidation reduces lactate production and improves systolic wall motion during demand-induced ischemia. We tested the hypothesis that partial inhibition of fatty acid oxidation with oxfenicine (a carnitine palmitoyl transferase-I inhibitor) reduces lactate production and increases regional myocardial power during demand-induced ischemia. Methods: Demand-induced ischemia was produced in anaesthetized open-chest swine by reducing flow by 20% in the left anterior descending coronary artery (LAD) and increasing heart rate and contractility with dobutamine (15 μg/kg/min i.v.) for 20 min. Glucose and fatty acid oxidation were measured with an intracoronary infusion of [U-14C] glucose and [9,10-3H] oleate, and hearts were treated with oxfenicine (2mmol/L in LAD blood); n=7) or vehicle (n=7). Regional anterior wall power was assessed from the left ventricular pressure – anterior free wall segment length loops. Results: During demand-induced ischemia, the oxfenicine group had a higher rate of glucose oxidation (6.9 ± 1.1 vs. 4.7 ± 0.8 μmol/min; $P<0.05$) and significantly lower fatty acid uptake. There was not difference between groups in the activity of pyruvate dehydrogenase (the key enzyme regulating pyruvate oxidation in mitochondria), thus dephosphophorylation of this enzyme was not required for greater pyruvate oxidation. The oxfenicine group had significantly lower lactate output integrals (1.11 ± 0.23 vs. 0.60 ± 0.11 mmol) and glycogen depletion (66 ± 6 vs. $43 \pm 8\%$), and higher anterior wall power index ($0.95 \pm 0.17\%$ vs. $1.30 \pm 0.11\%$) and anterior wall energy efficiency index ($91 \pm 17\%$ vs. $129 \pm 10\%$). Conclusions: This is the first direct evidience that partial inhibition of fatty acid oxidation reduces nonoxidative glycolysis and improves regional contractile power and efficiency during demand-induced ischemia.

1321 Profiling of changes in protein expression and activation following myocardial ischaemia and reperfusion in rabbits. Effects of alternative and classical complement pathway inhibition

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Background: Myocardial ischemia and reperfusion injury (MIR) can be related to leukocyte activation with release of cytokines and oxygen-derive free radicals. Activation of the complement system has been implicated in the pathogenesis of myocardial ischemia and reperfusion injury. In this regard, activation of transcription factors (i.e. NFkB), de novo protein synthesis and protein activation seems to play an important role. Therefore, we analyzed the changes in the myocardial protein pattern in rabbits after MIR.
Methods: In the present study we analyzed the myocardial protein expression following MI/R in a rabbit model(60min I+180min R), with and without complement inhibition with the synthetic serine protease inhibitor FUT-175 known to inhibit classical and alternative complement pathway. FUT-175 significantly reduced myocardial necrosis. The CK activities demonstrated increased activity for vehicle animals and reduced activity for FUT-175 treated animals, indicating preservation of myocardial tissue. The myocardial protein expression was analyzed by two-dimensional electrophoresis (IEF in the first dimension and SDS-PAGE in the second dimension) following MI/R in the different groups. The protein patterns were silver stained and evaluated by means of MELANIE III a computer-assisted gel analysis system. The biochemical identification of the proteins of interest was achieved using nanoHPLC/ESI-MS/MS.
Results: On average, 509 ± 25 protein spots were found on the gels. A pattern of 480 spots with identical positions was found on every gel (n=5/group). We analyzed 12 spot which were significantly altered by using mass spectrometry. SOD, aspartat transaminase, a-crystallin chain B, Mn SOD, ATP synthase A chain, mitochondrial stress protein, CK and troponin T (TnT)were identified by mass spectrometry. We compared sham group vs. vehicle group vs. FUT-175 treated animals. All of these anti-inflammatory proteins were preserved in the FUT-175 group following (MI/R)when compare to vehicle treated animals. Interestingly treatment with FUT-175 also preserved expression of structural proteins like CK and TnT.
Conclusions: The results present the dynamic in myocardial protein expression after ischemia and reperfusion and after treatment with the complement inhibitor FUT-175. Our results also demonstrate the influence of the complement inhibitor FUT-175 on the expression of cardioprotective proteins after MI/R. The results illustrate the application of proteomic analysis to discover possible new therapeutic targets or to detect not suspected effects of compounds.

1322 The administration of losartan from the beginning of the infarct unfavorably modifies the ventricular remodelling and the scar collagen concentration in rabbits

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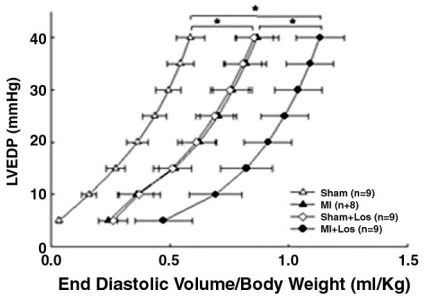
The effects of losartan (L) on myocardial infarct (MI) ventricular remodelling (VR) remains controversial. Objective: The goal was to determine if early administration of L to rabbits subjected to MI modifies VR.

Methods: 52 rabbits were subjected to ligature of the left coronary artery. Four groups were performed: G1 (sham; n=13), G2 (MI; n=13), G3 (Sham+L; n=13) and G4 (MI+L; n=13). L (12.5 mg/kg/d) was administered during 35 days starting from 3 hours post-MI. The animals were sacrificed at 35 days post-MI. Each group was randomized for histological evaluation (n=4) and for functional and morphometric analysis (n=9). Ventricular function was evaluated using Langendorff's technique to determine pressure-volume curves. Hearts were fixed in formaline, cut from apex to base and stained with Picrosirius Red and Masson trichrome. Collagen (C) was measured in scar areas. Infarct size (IS), scar (ScT) and septum thickness (ST), were measured by means of morphometric analysis.

Results: X ± SEM; *:p<0.05 vs G1; #:p<0.05 vs G2.

Morphometric measurement

	IS (%)	ScT (mm)	ST (mm)	Scar C (%)
G1			0.23 ± 0.02	
G2	25.40 ± 5.30	0.23 ± 0.03	0.30 ± 0.02 *	72.70 ± 3.78
G3			0.18 ± 0.03 #	
G4	21.90±4.10	0.16 ± 0.02 #	0.21 ± 0.02 #	62.40 ± 3.90 #



Diastolic presion volume relationships.

Conclusions: The early administration of L unfavorably modified post-MI VR, increasing ventricular dilation, reducing the ScT, ST and scar C concentration.

HOW TO ASSESS SYSTOLIC FUNCTION IN HEART FAILURE

1327 Patient characteristics, treatment, prognosis and adherence to guidelines in patients with left-ventricular systolic dysfunction as compared to preserved left-ventricular function: a report from the EuroHeart Failure Survey

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Background: Guidelines for heart failure are mostly based on randomised clinical trials and focus on patients with a left ventricular systolic dysfunction (LVSD). The EuroHeart Failure Survey provides an opportunity to explore whether patients with a preserved LV function were treated also according to these guidelines.

Methods and Patients: We performed a prospective survey in 115 hospitals from 24 countries and identified 10.701 patients (46.788 screened) with suspected heart failure. Patient characteristics with respect to investigations, interventions and pharmacological treatment were compared between patients with a LVSD and a preserved systolic LV function. LVSD was defined when the assessment of an echocardiogram revealed a moderate or severe systolic dysfunction or the ejection fraction (LVEF) was <0.40.

Findings: LVEF was known or assessment of LV systolic function was made in 6806 (64%) patients. 3473 (51%) had LVSD, while 3333 (49%) had a preserved LV systolic function. Patients with LVSD were on average 3.4 years younger and more often of male gender (71% vs 46%, respectively) than patients without LVSD. Prior myocardial infarction (50% vs. 28%) and diabetes mellitus (28% vs. 26%) was seen more often in patients with LVSD, while hypertension (50% vs. 58%) and respiratory disease (29% vs. 33%) were less frequent in these patients as compared to patients with a preserved LV function. When coronary angiography was performed, 24% LVSD and 33% patients with a preserved LV systolic function had no evidence of coronary artery disease.

Patients with LVSD were more often treated with ACE-inhibitors (78% vs. 59%), bèta-blockers (46% vs. 39%), cardiac glycosides (41% vs. 32%), nitrates (50% vs. 46%), positive inotropic agents (11% vs. 6%) and anti-arrhythmic drugs (21% vs. 14%). Patients with preserved LV systolic function received more often calcium antagonists (27% vs. 16%), while no differences in diuretic use were observed.

Conclusions: Heart failure with preserved LV systolic function appears common. Major differences were seen between these patients and those who had LVSD. Although few recommendations exist for the treatment of heart failure with preserved LVSD, such patients were commonly treated with ACE inhibitors and beta-blockers, possibly for the management of concomitant coronary disease or hypertension.

1328 Haemodynamic classification based on right-ventricular ejection fraction and pulmonary pressure identifies etiology and predicts prognosis in patients with ischaemic and non-ischaemic heart failure

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Background: Previous studies performed in patients (pts) with heart failure (HF) showed the usefulness of combining right ventricular ejection fraction (RVEF) and pulmonary artery pressure (PAP) in defining subgroups with different prognosis. Moreover, we observed a higher prevalence of right ventricular dysfunction (RVD) in idiopathic dilated cardiomyopathy (IDC) compared to ischemic heart disease (IHD) for any given value of PAP and left ventricular (LV) EF. Thus, we test the hypothesis that a combination of RVEF and PAP not only helps in risk stratification of HF pts, but also identifies hemodynamic patterns specific for the 2 etiologies.

Methods: Consecutive pts with chronic LVD, defined as a LVEF < 45% were studied invasively. Pts were categorized based on RVEF and PAP as follows: a value of RVEF <35% was used to define RV dysfunction, while a mean PAP > 20 mmHg was used to define pulmonary hypertension. By combining these 2 variables, 4 groups were obtained: group A (normal RVEF and normal PAP); group B (low RVEF and normal PAP); group C (high PAP and normal RVEF); group D (high PAP and low RVEF). Clinical and hemodynamic data were compared among the different groups. The end-point considered in the follow-up is transplant-free survival (TFS).

Results: The study cohort included a total of 260 pts (mean age 59±12 yrs, 82% males), with a mean LVEF of 31±9% and a mean RVEF of 39±12%. Of these, 85 pts (32.7%) were in group A, 27 pts (10.3%) in group B, 74 pts (28.5%) group C and 74 pts (28.5%) in group D. The relative distribution of IHD vs IDC in the 4 groups was as follows: group A: 55% vs 45%; group B: 15% vs 85%; group C: 61% vs 39%; group D: 19% vs 81%; p for trend: <0.0001). The 4 groups also showed an increasing clinical severity, with % NYHA functional class 3-4 of 19%, 22%, 32% and 53% respectively. At follow-up (mean 26 months, range 6-84), TFS was 91.8% in group A, 81.5% in group B, 83.8% in group C and 57% in Group D (p<0.0001). RVEF and PAP were independent predictors of prognosis, while etiology was not.

Conclusions: This study provides evidence that combined utilization of RVEF and PAP allows stratification of patients selected over a wide range of LVD. Pts with IDC are identified preferentially in groups with reduced RVEF, while pts with IHD represent the majority in groups with preserved RVEF. Severity of prognosis is less when both parameters are normal and intermediate when any of the 2 is abnormal, while a combination of high PAP and low RVEF determines a poor outcome and deserves an aggressive therapeutic approach.

1329 Force-frequency relationship during dobutamine-stress echo: non-invasive exercise-independent assessment of left-ventricular contractility in the echo lab

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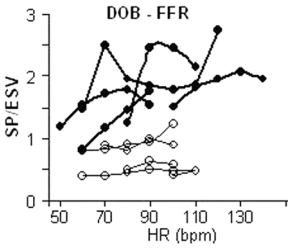
Background: Force-Frequency relationship (FFR) is a theoretically and methodologically robust assessment of left ventricular contractility and can be assessed noninvasively during exercise echo. Dobutamine might provide an exercise-independent alternative approach to assess inotropic reserve in patients unable to exercise.
Aim: To assess the feasibility of a totally noninvasive estimation of FFR during dobutamine stress in the echo lab.
Methods: We enrolled 10 consecutive patients (7 males, age 62± 8 years) referred for dobutamine stress echo (up to 40 mcg/kg/min). Seven patients had previous myocardial infarction, 3 chronic severe valvular heart disease. All had severely depressed resting left ventricular function (ejection fraction=29±8%). To build the FFR, the force was determined at different steps as the ratio of the systolic pressure (SP, cuff sphygmomanometer)/end-systolic volume index (ESV, biplane Simpson rule/body surface area). Heart rate was determined from ECG at different dobutamine steps.



Results: Dobutamine stress was uneventfully completed in all patients. An ischemic wall motion response developed in 2 patients. The FFR could be obtained in all, without expanding the imaging time and with only minor (<3 minutes) increase of off-line analysis. Five patients had an abnormal flat-downsloping, and 5 a normal upsloping FFR (figure), in spite of comparable resting ejection fraction (25.4±10.3 vs 32.4±2.3).
Conclusions: A totally noninvasive estimation of force-frequency relation is feasible during dobutamine stress in the echo lab. It unmasks a substantially heterogeneous contractile response in patients with similar values of conventional indices of left ventricular function.

1330 Systolic left-ventricular long-axis function during dobutamine stress echocardiography. Comparison with wall motion analysis for the prediction of recovery of left-ventricular dyssysnergies

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Objectives: Previous studies showed that systolic left ventricular (LV) long-axis function during dobutamine stress echocardiography (DSE) provides a promising, quantitative index for the detection of coronary ischemia. In the present study we assessed the contribution of the LV long-axis function during DSE, in predicting recovery of LV dyssynergies, after revascularization.
Methods: Forty patients with LV dysfunction due to old myocardial infarction scheduled for revascularization (24 PTCA and 16 CABG) underwent low-dose (5-10μgr/kg/min) DSE. The echocardiographic study included the standard protocol of LV wall motion analysis plus the measurement of LV long-axis shortening (LAS). The amplitude of LAS was estimated at rest and at every stage of dobutamine infusion, using 2D guided M-Mode, towards the four sites of the left atrioventricular plane (septal, lateral, inferior and anterior), from the apical 2- and 4-champers view. Resting two-dimensional echocardiography was also performed in all patients 101±14 days after successful revascularization.
Results: (see table) LAS showed a significant increase during dobutamine infusion only at LV dyssynergic sites with functional improvement in post-revascularization echocardiogram. In the remaining LV dyssynergic sites without functional improvement after revascularization LAS did not change significantly. Use of a LAS increase>2mm during DSE at any dyssynergic site of the left ventricle, resulted in a sensitivity of 91% and a specificity of 83% for the prediction of post-revascularization recovery of LV dyssynergies. When LV wall motion analysis DSE was used for the detection of reversible dysfunction, sensitivity and specificity were found to be 81.5% and 87.5%, respectively. When the two methods were in agreement, positive and negative predictive values were 100% and 84.2% respectively.

LAS during dobutamine stress echo

	LAS at PR improved LV DS (mm) (n=49)	LAS at PR non-improved LV DS (mm) (n=35)
Baseline	9.9 ± 1.6	9.1 ± 2
Low-dose dobutamine infusion	12.6 ± 1.5	9.3 ± 1.9
p value	<0.001	NS

PR: Post-revascularization, LV: Left Ventricular, DS: Dyssynergic Sites

Conclusions: Assessment of systolic LV long-axis function during DSE provides a promising quantitative adjunct to wall motion analysis for the prediction of recovery of regional LV dyssynergies after revascularization.

1331 Segmental contractile function by Doppler tissue imaging in an HIV population

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Doppler tissue imaging (DTI) is a quantitative method that evaluates segmental left ventricular (LV) myocardial function, a method applied in the assessment of several cardiac pathologies. The usual pulsed DTI pattern of the systolic s' wave corresponds to a single positive dome shape wave.
The aim of our study was to analyse during the systolic active phase, the segmental pulsed DTI myocardial pattern of an HIV population. We selected a group of 85 young HIV positive patients (pts), according to the following inclusion criteria: stage I HIV infection, class I NYHA classification, normal LV morphology, normal global LV systolic function indices by 2D-echocardiography, characterised by normal LV % fractional shortening (LV%FS>30%), ejection fraction (LV%EF>50%), and normal global LV diastolic (E/A>1) function by transmitral Doppler inflow. Our sample population registered a mean age of 34±11 years (17-44 years), 63.5% (54/85) male gender. Using a pulsed DTI approach and a LV model of 16 myocardial wall segments according to the A.S.E., we evaluated the presence of an abnormal segmental pulsed DTI profile (biphasic, triphasic and late peak wave) and calculated the mean and individual maximal inward velocity (Vmax-cm/sec) of the segmental systolic contractile s' wave. Other quantitative echocardiographic Doppler parameters were also calculated, such as the LV endsystolic (LVSD-mm), end diastolic (LVDD-mm) diameters, the interventricular septum (IVS) and posterior (PW) wall thickness (mm), the LV global mass (LVM-g), LV%FS and LV%EF. This HIV group was compared with an age-matched population of 30 normal subjects. Results: A total number of 1360 LV wall segments were analysed, revealing 21.2% (288/1360; p=0.01) with abnormal pulsed DTI systolic profile and without preferential myocardial location. The majority of these abnormal LV myocardial wall segments (74.6%-215/288; p<0.01) was related with HIV pts with LV%EF<60% and LV%FS<35%. We obtained significant positive correlations between the mean DTI Vmax s' wave and LV%FS (r=0.33; p=0.02) and LV%EF (r=0.45; p=0.01), increasing in the subgroup LV%EF<60 and LV%FS<35% to r=0.42 (p=0.01) and 0.56 (p<0.01), respectively. No other significant correlations were detected in our sample population.
Conclusions: In our study, the profile of the systolic contractile s' wave is already abnormal in a significant percentage of HIV cases. In a short range of LV global systolic function indices, the pulsed DTI profile and peak velocity of the segmental systolic s' wave of the LV myocardium is the major determinant for the LV global performance.

1332 Screening for undiagnosed systolic heart failure in the community with natriuretic peptides and electrocardiography

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Background: Natriuretic peptides are elevated in patients with systolic heart failure (SHF), often with ECG abnormalities.
Methods: We prospectively assessed the value of different natriuretic peptides in screening for undiagnosed SHF. 1360 subjects (45-80 years) were investigated using echocardiography and electrocardiography. Plasma was assayed for B-type (BNP), N-terminal proBrain (N-BNP) and N-terminal proAtrial (N-ANP) natriuretic peptides.
Results: There were 17 cases of definite, and 13 with borderline SHF. Receiver-operating-characteristic (ROC) curve analysis showed the superiority of BNP (ROC areas 0.942 for definite SHF, $P<0.03$; 0.934 for borderline SHF, $P<0.003$) in SHF detection. Peptide levels, major ECG abnormality and ischaemic heart disease (IHD) history were independent predictors of definite or borderline SHF. Logistic regression modelling incorporating these factors improved ROC areas for all natriuretic peptides (definite SHF 0.950-0.978; definite or borderline SHF 0.851-0.963). The specificity of natriuretic peptides is enhanced by consideration of ECG abnormalities and IHD history. Fig 1 shows the value of using BNP with ECG abnormalities (minimal model) and a history of IHD (full model).

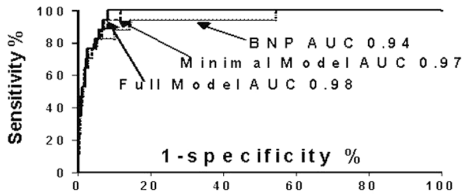

Figure 1. ROC curve for detection of SHF.

Conclusions: In screening for definite SHF in populations, the number of subjects requiring echocardiography to detect a case, falls from 44 when using BNP alone to 7 following consideration of major ECG abnormalities and IHD history. Similar improvements were evident for N-ANP (57 falling to 22) and N-BNP (42 falling to 15), and for all peptides when borderline SHF cases were included. Inclusion of major ECG abnormalities and IHD history improves the performance of any natriuretic peptide used in screening programmes for ruling in undiagnosed SHF.

CAN DIASTOLIC FUNCTION BE MEASURED?

1333 Population-based screening of left-ventricular diastolic dysfunction with N terminal pro-brain natriuretic peptide

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Background: The natural history of left ventricular (LV) diastolic dysfunction (DD) and methods for identifying the disease in its preclinical stages have not been delineated. Measurement of NT-BNP may be useful for the screening of LV ventricular systolic and diastolic dysfunction in a high-risk population.
Aim: To assess the value of NT-BNP as a screening tool for LV diastolic dysfunction in a population-based sample of older persons.
Methods: 2000 residents of Canberra, aged between 60-86 years, were randomly selected to participate in the ACT Heart Failure Survey. The response rate was 70%. For this substudy, subjects with a history of CHF or atrial fibrillation, significant (more than mild) valvular heart disease or a LVEF<40% were excluded. Data collected in 2002 are presented. 483 participants (mean age 69; 50% female) underwent examination with a transthoracic echocardiogram. Diastolic function was graded into 4 categories (normal; mild, moderate or severe dysfunction) according to Doppler measurements of mitral and pulmonary venous inflow and lateral mitral anulus velocity. Venous blood was collected after 10 minutes of sedentary rest and quantified by electrochemiluminescence sandwich immunoassay (ProBNP, Roche Diagnostics.

Median NT-BNP levels

	Normal	Mild DD	Moderate DD	Severe DD
Men	9 (5-15), n=166	10 (6-29), n=67	129 (28-229), n=2	107 (72-1069), n=3
Women	13 (8-18), n=152	13 (8-26), n=86	33 (23-40), n=5	127 (72-183), n=2
Total	11 (6-17), n=318	13 (7-27), n=153	33 (23-66), n=7	107 (72-183), n=5

Median, interquartile range, number

Results: Median (+IQR) NT-BNP levels for each category of LV DD are presented in the table, stratified for gender. NT-BNP levels for the normal and mild DD groups were similar, with considerable overlap between the groups. The area under the receiver operating characteristic curve for NT-BNP to detect any DD was 0.60 (95%CI, 0.56-0.65). The test performance was better in detecting normal from moderate-severe DD subjects (AUC 0.94; 95% CI, 0.91-0.96).
Conclusion: In a population-based sample, NT-BNP performs poorly as a screening test for the detection of any DD. This can be attributed to the high level of overlap in NT-BNP measurements in normal subjects and the mild DD group. However, NT-BNP reliably distinguishes between normal and moderate-severe DD.

1334 Inhibition of phosphodiesterase-5 and nitric oxide improve impaired diastolic function in hypoxia-induced pulmonary hypertension at high altitude

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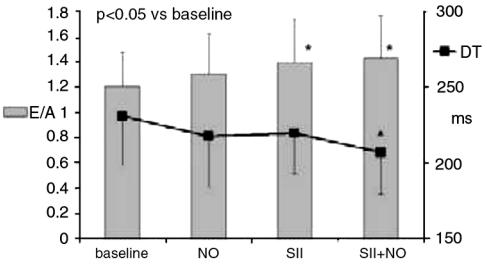
Background: Diastolic function of the left ventricle (LV) is impaired in mountaineers with hypoxia induced pulmonary hypertension at high altitude. We studied the effects of medical therapy on this in relation to changes in pulmonary pressure.
Methods: Doppler-echocardiography was performed in 22 healthy subjects (10 W, 12 M, age 29±12 years; O2-saturation 75±3%) 3 hours after they reached an altitude of 4559m. Measurements were repeated after NO (40ppm), the PDE5-inhibitor sildenafil (Sil; 50mg), and Sil plus NO. Changes in dimensions of cardiac chambers were assessed by M-Mode and 2D imaging. Pressure gradient across the tricuspid valve (dP TR), diastolic inflow of the LV (E/A-ratio; deceleration time DT), and tissue Doppler imaging were used (tissue E-wave: Em).
Results: There was a significant decrease in dP TR from 39±9mmHg (baseline) to 23±5mmHg (Sil+NO; $p<0.0001$). End-diastolic diameter of the right ventricle decreased (from 37.2±3.7 to 35.3±2.5mm, $p<0.05$) and of the LV increased (diameter from 47.3±2.9 to 49.9±3.6mm, $p<0.01$). Dimensions of both atria showed similar trends. The E/A-ratio increased and DT decreased (both $p<0.01$ ANOVA for repeated measures, figure; *$p<0.05$ vs baseline). The ratio of E/Em remained unchanged, indicating constant left-sided filling pressure. The changes in transmitral inflow pattern went parallel with the changes in the size of right and left ventricle.



Changes in diastolic function.

Conclusion: Impaired LV diastolic function at high altitude can be improved by reduction of pulmonary hypertension. Sil and NO were comparably effective and the combination acted synergistically. The interaction between both ventricles may be, at least in part, responsible for the improvement of diastolic function of the left ventricle.

1335 Evidence for atrial remodelling maximum indexed left atrial volume distinguishes pseudonormal from normal diastolic filling

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Background: Elevated left ventricular (LV) and left atrial (LA) pressures may lead to pulmonary congestion and heart failure symptoms. In such patients (pts.), pseudonormalization (PN) of the mitral inflow may mask diastolic dysfunction, especially if systolic function is preserved. However, increased LA pressures might be associated with atrial remodeling. Thus, indexed LA volume might be a useful marker to identify subjects with PN.
Methods & Results: 24 asymptomatic controls (age 58±6 years, CON group) and 41 patients (pts.) with PN (defined by an E/A-ratio 1-2, normal deceleration time (DT) and isovolumic relaxation time (IRT), E/A reversal during Valsalva (n=28) and/or mitral annular E' velocity derived from tissue Doppler < 7 cm/s (n=30), 60±10 y., PN group) underwent echocardiographic assessment of ejection fraction (EF), mitral flow (E/A-ratio, DT, IRT) and pulmonary venous flow velocities (PVS, PVD, PVAR). At end-systolic frames, maximum LA volume was derived from a single-area-length measure and indexed to body surface area. Subjects with pacemakers, atrial fibrillation, valve prostheses or >1+ mitral regurgitation were excluded. Adequate pulmonary venous flow recordings were obtained in only 17 of 24 controls (71%) and in 23 of 41 PN pts. (56%), and therefore were not included in the analysis.
table Using a cut-off value > 24.5 ml/m^2 for indexed LA volume (derived from receiver operating characteristic curve analysis), PN subjects were separated from controls with a sensitivity of 96% and a specificity of 94% (area under the curve: 0.98±0.01).

Group	NYHA class	EF (%)	E/A-ratio	DT (ms)	IRT (ms)	E' (cm/s)	LA vol (ml/m^2)
CON (n=24)	0	66±10	1.09±0.23	184±44	93±11	10.6±3.1	18.0±2.7
PN (n=41)	2.2±0.5*	47±19*	1.27±0.20	177±46	88±21	6.4±2.6*	34.3±5.7*

* p<0.01 vs. CON group

Conclusion: LA remodeling is present in subjects with PN. Indexed LA volume is a simple and reliable measure to identify symptomatic PN with moderate diastolic dysfunction and PN of the mitral inflow pattern, especially if adequate pulmonary venous flow recordings can not be obtained.

1336 Is left atrial volume a marker of left-ventricular diastolic burden in a population-based sample?

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Background: Classification of LV diastolic function with Doppler echocardiography is complex and requires the measurement of numerous LV parameters. Left atrial volume (LAV), which increases with chronic elevation of left atrial pressure, may provide additional information about LV diastolic burden.
Aim: To assess the value of LA volume in identifying LV diastolic dysfunction in a randomly selected sample of older persons.
Methods: 2000 residents of Canberra, aged between 60-86 years, were randomly selected to participate in the ACT Heart Failure Survey. The response rate was 70%. For this substudy, subjects with a history of CHF or atrial fibrillation, significant (more than mild) valvular heart disease or a LVEF<40% were excluded. Data collected in 2002 are presented. 466 participants (mean age 69; 49% female) underwent examination with a transthoracic echocardiogram. Diastolic function was graded into 4 categories (normal; mild, moderate or severe dysfunction) according to Doppler measurements of the mitral and pulmonary venous inflow, lateral mitral anulus velocity and CMM propagation velocity of LV inflow. Left atrial volume was quantified using the prolate-ellipsoid method.
Results: LA volume correlated moderately with body surface area (r=0.49, p<0.001) and indexed LAV was calculated for each subject. The median (+IQR) indexed LAV for each category of LV DD is presented in the table. LA volumes for the normal and mild DD groups were similar. The area under the receiver operating characteristic curve for indexed LA volume to detect any DD was 0.56 (95%CI, 0.51-0.61). Indexed LA volume was better in detecting normal from moderate-severe DD subjects (AUC 0.81; 95% CI, 0.76-0.85).

Median indexed LA volumes

Normal (mL/m^2)	Mild DD (mL/m^2)	Moderate DD (mL/m^2)	Severe DD (mL/m^2)
20 (17-24), n=318	20 (17-25), n=153	4 (18-34), n=7	33 (30-48), n=5

Median (Interquartile range), number

Conclusion: In a population-based sample, indexed LA volume does not adequately identify subjects with LV DD. Indexed LA volume may provide supplementary information to Doppler echocardiography in identifying patients with elevated LV diastolic pressures.

1337 Abnormal systolic function is a significant determinant of early and atrial propagation velocities in patients with delayed left-ventricular relaxation

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In spite of wide spectrum of available echocardiographic parameters classification of diastolic function (DF) is mainly based on mitral inflow profile. Also potential differences concerning quantitative staging of DF between patients (pts) with and without systolic dysfunction are not thoroughly examined.
Purpose: Our aim was to compare classic, propagation and tissue diastolic parameters between age-matched persons without systolic dysfunction and pts after myocardial infarction with mitral inflow classified as delayed relaxation (DR) in both groups.
Methods: Among 200 persons (80 healthy, 60 with coronary artery disease (CAD) and preserved EF and 60 after myocardial infarction (MI)) examined by transthoracic echocardiography we selected 97 subjects with DR profile. Than we compared: 63 persons without systolic impairment, mean age: 62.5±10, 32 male, mean EF 60±3% and 34 pts after myocardial infarction, mean age:62.7±9, 21 male, mean EF 38±10%.
Results: We did not observe any significant difference between pts with and without systolic dysfunction in early (Ev) and atrial wave (Av) velocity, E/A ratio, E deceleration time and isovolumetric relaxation time. However, mitral filling propagation velocities were significantly diminished in pts with systolic dysfunction: E wave propagation (Ep): 24±10 in pts after MI vs 35±8 cm/s, p<0.001 and A wave propagation (Ap): 42±13 in pts after MI vs 53±15 cm/s, p<0.001. Similarly, the early mitral inflow velocity to early propagation velocity ratio (Ev/Ep) and analogous parameter for atrial phase: Av/Ap ratio were higher in group with systolic impairment (2,3±0,9 vs 1,6±0,6, p<0,001 and 2±0,7 vs 1,6±0,7, p=0,009 respectively).
Conclusions: Contrary to classic mitral inflow parameters mitral E and A wave propagation differs in patients with and without systolic dysfunction presenting with delayed relaxation profile. Our results indicate that propagation analysis can further stratify the patients with delayed relaxation profile. Decreased elastic recoil or diastolic asynchrony in pts after MI is a significant determinant of mitral filling propagation velocities.

1338 What proportion of patients with heart failure and preserved left-ventricular systolic dysfunction has an elevated brain natriuretic peptide?

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Introduction: Many patients admitted to hospital with a diagnosis of "heart failure" are found to have preserved left ventricular (LV) systolic function. There remains, however, a great deal of uncertainty as to whether or not all of these patients really do have heart failure. We have determined what proportion of such patients has biochemical evidence of LV compromise i.e. an increased plasma concentration of B type natriuretic peptide (BNP).
Methods: 49 consecutive emergency admissions (42% male, mean age 76 years) fulfilling the Boston criteria for heart failure were studied. Transthoracic echocardiography (TTE) was performed and plasma BNP concentration measured. An elevated BNP was taken to be a concentration above the upper 95 percentile of a normal range established from a local healthy population aged over 70 years.
Results: 50% of patients had preserved LV systolic function on TTE. The median (range) BNP in patients with reduced LV systolic function was 580(165-1755) compared to 91(12-1048) pg/ml in patients with preserved systolic function (p<0.0001). 52% of the patients with preserved LV systolic function had an elevated plasma BNP concentration.
Conclusions: Only half of patients fulfilling standard diagnostic criteria for heart failure, but with preserved LV function, have biochemical evidence of LV compromise i.e. an increased plasma concentration of BNP. Epidemiological studies may have overestimated the prevalence of true heart failure in patients with preserved LV systolic function.

STRESS ECHOCARDIOGRAPHY CONTINUES TO EVOLVE

1339 Accuracy of dobutamine tissue Doppler echocardiography-derived myocardial velocity, strain and strain rate for assessment of local viability after myocardial infarction

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Background: Tissue Doppler echocardiography (TDE) is promising for accurate detection of local myocardial viability after acute myocardial infarction (MI).
Objectives: To determine the comparative accuracy of myocardial velocity, strain and strain rate, as assessed by dobutamine stress TDE, for assessment of myocardial viability after MI, with Thallium SPECT as a clinical gold standard for detection of tissue viability.
Methods and Results: Baseline and dobutamine (mean dose 15 μg/kg/min, baseline heart rate + 10 bpm) stress TDE was performed (2±1 days apart from MI) in 30 patients (mean age 57 years) who suffered a first acute reperfused (successful primary PTCA) MI. Maximal systolic and diastolic myocardial velocity, as well as maximal systolic strain and strain rate were determined in each myocardial segment, at baseline and under dobutamine, using the 17-segment model of the AHA. All patients underwent stress-redistribution-reinjection Thallium SPECT for detection of local viability, using the same model. A 4-grade scale model was used to visually assess thallium uptake within each segment. Out of the 510 segments analysed, 191 were dysfunctional on B mode echocardiogram (WMSI > 1). Among these, 121 were viable on SPECT and 70 were not. Under dobutamine, maximal systolic and diastolic myocardial velocities increased in viable (from 3.1±2.0 to 4.4±3.0 cm/s, and from -4.0±2.7 to -4.9±3.1 cm/s, all $p<0.01$), as well as in non viable segments as defined by SPECT (from 2.4±2.1 to 3.8±2.8 cm/s, and from -3.0±2.3 to -3.6±2.8 cm/s, all $p<0.01$). In contrast, maximal systolic strain and strain rate increased exclusively in viable segments (from -6.5±12.6 -12.2±14%, and from -0.6±1.0 to -0.9±1.2/s, $p<0.01$), whereas they remained unchanged in non viable myocardium (from -3.8±11.5 to -4.0±11.8%, and from -0.5±0.9 to -0.6±1.1/s, respectively, NS).
Conclusions: When compared to SPECT, stress TDE-derived strain and strain rate are more accurate for assessment of local viability after MI than myocardial velocity, which seem to be significantly altered by through plane motion of the heart and/or tethering from adjacent segments.

1340 Quantitative evaluation of regional perfusion during dipyridamole stress by myocardial contrast echo before and after revascularization of left anterior descending coronary artery

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Purpose: To assess whether real-time myocardial contrast echo (MCE) can detect changes in regional myocardial perfusion before and after successful revascularization of left anterior descending coronary artery (LAD) and to correlate these changes with regional wall motion abnormalities (RWMA)and quantitative angiographic data.
Methods: 14 pts, 9 male, aged 58 ± 8 years with > 50% stenosis of LAD underwent real-time MCE with SonoVue® using Power Doppler Harmonic Imaging (Vivid 7 GE)at baseline and during Dipyridamole stress and quantitative coronary angiography (QCA) before and 1 month after successful coronary revascularization of LAD by coronary angioplasty or bypass surgery. MCE time intensity data in 2 regions of interest (proximal (PSE) and distal septum (DSE)) were fitted to the exponential function y= A (1-e -bt)+ c, where A is the peak plateau signal intensity, b the rate of signal increase and the product A x b is proportional to myocardial blood flow.
Results: see table.
Conclusions: In patients with critical LAD disease real-time MCE shows an abnormal response of regional myocardial perfusion parameters to vasodilator stress associated with transient RWMA and a significant improvement of these parameters with restoration of coronary reserve after successful LAD revascularization. Thus, real-time MCE can be an useful tool to quantify regional myocardial perfusion in coronary patients undergoing myocardial revascularization.

	Before revasc		After revasc	
	basal	peak	basal	peak
A distal septum	26.14±9.29	31.6±24.79	27.16±8.4	25.98±11.41
b distal septum	0.31±0.19	0.33±0.28	0.47±0.24	0.93±0.15 (a) (b)
A x b distal septum	1.43±0.73	1.92±1.63	2.59±1.19	4.84±3.04 (a) (b)
b reserve		1.63±1.66		2.42±1.39
transient WMA		10/14 pts		0/14 pts
MLD mm	0.7±0.6		2.26±0.24 (c)	
%DS	72.32±17.43		11.39±3.52 (c)	

revasc= revascularization; RWMA= regional wall motion abnormalities; DS= diameter stenosis; MLD= minimal luminal diameter; (a)= $p<0.01$ vs basal after revasc; (b)= $p< 0,01$ vs peak before revasc; (c)= $p< 0.0001$

1341 Interpretation of stress echocardiography is facilitated by automated analysis of regional myocardial displacement and strain

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Background: Interpretation of stress echocardiography is limited by the subjective nature of visual analysis of wall motion on B-mode images and by the need for appropriate long-term training of the readers. Quantitative approaches have been proposed to overcome these limitations but they may be difficult to apply in clinical stress-echo practice and require significant time for image processing. Recently, automated calculation of regional myocardial displacement and strain from long-axis myocardial velocities has been implemented in commercially available ultrasound scanners. Both local displacement and strain can be represented as a color map over the left ventricular (LV) myocardium for a semiquantitative rapid interpretation of systolic regional myocardial function. AIM. The aim of this study was to assess the feasibility and accuracy of systolic displacement and strain for detection of coronary artery disease (CAD) in the setting of stress echocardiography compared to standard visual wall motion analysis.
Methods: Thirty-one patients (pts) (age 59±12 years, 21 males) underwent both coronary angiography and stress echocardiography with dypiridamole-atropine (18 pts) or dobutamine-atropine (13 pts). For each patient three standard apical views were collected in cineloop format at baseline and peak stress using a GE Vivid 7 echo scanner with simultaneous acquisition of both gray scale and tissue Doppler information. Two independent observers, who ignored results of angiography, interpreted regional myocardial displacement and strain obtained by analysis of tissue color Doppler images as well as regional wall motion (RWM) on the B-mode gray-scale images using a 16 segment LV model. Maximal segmental displacement and strain displayed at end-systole were compared with RWM for prediction of significant CAD.
Results: Analysis of regional displacement and strain was feasibile in all pts. Sensitivity and specificity for prediction of significant CAD were: 82% and 76% for RWM, 86% and 79% for displacement (NS vs RWM), and 92% and 88% for strain ($p<0,05$ vs RWM). Interobserver agreement was better for strain and displacement than for RWM.
Conclusions: Evaluation of both regional myocardial displacement and strain is feasible and accurate in the setting of stress echocardiography and can facilitate the diagnosis of CAD proving an objective and reproducible assessment of local systolic LV function. Regional strain assessment seems to be more accurate than displacement compared to conventional wall motion analysis.

1342 The prognostic value of pharmacological stress echo is affected by concomitant anti-ischaemic therapy at the time of testing

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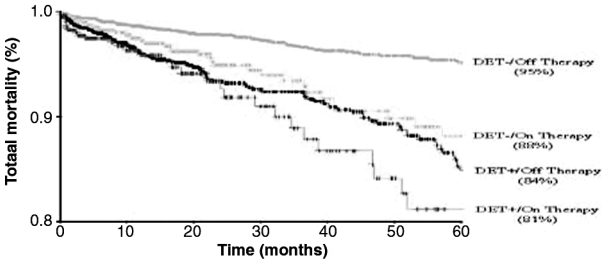
Aim: To determine whether antianginal medications affect the prognostic value of pharmacologic stress echocardiography.
Methods: From the EPIC - EDIC Data Bank 7333 patients (5452 males; 59±10 years) underwent pharmacologic stress echocardiography with either high dose dipyridamole (0.84 mg/kg over 10') (n= 4984) or high dose dobutamine (up to 40 mcg/kg/min) (n= 2349) (DET) for diagnostic purposes. One-thousand and ninety-one patients were on antiischemic therapy at time of testing (nitrates and/or calcium antagonists and/or beta-blockers). Patients were followed-up for a mean of 2.6 years (range 1 to 206 months).
Results: DET was positive for myocardial ischemia in 2854 (35%) and negative in 4479 (61%) patients. The total mortality was 336 (4.5%). Death was attributed to cardiac causes in 161 patients (2.1%). Survival was highest in patients with negative DET off therapy, and lowest in patients with positive DET studied on therapy. Survival was comparable in patients with positive test off and in patients with negative test on therapy(Figure).



Conclusions: Ongoing antiischemic therapy at the time of testing heavily modulates the prognostic value of pharmacological stress echo. In presence of concomitant anti-ischemic therapy, a positive test is more prognostically malignant, and a negative test less prognostically benign.

1343 Mental stress and myocardial ischaemia: stress echocardiography study

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Introduction: Indirect evidences have suggested a link between mental stress and coronary artery disease (CAD), but direct evidence of myocardial ischemia during mental stress has not been systematically and prospectively demonstrated.
Objective: The aim of this study was to evaluate in prospective manner, the feasibility of mental stress test and the relation between mental stress and occurrence of myocardial ischemia as evaluated by echocardiography.
Methods: All laboratory sessions began at noon, and the patients were studied off antianginal therapy. Study population included 38 patients with angiographically proven CAD (31 male, 7 female, mean age 48±10 years; multivessel CAD in all patients) and previous positive exercise stress test (development of chest pain and ST depression >1mv, 0.08 sec after J point). 12-leads ECG, blood pressure, and echocardiography for wall motion abnormalities were continuously monitored. Test protocol consisted of rest phase (30 min in a partially darkened room), mental task phase: mental arithmetic (5 min, subtract 7s' serially from a 4-digit number) and simulated public speech task (10-15 min, describing their personal faults and shortcomings). After mental stress test, in all patients submaximal Bruce treadmill protocol was performed.
Results: Mental stress test was successfully performed in all patients (feasibility 100%). During mental stress test, chest pain occurred in 5/38 pts (13%), ischemic ECG changes developed in 9/38 pts (24%, p=ns vs. angina) and new or worsening of wall motion abnormalities was observed in 22/38 (58%, p< 0.05 vs. angina and ECG). Exercise stress echocardiography test after mental stress test was positive in 35/35 pts (100%; in 3 pts exercise stress test was not performed because of hypertensive reaction during mental stress test).
Conclusion: These results showed excellent feasibility of mental stress test and direct evidence that myocardial ischemia in significant number of pts with severe coronary artery disease is related to mental stress.

1344 Clinical significance of left-ventricular obstruction during dobutamine stress echocardiography: comparison with exercise echocardiography

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Background – About 20% of patients undergoing dobutamine stress echocardiography (DSE) develop a significant dynamic subaortic pressure gradient. Symptoms such as chest pain, dyspnea have been attributed to this phenomenon and the use of beta-blockers has been recommended.
Methods – To determine its clinical significance, DSE was compared to exercise echocardiography (EE). Left ventricular (LV) outflow tract diameter, septal thickness, LV ejection were measured. Subaortic flow velocities were obtained by Doppler assessment at rest and during stress. The effect of LV hypertrophy and the use of atropine on gradient profile were tested.
Results – Of 232 consecutive patients submitted to DSE, 31 developed significant subaortic obstruction (velocity > 3 m/s). Of these 31, 24 patients capable of exercising underwent EE. During DSE, systolic anterior motion of the mitral valve was observed in 9 patients (6 with septal contact) and 8 had Dobutamine-induced hypotension. LV hypertrophy was associated with the precocity of significant obstruction (p=0.02). Atropine had no influence on the pressure gradient profiles. During EE, no patient developed dynamic obstruction: peak velocities ranged from 0.9 to 2.2 m/s.
Conclusions – Dynamic LV obstruction developing during DES is not reproducible during exercise in an individual patient. This physiologic phenomenon has no clinical significance and specific therapy does not seem to be warranted.

EXERCISE IN PATIENTS WITH HEART FAILURE

1345 Evidence for distinct mechanisms of reduced exercise capacity versus cardiac cachexia in chronic heart failure

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Apoptosis has been found in skeletal muscles of patients with heart failure and has been associated with exercise intolerance. Cachexia is characterized by neurohormonal activation and muscle loss. Neurohormonal activation, which is characteristic of cachexia, leads to cell death and fibrosis. The purpose of the study was to determine the severity of apoptosis and fibrosis in skeletal muscles of patients with heart failure and cachexia and its relationship to exercise intolerance in these patients.
Methods and Results: Skeletal muscle biopsies of 21 patients with CHF (8 with cachexia) and 4 age matched controls have been studied by In situ end labeling (ISEL) for apoptosis and by the Picrosirius Red technique for collagen. Peak oxygen consumption was determined by cardiopulmonary exercise test with the Weber protocol. Apoptosis in skeletal muscles was detected by ISEL in 52% of the patients with CHF (11 out of 21) and in none of the healthy controls. Patients with apoptosis positive skeletal muscles had impaired exercise tolerance (peak oxygen consumption 11.4 ± 5.7 vs 16.91 ± 6.6, p=0.029). Increased collagen was detected by picrosirius red in 8 out of 21 patients with CHF and in none of the controls. Apoptosis, in the peripheral muscles, was similar between cachectic and noncachectic patients. However, fibrosis (increased collagen content)was detected in 6 out of 8 patients with cachexia but only in 2 out of 13 patients without cachexia (p=0.01). Exercise capacity as expressed by peak oxygen consumption was similar between cachectic and non cachectic patients.
Conclusions: Patients with cachexia have increased fibrosis in skeletal muscles compared to patients without cachexia, but apoptosis was similar in both groups. These findings suggest that the neurohormonal factors which are activated in cachexia lead to necrosis and fibrosis and contribute by a different mechanism to skeletal muscle myopathy of CHF patients. In conlusion, in chronic heart failure syndrome, different pathophysiologic mechanisms lead to reduced exercise capacity and to cardiac cachexia.

1346 Exercise training by electrical muscle stimulation in normal subjects has a beneficial effect on exercise capacity, muscle strength and body mass index

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Introduction: Electrical muscle stimulation (EMS) of large muscle groups in the legs produces cardiovascular exercise. The physiological response to this form of exercise is repeatable. We aimed to assess whether EMS-induced exercise training can produce a training stimulus in normal healthy subjects.
Methods: 11 healthy subjects were enrolled into a randomized crossover study involving a 6 week period of exercise training using EMS of the legs, a 6 week period of detraining and a 2 week washout period in between when no training was allowed. EMS was delivered to the quadriceps, hamstring and gluteal muscles from a hand held battery-operated EMS device via appropriately placed silicon rubber electrodes incorporated into a pair of tight fitting shorts extending to the knees. Cardiopulmonary gas exchange, 6 minute walk distance, quadriceps muscle strength and body mass index(BMI)were assessed at baseline, 6 weeks and 14 weeks.
Results: Subjects included 6 males and 5 females with a mean age of 51.8 $\pm$ 12.5 yrs. At baseline the mean values for peak VO2, 6 minute walk distance,maximal quadriceps muscle strength and BMI were 29.5 $\pm$ 5.6 ml/kg/min, 483.8 $\pm$ 37.9 m, 340.4 $\pm$ 111.5 N and 26.8 $\pm$ 3.5 kg/m^2 respectively. After training with EMS peak V02 increased by 2.6 $\pm$ 3.2 ml/kg/min vs a drop of 0.7 $\pm$ 3.3 ml/kg/min (P=0.0287)following detraining. The 6 min walk distance increased by 35.6 $\pm$ 17.6 m post EMS training vs a decrease of 15.3 $\pm$ 32.7m post detraining (P=0.0010). Maximal quadriceps muscle strength post training was higher by 91.3 $\pm$ 58 N vs a decrease after detraining by 31.6 $\pm$ 38 N (P=0.000001).BMI post EMS training reduced by 0.4 $\pm$ 0.5 vs a rise of 0.9 $\pm$ 0.6 post detraining (P=0.0002).
Conclusion: A 6 week period of EMS induced exercise training significantly increases peak VO2, 6 minute walk distance, and maximal quadriceps muscle strength, while reducing BMI.

1347 Excessive ventilation during early phase of exercise predicts poor outcome in patients with chronic heart failure

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Background: Excessive ventilation during exercise is related to unfavourable outcome in patients with chronic heart failure (CHF). In most studies, however, ventilatory data were derived from the whole maximal cardiopulmonary exercise testing (CPX). Prognostic value of ventilatory response to early phase of exercise in CHF patients remains unknown.
Methods: We investigated 160 consecutive CHF patients (138 men, age: 59 $\pm$ 12 years, NYHA class I/II/III/IV: 20/71/55/14; left ventricular ejection fraction [LVEF]: 31 $\pm$ 7%) who underwent CPX. Ventilatory response to exercise, expressed as minute ventilation per unit of CO2 production (VE-VCO2 slope) was calculated from the data obtained during: 1)the whole CPX [VE-VCO2(100%)] and 2) the early phase of exercise – i.e. the first 180 seconds [VE-VCO2(180s)].
Results: CHF patients demonstrated elevated values of VE-VCO2(100%) and VE-VCO2 (180s) (mean: 35.6 and 34.4, respectively, both $p<0.0001$ vs. reference values in our laboratory). VE-VCO2(180s) correlated with VE-VCO2(100%) (r=0.82, $p<0.0001$), peak oxygen consumption (peakVO2) (r=-0.41, $p<0.0001$), and was strongly related to the severity of CHF expressed as NYHA class [VE-VCO2(180s) for NYHA I/II vs. III/IV: 32.1 vs. 37.1, $p<0.01$]. During the follow-up (mean: 583 $\pm$ 364 days) 30 (19%) patients died. Augmented ventilation during early phase of exercise [prospectively defined as $>$ mean+2SD of age-matched controls, i.e. VE-VCO2(180s)$>$33] was related to impaired survival in univariate (hazard ratio 3.3, 95%CI: 1.5–7.5, p=0.004) and multivariate analyses (adjusted for NYHA class, LVEF and peak VO2; $p<0.05$). The 18-month survival for CHF patients with VE-VCO2(180s)$<$33.0 was 87% (95% CI: 77-97%) vs. 67% (95% CI: 53-81%) in those with VE-VCO2(180s)$>$=33.0 (p=0.03).
Conclusions: In CHF the excessive ventilation during early phase of exercise predicts poor outcome. Our findings extend the application of the ventilatory assessment for prognostic stratification to those CHF patients who are not able to perform maximal CPX.

1348 Dyspnea-induced "training of the diaphragm augments local antioxidative protection in an animal model of heart failure

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Background and Purpose: Increased muscle activity (e.g. associated with exercise training) has been shown to enhance local skeletal muscle antioxidative enzyme capacity. In chronic heart failure (CHF) the diaphragm is also subjected increased activity due to tachypnea. Aim of this study was to determine whether the diaphragm as a skeletal muscle would show a similar increase in antioxidative enzyme capacity as a result of the dyspnea-related training effect as opposed to the untrained quadriceps.
Reactive oxygen species can affect muscle contractility by reacting with nitric oxide (NO) to peroxynitrite, a known inhibitor of aerobic metabolism. To assess the interaction between antioxidative activity and energy metabolism we also measured local cytochrome c oxidase (COX) activity.
Methods: Male Wistar Kyoto rats (250 g) were subjected to LAD ligation (MI, n=19) or sham operation (S, n=9). After 12 weeks left ventricular function was analyzed by echocardiography and LV catheterization with a 2F micromanometer-tipped catheter. Catalase, superoxide dimutase (SOD), and glutathione peroxidase (GPX) activities were measured photometrically and their expression assessed by quantitative RT-PCR (Light-Cycler). Local COX activity was quantified by the Clark oxygen electrode.
Results: After 12 weeks MI rats showed significant LV contractile dysfunction (dp/dtmax: 4.47$\pm$0.24 versus 6.03$\pm$0.42 mm Hg/ms, p=0.003). GPX activity (91.8$\pm$4.0 versus 67.4$\pm$5.71 mU/mg in S, p=0.002) and MnSOD activity (2.0$\pm$0.3 versus 0.6$\pm$0.24%inhib/μg protein in S, p=0.009) were both significantly elevated in the diaphragm. This trend was also evident in diaphragmatic GPX expression (117$\pm$40 versus 89$\pm$19 in S, p=NS). Catalase and Cu/Zn SOD activity and expression were unchanged. COX activity in the diaphragm was largely unchanged (126.9$\pm$11.06 versus 156.0$\pm$17.13 nmol O2/min mg in S, p=NS), in contrast, it was was reduced in the quadriceps (67.81$\pm$7.98 versus 130,5$\pm$18.43 nmol O2/min mg in S, p=0.001).
Conclusions: In experimental heart failure the dyspnea-related increase in diaphragm muscle activity is associated with increased activity of key antioxidative enzymes (GPX, Mn SOD). While COX activity was significantly reduced in the peripheral skeletal muscle it remained unchanged in the diaphragm. The increased antioxidative protection in the diaphragm could have reduced local peroxynitrite generation in the presence of iNOS-produced NO thereby preventing toxic inhibition of COX activity.

1349 Expression of protein phosphatase 2A in skeletal muscle after development of chronic heart failure: impact of inflammatory cytokines

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Background: Intrinsic alterations of skeletal muscle (SM) metabolism and gene expression as well as elevated plasma cytokine levels have been described in chronic heart failure (CHF). These studies, however have only analyzed the differential expression of selected genes, therefore their gain of new information is limited. The aim of this study was to compare the gene expression profile in SM of rats with CHF and healthy controls and to analyze the impact of inflammatory cytokines on gene expression in SM.
Methods: Ten Wistar-Kyoto rats were subjected to either LAD ligation (Lig, n=5) or sham operation (Con, n=5). Twelve weeks after LAD ligation left ventricular dysfunction was confirmed by cardiac catheterization (Millar, dp/dtmax: Lig 6.6$\pm$0.6 mmHg/ms vs Con 4.8$\pm$0.4 mmHg/ms, $p<0.05$) and mRNA was isolated from quadriceps muscle of both groups. Differential gene expression was studied by suppression subtractive hybridization. To study whether the differential expression could have been caused by inflammatory activation the expression of one exemplary protein was quantified in cytokine incubation experiments with L6 skeletal muscle myoblasts.
Results: Out of 800 picked clones 24 differentially expressed genes were identified by sequencing and reverse Northern blotting. Among the upregulated genes was protein phosphatase 2A (PP2A) which plays an important role in intracellular signalling and exerts a proapoptotic effect via the dephosphorylation of proteins of the Bcl-2 family. Because of this functions PP2A was chosen for further investigations. Incubation of L6 rat skeletal muscle myoblasts with single cytokines (TNF-alpha, IL-1beta, IFN-gamma) or combinations of TNF-alpha/IL-1beta or TNF-alpha/IFN-gamma caused no significant changes in PP2A expression. However, incubation with combinations of either IL-1beta/IFN-gamma or TNF-alpha/IL-1beta/IFN-gamma caused a significant upregulation of PP2A mRNA (IL-1beta/IFN-gamma: 2.0$\pm$0.4fold expression, p=0.03; TNF-alpha/IL-1beta/IFN-gamma: 3.0$\pm$0.7fold expression, p=0.03) and protein expression (IL-1beta/IFN-gamma: 2.3$\pm$0.5fold expression, p=0.02; TNF-alpha/IL-1beta/IFN-gamma: 2.1$\pm$0.4fold expression, p=0.04) vs. untreated cells.
Conclusion: The results of this study suggest that CHF is accompanied by changes in expression of genes involved in intracellular signalling and apoptosis in the skeletal muscle, e.g. PP2A. The upregulation of PP2A, an important regulator in intracellular signalling and apoptosis, may be due to an increase of inflammatory cytokines.

1350 Ergoreflex contribution to ventilatory response assessed during exercise of forearm and quadriceps muscles in patients with chronic heart failure

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Background: The overactivation of ergoreceptors (afferents sensitive to metabolic products of skeletal muscle work) contributes to enhanced ventilation and exercise intolerance in patients with chronic heart failure (CHF).
Methods: We assessed ergoreceptor activity within two muscle groups (forearm and quadriceps muscles) in 21 men with CHF (age - 59±7 yrs, NYHA class I/II/III: 4/10/7, LVEF: 30 ± 8%) and 7 healthy age-matched men (age: 56 ± 9 yrs, LVEF: 61 ± 4%). Test involved 5 minute exercise at 30% of maximal strength followed by 3 minute post-exercise regional circulatory occlusion (PE-RCO). The contributions made specifically by ergoreflex to ventilatory responses (ERGO-arm, ERGO-leg) was assessed as difference in minute ventilation between PE-RCO (2. and 3. minute) and the recovery period without PE-RCO.
Results: Ventilatory responses to ergoreceptor stimulation within both forearm and leg were augmented in CHF patients when compared to controls (ERGO-leg: 4.3 ± 3.6 vs. 0.7 ± 0.6 l/min, $p<0.05$; ERGO-arm: 2.1 ± 2 vs. 0.2 ± 0.3 l/min, $p<0.05$). In CHF patients ERGO-leg was greater than ERGO-arm when analysed in absolute units (4.3 ± 3.6 vs. 2.1 ± 2.0 l/min, $p<0.05$), but there were no differences in ERGO-leg and ERGO-arm when expressed in minute ventilation per kg of muscle mass assessed using DEXA (0.5 ± 0.5 vs. 0.7 ± 0.7 l/min/kg, p= ns).
Conclusions: Ergoreflex activity is significantly enhanced in CHF patients, both forearm and leg exercise can be used to differentiate the ventilatory response due to ergoreceptor stimulation.

THE DIAGNOSTIC CHALLENGE OF HEART FAILURE IN EVERYDAY CLINICAL PRACTICE

1384 The diagnostic challenge of heart failure with preserved systolic function in primary care setting

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Heart failure (HF) with preserved systolic function (PSF) is a prevalent condition generally treated in primary care (PC). HF/PSF early stages are specially difficult to diagnose. HF diagnosis requires clinics and the evidence of cardiac dysfunction at rest. Echocardiography (echo), is the most common method of evaluating cardiac function. It is still not easily available in many routine settimgs and its costs limits its use as a routine screening tool. Studies have found brain natruretic peptide measurement (BNP) to be higly sensitive and specific in diagnosing HF. Its diagnostic role has been studied most extensively in symptomatic HF and systolic dysfunction. It has been used to a limited extend as a screening tool in PC setting. Whether BNP could aid in the diagnosis of HF/PSF remains unanswered.
Aim: To evaluate the accuracy of BNP for the diagnosis of HF/PSF in PC setting.
Methods: Patients were selected from an epidemiological cross-sectional sudy of the population from PC centers in Madeira, Portugal: the EPICA-RAM study. 644 consecutive PC centers attendants were included. HF cases were diagnosed according to ESC guidelines; symptoms and signs of HF and evidence of cardiac dysfunction - shortening fraction > 28% and increased left ventricular mas index (LVMI) and/or left atrial (LA) (Henry's criteria), assessed by echo. The estimated global prevalence of HF was 4.7% and of HF/PSF: 2.7%.1/2 patients were in NYHA class I and 1/4 in class II. BNP was mesured in all HF patients (IRMA, Shionogi, Osaka, Japan)The accuracy of BNP for the diagnosis of HF/PSF, increased LVMI and dilated LA was evaluated by the areas under the receiver operating curve (AUC).
Results (table): The AUC were acceptable for detecting dilated LA(0.89), but at or below 0.56 for detecting HF/PSF, and LVMI.

Accuracy of BNP for the diagnosis of HF/PSF, increased LVMI and dilated LA

BNP	AUC	95% CI
HF with preserved systolic function	0.56	0.44 - 0.67
Increased LVMI	0.54	0.45 - 0.64
Dilated LA	0.89	0.77 - 1.00

Conclusion: In our community-based sample the accuracy of BNP for the diagnosis HF/PSF was suboptimal, suggesting limited usefulness of BNP as a screening tool in the PC setting, at least in the early stages of HF/PSF.

1385 Quality of heart failure diagnosis in hospitalized patients

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Heart failure (HF) is a severe condition with a high prevalence and mortality among the population. HF patients have a reduced quality of life. They are mostly managed in primary care and admitted to internal medicine wards. An adequate prevention of risk factors and accurate diagnosis are urgently required. Scientific societies have published updated guidelines for diagnosis and therapy of HF.
Aims: To assess the accuracy of the diagnosis of HF in patients admitted to an internal medicine ward of an urban teaching center in a southwestern European country.
Methods: Over a six month period, we carried out a retrospective observational study of discharge records from all consecutive patients discharged from our internal medicine ward. We reviewed records with either the diagnosis of HF or cardiovascular diseases that are potential precursors of HF. Then we analyzed the percentages of correct HF diagnosis, of cases discharged without the diagnosis mentioned but having HF and of misdiagnosed cases. In accordance with the ESC guidelines, we considered HF all patients presenting HF symptoms/signs and objective evidence of cardiac dysfunction at rest. All records were also evaluated in order to assess the tests used to diagnose HF.
Results: 1038 patients were admitted from January to July 2001. 195 discharge records were enrolled and 180 fulfilled the ESC criteria for a diagnosis of HF. In 132 (67.7%) the diagnosis was correctly recorded at discharge. Nevertheless, 38 patients (19.5%) showed evidence of HF but the diagnosis was not mentioned in the medical information given to the patient. Moreover, 26 patients (13.3%) had an incorrect diagnosis of HF. Chest X-Ray was described on 81% of the records and 60% showed anomalies due to HF. The ECG was recorded in 86.7% and changes were present in 71.1% of the HF cases.
Conclusion: Although HF diagnosis was accurate in the majority of patients, in one fifth of all cases the syndrome was misdiagnosed. Since a correct diagnosis of HF was not always recorded at discharge, this may lead to inadequate primary care management of the syndrome. Diagnosis protocols for HF should urgently be followed in internal medicine wards.

1386 Diagnosis of heart failure in the community – how does echocardiography compare with brain natriuretic peptide?

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Recently, we have demonstrated the high negative predictive value and usefulness of N-BNP as a "rule out" test for diagnosis of heart failure (HF) in the community.
Aims: This study aimed to determine whether echo measurements of systolic and diastolic function could be used in a similar discriminative manner as N-BNP.
Methods: Pts were those in the Natriuretic Peptides in the Community Study who presented to their general practitioner with HF symptoms. They underwent clinical evaluation, N-BNP assay and echocardiography. The gold standard diagnosis of HF was the decision of an expert panel using ESC criteria. Receiver-operating characteristic (ROC) curves were used to assess the N-BNP assay and echo variables as diagnostic tests for HF, first in the whole group and then in the group of pts with abnormal N-BNP (>50pmol/l).
Results: 305 pts were included, 65% female, mean age 72 yrs (SD 11.4), 77 (25%) met the case definition of HF. 161 patients had N-BNP > 50 pmol/l, of whom 70 met the case definition of HF. No echo variable was superior to the N-BNP for HF diagnosis; LA area was the best single echo variable for the whole group. In the pts with abnormal N-BNP, both FS and mitral annular systolic velocity (SM) performed as well as N-BNP

	All Patients (n=305)	Patients with N-BNP > 50 (n=161)
N-BNP	0.852	0.789
Left atrial area	0.768	0.681
Mitral filling pattern	0.687	0.692
E/E' ratio	0.654	0.656
Annular systolic velocity	0.651	0.756
Fractional shortening	0.637	0.796
Deceleration time	0.646	0.686
E/A ratio	0.598	0.700

Conclusions: No single echo measurement reached the diagnostic accuracy of N-BNP for HF diagnosis in this cohort of pts. However, in the subgroup with abnormal N-BNP, both FS and SM reached similar levels of diagnostic accuracy. Whilst N-BNP should be the initial diagnostic test for symptomatic pts, echo is useful in those pts with abnormal N-BNP results.

1387 Using brain natriuretic peptide and N terminal pro-brain natriuretic peptide to rule out heart failure: does it work in clinical practice? Results of the UK natriuretic peptide study

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Small, single centre studies have suggested that the measurement of plasma natriuretic peptide (NP) concentrations may be used to 'rule out' heart failure (HF). It is not known whether these findings can be replicated in UK hospital and primary care routine practice. We report the results of a multi-centre study designed to test the diagnostic value of the measurement of plasma BNP and NT-proBNP in patients presenting to their general practitioner (GP) with symptoms that the GP thinks are due to development of HF for the first time.
Methods: Patients were recruited at 5 centres that ran a specialist rapid assessment clinic to which GPs referred patients with new symptoms that they considered to be due to HF. All patients were examined and had chest radiograph, ECG and transthoracic echocardiogram. Blood was drawn for the measurement of urea and electrolytes and for both BNP (near-patient testing) and NT-proBNP (lab. test). The examining doctor, who was blind to the NP result, employed the European Society of Cardiology guidelines for the diagnosis of HF. The diagnostic value of the NPs was compared with the clinical diagnosis.
Results: Data will be presented on all 300 patients recruited to the study (completing March 2003), but this abstract relates to the first 173 patients. 58 (33%) had the diagnosis of HF confirmed. Plasma BNP and NT-proBNP were highly correlated (R=0.87 P<0.001). Both peptide levels were higher in those with HF (BNP: median 292 pg/ml [90% range] 28-1300; NT-proBNP 1535 pg/ml [100.5-12002]) than in those without (BNP: median 51 pg/ml [6-312]; NT-proBNP 206 pg/ml [20-2085])(Both P<0.001). The areas under the receiver operating characteristics curves were almost identical for BNP and NT-proBNP at 0.86 [95%CI 0.80- 0.92] and 0.84 [0.77-0.91], respectively.

Natriuretic peptide	Cut-point	Sensitivity	Specificity	Positive predictive value	Negative predictive value
BNP	40pg/ml	95%	42%	45%	94%
NTproBNP	166pg/ml	94%	42%	43%	93%

The table summarises the diagnostic performance of BNP and NTproBNP.

1388 Accuracy of N terminal pro-brain natriuretic peptide for the diagnosis of congestive heart failure in patients admitted with dyspnea in the emergency department

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We sought to compare the diagnostic value of N terminal pro-Brain Natriuretic Peptide (NT pro- BNP) to Brain Natriuretic Peptide (BNP) and clinical judgment in the diagnosis of the cardiac origin of dyspnea in 113 consecutive patients (pts), mean age 74±13 years, presenting to the emergency department (ED). Plasma BNP levels were measured by using a radioimmunoassay (Shionoria BNP kit ®) and NT pro-BNP by using an electrochemiluminescence immunoassay (pro- BNP test Elecsys ®). The final diagnosis, assessed by independent cardiologists blinded to BNP results, on the basis of the case report, ECG, chest x-ray, the echocardiogram and the clinical evolution, was congestive heart failure in 54 pts (group A) and other aetiology in 59 pts (group B). The correlation coefficient between NT pro-BNP and BNP was r=0.815 (p<0.0001). NT pro-BNP and BNP plasma levels were higher in A (median, 6088 pg/mL and 328 pg/mL) than in B (median, 987 pg/mL and 47 pg/mL, p<0.001). Clinical judgment accuracy of ED physicians was 81%. BNP>84 pg/mL had a diagnostic accuracy of 79% and NT pro-BNP>2032 pg/mL of 80%. Misclassified pts in group A, on the basis of NT pro-BNP and BNP results (n=13) were older (median, 78 vs 70 years, p<0.05), and had a lower creatinine clearance (57±26 vs 78±31 ml/min,p<0.05), than correctly classified patients of group B. In conclusion, our study demonstrates that NT pro-BNP and BNP plasma levels measurements have a similar diagnostic accuracy in the determination of the aetiology of dyspnea, but should be cautiously interpreted according to the age and renal function of pts admitted in the ED.

1389 Diagnostic implications of release of myocardial necrosis markers in patients with acute pulmonary edema

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The diagnostic and prognostic relevance of a release of markers of myocardial necrosis in patients with acute coronary syndromes is well established but its significance in those with acute pulmonary edema(APE) is uncertain.
We prospectively studied 216 consecutive patients admitted to our Emergency Room with APE of =<6 hours duration. Serial blood sampling for cardiac cTnI and CPK MB mass were performed in 212, age 74±10 years, and the nature of underlying cardiac disease was assessed by clinical, electrocardiographic, echocardiographic and angiograpphic studies. There were 112 males (52%) and in 185 a diagnosis of coronary artery disease (CAD) was made based on a history of myocardial infarction, presence of angina with ECG changes, coronary estenosis >70% in ≥1 vessel or scintigraphic evidence of reversible ischemia. Among the 31 patients without CAD,10 presented isolated valvular heart disease (5%), 10 hypertensive cardiomyopathy (5%) and 11 other diagnosis (5%).
Necrosis markers were increased in 82% of patients with CAD and in 32% of those without CAD (p<0.001), with a larger peak value in the former group (76± 129 vs 11±31,micg/L, p=0.009).There was a good correlation between CKMB mass and cTnI (r:0.86). A coronary angiography performed in 99 unselected patients with CAD documented multivessel disease in 89 (91%), with a 32% incidence of significant left main disease, that was independent of the kind of underlying coronary syndrome. Patients without angina or ST segment changes duirng APE (n:75)presented a median of MBmass of 6, those with angina (n:36) 9, those with ST segment shift (n:37) 29, and those with angina and ST segment shift (n:68) 49 mcg/L.
Conclusions: Our results indicate that >75% of patients presenting with an APE have increased plasma levels of cTnI and CPK MB mass. The increase is more frequently observed in those with CAD who present a much larger peak value than those without CAD. The high prevalence of extensive CAD along with the high frequency of enzyme release strongly suggest that myocardial ischemia/necrosis is the trigger of APE in a large proportion of patients.

ATRIAL FIBRILLATION AND THROMBOEMBOLIC RISK FACTORS

1436 Hyperhomocysteinemia as a risk factor for transient ischaemic attack and stroke in patients with atrial fibrillation

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High levels of homocysteine (Hcy) are associated with an increased risk of cerebrovascular disease (TIA/stroke) whereas scarce data are available on their prevalence in non-rheumatic atrial fibrillation. The aim of this study was to determine Hcy levels in AF patients with and without history of cerebral embolism to investigate if hyperhomocysteinemia can play a role in the occurrence of cerebrovascular complications in these patients. We studied 247 patients: 144 patients with AF who had had a previous TIA or stroke (76 males, 68 females, mean age 74 ± 8) (group A) and 103 patients with AF and without history of cerebral embolism (64 males, 39 females, mean age 72.4 ± 8.3) (group B). Two hundred healthy subjects, recruited from the blood donors and staff of our hospital, were used as controls. Plasma homocysteine was measured by HPLC and fluorimetric detection. Hcy plasma levels were significantly higher (p < 0.0001) in group A patients (median 15.2 umol/L, range 5.4 - 54.1) than in group B patients (median 13.9 mol/L, range 6.7 - 38.6) and in controls (median 9.3 umol/L, range 4.8 - 23). Hyperhomocysteinemia, defined as a Hcy concentration above the 95th percentile of controls, was diagnosed in 86 patients of group A (59.7%), in 46 patients of group B (44.6%) and in 10 controls (5%). Both at the univariate analysis and at the multivariate analysis adjusted for age, sex and classic cardiovascular risk factors, hyperhomocysteinemia was significantly associated with AF in either groups studied [group A: OR = 17.5; IC 95% 8.5 - 36.2; p < 0.0001/group B: OR = 12.1; IC 95% 5.5 – 26.4; p < 0.0001]. Moreover, we documented a significant positive correlation between Hcy plasma levels and left atrial size in either group of patients with AF (r = 0.46; p < 0.0001). In addition, we performed a multivariate analysis, adjusted for age, sex, left ventricular function, left atrial size and classic cardiovascular risk factors, comparing group A and B, which demonstrated that hyperhomocysteinemia increases the thromboembolic risk in patients with AF (OR = 1.9; IC 95% 1 – 38; p < 0.059). In conclusion, this study indicates that: 1) there is a higher prevalence of moderate hyperhomocysteinemia in AF patients; 2) this prevalence is higher in those patients with history of TIA or stroke; 3) hyperhomocysteinemia could play a role in the atrial dilatation and remodelling in AF patients.

1437 Atrial fibrillation: a more potent risk factor for stroke and cardiovascular death in women than in men. The Copenhagen city heart study

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Purpose: Atrial fibrillation (AF) is a risk factor for stroke and death. We studied whether the impact of AF on the risk of first-ever stroke and cardiovascular death was of equal size in men and women.
Methods: The Copenhagen City Heart Study is a population-based cohort study. We used baseline data, including 12-lead ECGs, from 3 cohort examinations (1976-78, 1981-83 and 1991-94) in order to determine the independent, sex-specific impact of AF on the risk of first-ever stroke and cardiovascular death during 5 years of follow-up from baseline examinations.
Results: A total of 29,310 baseline entries representing 15,206 individuals free from prior stroke were entered into Cox regression models. During 137,391 (mean: 4.7) person years of follow-up, 635 first-ever strokes were identified. AF was documented in 276 subjects (166 men and 110 women). In these, 35 strokes were encountered of which 22 occurred in women. After adjustment for age, arterial hypertension, diabetes, myocardial infarction, lung function, smoking and electrocardiographic left ventricular hypertrophy, the independent impact of AF on the risk of stroke was 4.6-fold (2.3 to 9.3-fold) greater in women (hazard ratio: 7.8; 95% CI: 4.9-12.5) than in men (hazard ratio: 1.7; 95% CI: 1.0-2.9). Cardiovascular death occurred in 1122 subjects, 63 of which occurred in subjects with AF (28 in women and 35 in men). The independent impact of AF on the risk of cardiovascular death was 2.5-fold (1.5 to 4.2-fold) greater in women (hazard ratio: 4.4; 95% CI: 2.9-6.6) than in men (hazard ratio: 2.2; 95% CI: 1.6-3.1).
Conclusion: AF is a much more powerful risk factor for stroke and cardiovascular death in women than in men. This finding may have important implications in the selection of patients for anticoagulation therapy.

1438 Hypercoagulable state detected in atrial fibrillation patients is unrelated to clinical predictors to embolism

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Thromboembolic risk in atrial fibrillation (AF) has been established by recognised embolic risk factors. Several studies have demonstrated a prothrombotic state in selected AF patients, which may be additive to increase this risk for embolism. However there are no studies about its significance in the dairy clinical practice. Whether this hypercoagulable state is associated with thromboembolic risk factors or is caused by the arrhythmia itself remains unclear. The aim of this study was to evaluate the relationship between hypercoagulable state, AF and thromboembolic risk factors in a wide consecutive non-selected cohort of AF patients.
Methods: We studied 200 consecutive patients (101 male; 72.1±9.1 years) with non-rheumatic AF lasting more than four weeks, referred to our anticoagulation outpatient clinic. None of them had received any anticoagulant agents. All of them showed no haemodinamic impairment in the 4 weeks before. Embolic risk factors (age, sex, hypertension, diabetes, heart failure or systolic dysfunction and previous embolism) were recorded. AF was classified in paroxysmal, persistent and permanent by ESC-Guidelines. Prothrombotic state was assessed by prothrombin fragment F1+2 (F1+2), measured in citrated plasma by ELISA. Additionally we studied 74 subjects in stable sinus rhythm without history of AF, with similar clinical risk factors.
Results: Patients with AF showed higher levels of F1+2 than controls (1.33 [1.02-1.87] vs 1.07 [0.88-1.28] nmol/L; median [IQR]; $p<0.001$). We did not find any significant association between F1+2 levels and recognised embolic risk factors. Moreover, in multivariate analysis, only the presence of AF was independently associated with F1+2 plasmatic concentration (linear regression; $p< 0.001$). We found no statistical differences in F1+2 levels between clinical subgroups of AF.
Conclusions: We detect an independent hypercoagulable state in AF patients, unrelated to clinical predictors to embolism. Interestingly there were no statistical differences in F1+2 values between paroxysmal, persistent and permanent AF patients.

1439 Incidence of cerebral embolism in high-risk patients with atrial fibrillation: a prospective and serial study using cerebral magnetic resonance imaging

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Background: Patients (pts) with atrial fibrillation (AF) and spontaneous echo contrast (SEC) have an increased stroke risk. The aims of this prospective study were (1) to evaluate the prognosis of pts with dense SEC and (2) to assess the incidence of cerebral embolism with MR-imaging (MRI) under continued oral anticoagulation therapy.
Methods: The study group consisted of 64 pts with SEC and AF. 28 pts with sinus rhythm served as controls. All pts received oral anticoagulation therapy during the follow-up period (an INR > 2 was defined as effectively anticoagulated). To document the incidence of cerebral embolism all pts underwent the following examinations at admission and at 1, 3 and 12 months: transthoracic and transesophageal echocardiography, cranial MRI including diffusion- weighted MRI, assessment of the anticoagulation level and neurological assessment.
Results: 2 pts had clinically silent cerebral embolism at the index examination. Two patients (3%) had cerebral embolism with a neurological deficit during the follow-up period. Four (6%) pts died during the observation period due to stroke. 11 (17%) pts had focal diffusion abnormalities in the MRI during the follow-up. 45 (70%) pts were effectively anticoagulated, 19 (30%) pts were anticoagulated inadequately during the 12 months. One patient with inadequate anticoagulation had an embolic lesion during the follow-up, 12 pts who received effective anticoagulation had cerebral embolism or died during the follow-up ($p=0.22$). Controls did not display cerebral lesions during the study period. Pts with cerebral embolism had lower left atrial appendage peak empty velocities (0.22 ± 0.14 vs. 0.38 ± 0.21; $p<0.01$) and denser SEC (2.8 ± 1.1 vs. 1.6 ± 1.4; $p<0.01$) than pts without cerebral events.
Conclusions: Pts with AF and SEC have an increased risk of cerebral embolism despite oral anticoagulation therapy. Low peak empty velocities of the left atrial appendage and dense SEC are echocardiographic predictors for a cerebral event. The findings of this study have important implications for the clinical management of high risk pts with AF.

1440 Echocardiographic follow-up after percutaneous left atrial appendage occlusion in patients with increased thromboembolic risk

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Background: A new interventional occlusion system of the left atrial appendage (PLAATOtm) has been introduced as an alternative treatment in patients with an increased thromboembolic risk due to atrial fibrillation (AF) and contraindications for oral anticoagulation (OAC). The aim of this prospective study was to evaluate the immediate success of the occlusion procedure as well as the long-term follow up by means of serial echocardiographic assessment.
Methods: 9 patients with persistent AF and dense spontaneous echo contrast were included in the study. Transthoracic (TTE) and transesophageal echocardiographic (TEE) examinations were performed 24 hours prior to the procedure and during the occlusion procedure. The follow-up examinations were accomplished after 1 week, 1 month, 6 month and after one year. The following parameters were assessed: size of the left atrial appendage (LAA), peak emptying velocities of the LAA, peak systolic left upper pulmonary vein flow, presence of thrombi on the surface of the device as well as existence of atrial septal defects resulting from the transseptal approach.
Results: The occlusion of the LAA was successfully performed in all patients. The maximal area of the LAA was significantly reduced from 6.29 ± 1.55 cm^2 to 0.95 ± 0.55 cm^2 after the implantation procedure ($P=0.001$). Peak flow velocities of the LAA prior to the procedure were 0.23 ± 0.08 m/s. Follow-up examinations revealed persistent LAA flow activity in 3 out of the 9 patients. Atrial thrombi or thrombi on the surface of the device were found neither perinterventionally nor during the follow-up. Systolic peak flow velocities of the pulmonary veins were not significantly higher after the positioning of the device (0.55 ± 0.11 prior versus 0.63 ± 0.03 m/s after the occlusion, $P<0.05$). 2 out of 9 patients had persistent atrial septal defects 6 months after the procedure.
Conclusions: The implantation of a new percutaneous left atrial appendage occlusion system (PLAATO) reduces the size of the LAA significantly and usually results in complete elimination of LAA function. De novo thrombotic appositions on the device were not found during the follow-up period. The function of the left pulmonary vein is not affected by the PLAATO-device.

1441 Long-term significance of severe left atrial spontaneous echo contrast at the time of electrical cardioversion of atrial fibrillation: an acute trial substudy with 6-month follow-up

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Background: The significance of severe left atrial spontaneous echocardiographic contrast (LA-SEC) at the time of cardioversion of atrial fibrillation (AF) is poorly understood. The purpose of this study was to determine the 6 month prognostic significance of severe LA-SEC immediately prior to successful electrical cardioversion of AF.
Methods: The ACUTE Trial, randomized 619 patients with AF to TEE-guided cardioversion. Successful cardioversion was performed in 327 (53%) of these patients. LA-SEC was graded as severe, mild or absent. At 6 months follow-up, patents were evaluated for AF recurrence, repeat cardioversion, embolic events, bleed and death. Baseline characteristics and 6 month adverse events (available for 325 patients) were compared between patients with severe LA-SEC and those with mild or absent LA-SEC using univariate analysis and multivariate adjustment for possible confounders.
Results: At the time of cardioversion, 40 (12%) patients (32 male, mean age 66 $\pm$ 12 yrs) had severe LA-SEC and 285 (88%) patients (189 male, mean age 65 $\pm$ 13 yrs) had mild or no LA-SEC. There were no significant differences in clinical characteristics between these two groups. However patients with severe LA-SEC had a significantly larger LA diameter (5.2 $\pm$ 0.8 vs. 4.9 $\pm$ 1.0 cm, p=0.036). The presence of severe LA-SEC was associated with adverse clinical outcomes at 6 months (Table 1). After adjusting for possible confounders, the association of severe LA-SEC with adverse outcomes remained.

Table 1. Adverse Events at Six Months

	Mild or No LA-SEC (n=285)	Severe LA-SEC (n=40)	Relative Risk (95% CI)	p value
Embolic Event	1%	5%	6.30 (0.90 - 43.6)	0.033
Bleed (major and minor)	3%	8%	2.70 (0.70 - 10.1)	0.126
Death	4%	3%	0.70 (0.09 - 5.40)	0.733
AF Recurrence	36%	53%	1.46 (1.03 - 2.08)	0.055
Repeat Cardioversion	12%	24%	2.03 (1.03 - 3.98)	0.044

Conclusions: At the time of cardioversion for AF, the presence of severe LA-SEC by TEE is associated with increased embolic events, repeat cardioversion and a trend for increased bleeding and AF recurrence at 6 months. Severe LA-SEC identifies a subgroup of AF patients who are at increased risk of long-term complications following successful electrical cardioversion.

ATRIAL ARRHYTHMIAS AND DEVICE INTERACTION

1442 Prevalence of asymptomatic atrial tachyarrhythmias in pacemaker patients: results of the BEATS study

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Objective: The prevalence of asymptomatic atrial tachyarrhythmias (ATs) in patients (pts) with or without documented ATs is not clear since many paroxysmal asymptomatic AT episodes may remain undetected. Pacemakers with dedicated memory functions allow continuous monitoring of the atrial rhythm and automatic AT detection for a long-term period thus increasing our knowledge of the true prevalence of asymptomatic ATs.
Methods: Pts with a conventional indication for permanent pacing were enrolled into the BEATS (Balanced Evaluation of Atrial Tachyarrhythmias during Stimulation) study. Devices with special memory functions including atrial electrograms (EGMs) were implanted (Pulsar and Discovery, Guidant Co.) and followed for up to 12 months. During control visits (1, 6, and 12 months after implantation), pts were interviewed for AT related symptoms, a resting ECG was recorded (additional 24h Holter recording at the 1 month control), pacemaker counters were interrogated and stored EGMs were printed out and subsequently analyzed.
Results: A total of 253 pts (70$\pm$11 years, 157 male) were enrolled and followed for a mean of 8$\pm$4 months, 212 pts without and 41 pts with ATs documented before device implantation. The prevalence of AT related symptoms (25%) and ECG documentation of ATs (7%) were significantly lower than the prevalence of pacemaker counters positive for AT (77%) and AT documentation by stored EGMs (45%; p<0.01, cf. table). EGM documented AT prevalence was higher in pts with vs without ATs known before pacemaker implantation (66 vs 42%, p<0.01). In 23/62 pts (37%) with symptoms typical for ATs, no arrhythmia was documented by EGM while 76/115 pts (66%) with ATs documented by EGM had not perceived any AT related symptoms.

Prevalence of AT

	no. of pts	%
AT related symptoms	62	25
ECG documentation of AT	18	7
counter positive for AT	194	77
EGM documentation of AT	115	45

Conclusions: This prospective study with continuous atrial rhythm monitoring for 8 months documents a high prevalence of clinically asymptomatic ATs. This finding has important therapeutic implications with regard to the need of permanent anticoagulation.

1443 Validation of atrial tachycardia detection in dual-chamber pacing with the use of stored electrograms

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Inappropriate detections due to sensing or timing problems may compromise pacemaker diagnostic data counters. Especially in atrial tachycardias diagnostic and/or therapeutic decisions may be based upon such data.
Aim of the study was to validate pacemaker based atrial tachycardia (AT) detection using dual chamber pacemaker stored electrograms (EGMs).
Methods: The study includes 351 pts, mean age 71 $\pm$ 10 y, 191 male, with a standard indication for a primary DDDR pacemaker implantation. All devices (PulsarMax II 1280 and Discovery II 1284, Guidant Inc.) were implanted with bipolar atrial leads. At pre-discharge a maximum storage of 5 dual chamber EGMs with a duration of 8 s, including 4 s of onset-recording was programmed. The atrial tachycardia trigger was set to 4 atrial cycles at 170 bpm. The EGMs were interrogated and analysed after a 3 month follow-up period.
Results: 640 AT-EGMs were stored in 172/351 patients (49%). The mean number of AT EGMs per patient was 3.7. EGM analysis confirmed atrial tachycardia in 399/640 episodes (62%). In the remaining 241 AT episodes (38%) other events than atrial tachycardias were stored, thus being false-positive.
In 85/172 patients (50%) all AT episodes were confirmed by EGMs. In 52/172 patients (30%) all AT episodes were false-positive. In 35/172 patients (20%) both confirmed and false-positive episodes were shown in parallel.
False-positive AT episodes were due to: Atrial sensing of ventricular far-field signals in 62% (149/241), atrial noise and myopotential sensing in 34% (82/241) and double counting in 4% (10/241).
Conclusion: In this study 62% of pacemaker detected atrial tachycardia episodes were confirmed by stored electrograms. 38% of the atrial tachycardia episodes have been incorrectly classified by the diagnostic counters. Although bipolar atrial leads have been used, atrial sensing of ventricular far-field signals was the major cause. Stored electrograms provide a verification of counter data. Diagnostic or even therapeutic decisions should not be based on unvalidated counters alone.

1444 Is anti-tachycardia pacing efficacy impacted by the regularity of atrial tachyarrhythmias before delivery? Does regularity impact the early recurrence rate of atrial fibrillation?

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Anti Tachycardia Pacing (ATP) is used to reduce atrial flutter in clinical practice. Based on the unique atrial electrogram recorded in Pacemaker memories, Atrial Tachyarrhythmias (AT) are generally classified according to the frequency and the regularity of the AA cycle intervals. Classified as irregular AT (IrrAT) are Atrial Fibrillation (AF), salvos of atrial ectopies, and atrial tachycardia with unstable reentry circuits. Such IrrAT are believed to have a low ATP success rate but there is no accurate data comparing ATP efficacy on regular AT (RegAT) vs. IrrAT.

Methods: In the LEAF trial, AT500 (Medtronic) was implanted in 200 pts (50.6% male, 71 $\pm$ 9 years) with documented AT (86% paroxysmal AF) six months prior to implant. ATP was automatically delivered upon AT with AA cycle-length between 160 and 400 ms. Success was declared when sinus rhythm was restored within 20 seconds after delivery. We analyzed the last 10 seconds before ATP delivery. AT was classified as regular when AA variation was below 10% of the 10-cycle-average. IrrAT was defined when variation was higher than 10%. Early Recurrence of AF (ERAF) was defined as AT occurring within 60 seconds after an initial ATP success. Absolute termination was declared when a successful ATP was not followed by an ERAF.

Results: At a mean 8 month follow-up, 56 pts experienced 854 AT treated by ATP. Results are summarized in the table.

854 treated episods	Mean AA cycle length (ms)	Initial ATP success	ERAF	Absolute termination
RegAT: 551	257 $\pm$ 53	375 (68%)	82 (22%) *	293 (53%) *
IrrAT: 303	269 $\pm$ 24	203 (67%)	17 (8.4%) *	186 (61%) *

* $p < 0.0001$

Conclusion: AT regularity just before ATP delivery does not influence primary ATP efficacy. But when considering ERAF, termination rate is higher on irregular AT. This finding implies irregularity as the expression of unstable reentry circuits accessible to ATP therapy.

1445 Comparison of triggered and triggered plus continuous pacing on the prevention of paroxysmal atrial fibrillation

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Purpose: Two different approaches have been developed for the prevention of paroxysmal atrial fibrillation (AF): Continuous atrial overdrive pacing of the sinus rhythm and pacing after the detection of specific triggers like premature atrial contractions (PACs) for a limited time. The actual most often used approach is to activate all available pacing functions. The aim of the study was to compare the effects of triggered pacing alone with triggered and continuous overdrive pacing.

Methods: The study included 77 patients (pts) with sick sinus syndrome and paroxysmal AF who had received the DDDR pacemakers (PM) Selection 9000 or Prevent AF (Vitatron BV, Netherlands). The pts were randomised either to be paced with 3 triggered pacing functions (PAC Suppression, Post PAC Response, Post Exercise Response) or with the triggered pacing functions and continuous pacing (PACE-Conditioning) for 3 months. Each patient was crossed to the opposite arm for additional 3 months. Antiarrhythmic medication remained unchanged during the study period. After each period the PMs were interrogated and the AF-burden (AF-time/follow-up time), the number of AF episodes and the mean time in sinus rhythm were assessed. Since atrial pacing can only be established in AF free intervals, it was defined as atrial pacing (%) in relation to the AF free time.

Results: There were 40 pts (67 $\pm$ 17 years) in the group with triggered pacing (TRI) and 37 pts (71 $\pm$ 15 years) in the group with triggered and continuous pacing (CON). The percentage of atrial pacing was in TRI group with 76.5 $\pm$ 23.6% (median: 84%) significantly lower than in group CON with 96.7 $\pm$ 35.6% (median: 98%) ($p < 0.01$). AF-burden was significantly lower in the TRI group (3 $\pm$ 7%; median 0.1%) than in the CON group (13 $\pm$ 12%; median: 1.9%; $p < 0.05$). There were less frequent AF episodes in the TRI group (490 $\pm$ 1735; median: 9,5) than in the CON group (628 $\pm$ 1420; median 50; $p < 0.05$). The average time in sinus rhythm was significantly longer in the TRI group with 1084 $\pm$ 1200 h (median: 240 h) than in the CON group with 610 $\pm$ 893 h (median: 50 h; $p < 0.05$). There were no significant differences between the two groups in the programmed pacing parameters.

Conclusions: The additional activation of continuous pacing significantly increased the frequency of atrial pacing, which was associated with an increase of AF-burden, the number of AF episodes and a shorter time in sinus rhythm. The continuous pacing function in addition to the 3 triggered pacing functions had no beneficial effects for the prevention of paroxysmal AF.

1446 Pacing for the prevention of recurrent atrial fibrillation: results from the VIP registry

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Purpose: Pacemaker (PM) therapy is one of the interventional techniques to prevent recurrent atrial fibrillation (AF). So far, preventive pacing did demonstrate only a moderate and clinically not convincing effect in non-selected patients with recurrent AF. Therefore, the VIP registry was initiated to identify subgroups of patients being more likely responders to preventive pacing algorithms.

Methods: The registry included 496 patients with recurrent AF and a conventional indication for PM therapy. Patients received a dual chamber device with detailed AF diagnostics and 4 different preventive algorithms (Selection series, Vitatron). Following implantation a 3 month diagnostic phase with conventional pacing identified pts. with "substrate-AF" (>70% of AF episodes with less than 2 premature atrial contractions (PACs) before AF onset) from "trigger-AF" (<70% of AF episodes with less than 2 PACs before AF onset). For a consecutive follow-up of 3 month pts. with trigger-AF were programmed to PAC-initiated preventive pacing algorithms whereas pts. with substrate-AF underwent continuous overdrive pacing.

Results: 82 patients (68.4$\pm$10.5 yrs., 34 male) completed so far diagnostic and preventive pacing phases: AF-burden during conventional pacing of 14.7$\pm$20.7% (median 7.5) was significantly reduced to 10.9$\pm$16.1% in the entire study group (median 16.1; p=0.05). Comparing the AF subgroups, pts. with trigger-AF exhibited an AF burden reduction of 41.8% correlated to a significant reduction in PACs/h with preventive pacing (AF burden: 14.2$\pm$22.2% vs 8.2$\pm$15.1%; PACs: 111.7$\pm$180.9/h vs 68.0$\pm$163.7/h) whereas pts. with substrate-AF demonstrated only a slight burden reduction of 11% and a minor increase in PACs/h (AF burden: 15.3$\pm$19.3% vs 13.6$\pm$16.9%; PACs: 19.4$\pm$44.0/h vs 22.2$\pm$72.4/h).

Conclusions: Patients with trigger-AF did demonstrate a relevant reduction of 41.8% in AF burden with preventive pacing as compared to patients with substrate-AF who exhibited only slight reduction of 11%. Interestingly, PAC activity before AF onset was significantly reduced in patients with trigger-AF in parallel to the reduction in AF burden, whereas substrate-AF patients with a minor burden reduction did not demonstrat reduced PACs. Our results indicate that patients with trigger-AF are more likely responders to preventive pacing presumably as an effect of PAC-suppression.

1447 A benefit on recurrence of episodes and burden of atrial fibrillation using pacemaker diagnostics

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Background: The efficacy of prevention pacing therapies of atrial fibrillation (AF) is being evaluated in several studies but the programming of the device is usually predefined, without considering the individual onset triggers for AF. A strategy of management of paroxysmal AF with diagnostic tools has still not demonstrate its benefit. This study assessed the clinical benefits of the diagnostic functions (AF1.0) of the Selection® pacemaker in the management of AF in terms of recurrence of AF after the therapeutic adjustments performed using AF 1.0.
Methods: In a multicenter prospective study, 48 patients, 72 ± 9 y, with documented AF and conventional pacing indications, received a Selection® DDDR (Vitatron, NL). Antiarrhythmic agents were prescribed in 90% of the patients. AF1.0 was programmed to document AT burden, onset daily distribution, duration, premature atrial beats before onset and the onset of the last 12 AT episodes exceeding 180/min. After follow-up (FU) at 3 months using AF 1.0, therapeutic adjustments were performed in 53% of the patients (pacing parameters 38%, preventive pacing algorithm 38%, medication 19%, others 5%). The evaluation of the efficacy of management using AF 1.0 was evaluated at the 6-month FU, each patient being its own control.
Results: AF recurrences were documented in 69% of the FU. At 6-month FU, median value of AF burden was reduced (0.85% vs 1.35%, -37%) as was median values of AF duration (12.9 hours vs 24.8 hours, -48%) and of number of AF episodes (5 vs 8, -38%). The median of the sinus rhythm duration between 2 AF episodes increased (88 hours vs 80 hours, +10%). At last, the percentage of patients with no AF recurrence increased from 25% at the 3-month FU to 33% at the 6-month FU (p=0.008).
Conclusion: A strategy of therapy of AF guided by AF 1.0 diagnostic functions using specific types of therapeutic adjustments (pacing parameters, preventive pacing algorithms and/or medication) is associated with a decrease in the percentage of patients with recurrence of AF and with an overall decrease in AF burden and number of AF episodes. A controlled study with a longer FU is needed to confirm these results.

CLINICAL APPLICATIONS OF CORONARY FLOW RESERVE

1453 In majority of patients with intermediate coronary lesions increased doses of intracoronary adenosine are required for the reliable assessment of fractional flow reserve

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Background: An assessment of fractional flow reserve (FFR) is one of the functional methods used for the identification of hemodynamically significant coronary lesions. For the reliable FFR measurements it is obligatory to obtain maximal hyperaemia within evaluated coronary artery. In this purpose, in most cases different doses of adenosine are administered intracoronary. Albeit too small doses of adenosine can cause only partial hypereamia with the subsequent overestimation of FFR value.
The aim of this study was to establish the effect of different doses of adenosine administered intracoronary on FFR values and evaluate the patients' tolerance of applied doses.
Methods: Between October 2000 and December 2002 we assessed FFR in 53 intermediate lesions revealed by quantitative coronary angiography in 36 patients with stable angina (23 men, age: 59 ± 10 years, left ventricular ejection fraction ≥ 50%). In all lesions FFR was assessed during the intracoronary administration of 30 μg adenosine (FFR30), and afterwards during the administration of 60 μg adenosine (FFR60). In 29 lesions localized in left coronary artery, FFR was additionally measured during the administration of 90 μg adenosine (FFR90).
Results: There were no serious side effects or complications observed during FFR measurement with the application of 3 various doses of adenosine. In one patient after the administration of 60 μg adenosine to the right coronary artery, the episode of asymptomatic intermittent second-degree atrio-ventricular block was observed. Mean value of FFR30 was higher than FFR60 (respectively, 0.854 ± 0.152 vs. 0.836 ± 0.162, p<0.001); mean difference between these measurements was 0.018 ± 0.036. In 29 evaluated lesions (55%) FFR30 was greater than FFR60 (in 12 measurements [23%] the difference was greater than 0.02 and in 8 cases [15%] – greater than 0.05). There were no differences between FFR90 and FFR60 (respectively, 0.900 ± 0.092 vs. 0.896 ± 0.092, p=0.2) and an increase of adenosine dose from 60 to 90 μg did not result in the subsequent reduction of FFR values.
Conclusions: FFR assessment with intracoronary administration of all applied doses of adenosine (i.e. 30, 60 and 90 μg) is safe and well tolerated. An increased adenosine dose (60 μg) resulted in the reduction of FFR values in more than 50% patients when compared with the dose of 30 μg adenosine. This observation can be potentially significant when selecting patients to invasive or conservative treatment. In contrast, an application of 90 μg adenosine was not followed by the subsequent decrease of FFR values.

1454 Coronary flow reserve immediately after primary coronary stenting predicts wall motion recovery in patients with first anterior acute myocardial infarction

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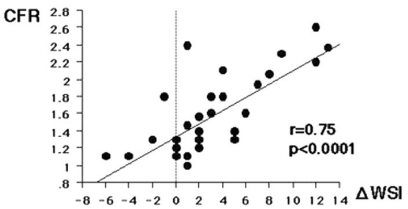
Background: The clinical value of coronary flow reserve (CFR) measured immediately after primary coronary angioplasty has not been discussed fully. We examined whether CFR immediately after primary coronary stenting could predict the recovery of left ventricular wall motion in patients with acute myocardial infarction (AMI).
Methods: By using a Doppler guidewire, we measured CFR immediately after primary coronary stenting in 40 patients with a first anterior AMI. A two-dimensional echocardiography was performed at admission and at 3 weeks to assess the change of wall motion score (WMS; normal=0 to dyskinesia=4). For each patient, wall motion recovery was defined as an improvement of wall thickening in two or more contiguous segments at 3 weeks.
Results: The CFR threshold that maximized the sensitivity and specificity to predict wall motion recovery was 1.3 (sensitivity=85%, specificity=82%). By regression analysis, CFR significantly correlated to the change of WMS (r=0.75, p<0.0001).



CFR and WMS.

Conclusion: CFR measured immediately after primary coronary stenting can predict wall motion recovery in patients with a first anterior AMI.

1455 Prognostic value of fractional flow reserve after coronary stenting: a multivariate analysis

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Background: Retrospective data from a large multicenter registry have shown that fractional flow reserve (FFR) predicts outcome after coronary stenting. However, not all parameters known to be associated with adverse events after stenting were included in this registry. We sought to determine the predictive value of FFR measurements including additional angiographic and clinical risk factors collected from the data base of a single center of the FFR stent registry.
Methods: In 119 pts undergoing PTCA, a final FFR was determined after successful stent implantation. Additional potential predictors analyzed were multiple patient and lesion characteristics. Endpoints were cardiac death, myocardial infarction or any coronary revascularization procedure. Odd ratios (OR) and 95% confidence intervals (95% CI) were calculated using multivariate logistic regression analysis.
Results: During follow-up, 18 cardiac events occurred including 14 clinically driven TVR. Bivariate variable screening on a p<0.20 level revealed post interventional FFR>0.95, LV-function, length, diameter of stents and the presence of diabetes as potential predictors for cardiac events. In the multivariate analysis, only the presence of diabetes (OR 3.73; 95% CI 2.11-6.81), LV-function (0R 0.96; 95% CI 0.85-0.97), stent length (0R 1.442; 95% CI 1.123-1.578), and FFR post PCI >0.95 (0R 0.314; 95% CI 0.213-0.646) were statistically significant (p<0.05) predictors of cardiac events.
Conclusion: In addition to morphologic and clinical risk factors for adverse outcome after stent implantation, post-interventional FFR as a functional parameter was independently associated with adverse events at 6 months. Further studies are needed to test whether guiding a PCI procedure with by FFR might improve outcome.

1456 Coronary pressure-based fractional flow reserve in patients with coronary stenosis. A decision analysis

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Background: Although many patients with coronary stenosis undergo percutaneous transluminal coronary angioplasty (PTCA) in the absence of prior documented ischemia, the effectiveness of this strategy is unknown. Coronary pressure-based fractional flow reserve (FFR) is an accurate invasive test for myocardial ischemia. Coronary pressure wires have evolved from investigational devices to simple and often indispensable diagnostic tools. The objective of this study was to assess the clinical effectiveness and the cost-effectiveness of deferral vs. performance of PTCA in patients with chest pain.
Methods: Outcomes for patients with one-vessel coronary stenosis and mild angina but without documented ischemia were simulated in a decision-analytic Markov model. The compared strategies were (1) deferral of PTCA in patients with no inducible ischemia based on FFR (DEFER) and (2) performance of PTCA without FFR testing (PERFORM). Clinical predictions and a cost-effectiveness analysis were performed in age (30-70 years) and gender subgroups. One-way and multi-way sensitivity analyses were conducted on uncertain model parameters.
Results: Overall, men and women had similar patterns, showing DEFER as the less costly but slightly less effective strategy. For the base case (60 year old man, 3% discount rate) we calculated the following results (PERFORM vs. DEFER): incremental costs $4,400; incremental life expectancy 10.9 days; 17.5 incremental QALDs. Costs were $145,000 per life year gained and $90,000 per QALY for PERFORM compared to DEFER. In sensitivity analyses we changed the mortality reduction associated with PTCA in patients with no ischemia from the base-case value of 8.2% to 0%. For a 60-year-old man, this reduced the incremental effectiveness to 4.5 quality-adjusted life days (QALDs), increased the cost-effectiveness ratio to $354,000/QALY and made DEFER the dominant strategy using survival as outcome (DEFER saved 4.8 life days and $4,300). Changing prior probability of ischemia from 56% to 92% decreased the cost-effectiveness ratio of PERFORM below the widely accepted threshold of $50,000/QALY.
Conclusions: Although pressure-based deferral of angioplasty is less costly in patients without documented ischemia, its long-term effectiveness remains unclear. However, as differences in effectiveness are likely to be small, deferral of PTCA may be considered in patients without functional stenosis assessed by coronary pressure measurement if health care resources are constrained.

1457 Measurement of coronary flow reserve with the intracoronary pressure wire

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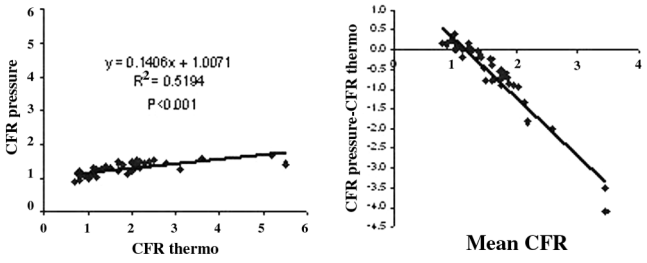
Purpose: A novel technique for measuring coronary flow reserve (CFR) with the intracoronary pressure wire has been developed. This thermodilution technique has been validated with corresponding velocity measurements from the Doppler flow wire. However, CFR can also be derived directly from pressure measurements. Flow (Q) is proportional to the square root of the pressure gradient, (root delta P), so theoretically CFR (Q at hyperaemia/Q at rest) is calculated from root delta P at hyperaemia/root delta P at rest. We sought to validate CFR calculated from delta P values obtained from the coronary pressure wire against the thermodilution method of CFR measurement.
Methods: We instrumented 40 vessels (36 patients) undergoing percutaneous coronary intervention with an intracoronary pressure wire. Prior to dilatation of the target lesion, the pressure gradient (aorta-distal coronary artery) was measured, and thermodilution CFR was assessed with saline bolus injections. Maximal hyperaemia was induced and the pressure gradient and CFR were measured again in a similar way.
Results: Thermodilution CFR measurements were strongly correlated with CFR values mathematically derived from the pressure gradient (r=0.72; P<0.0001). This correlation is shown in the graph. However, the Bland-Altman plot on the right illustrates that CFR is under-estimated using root delta P values and this under-estimation is directly proportional to the CFR value.



Conclusions: CFR is underestimated when calculated from root delta P values. This may be because Q is only directly proportional to root delta P when energy loss due to friction is negligible. As Q (and thus CFR) increases, such energy loss becomes more important, thus leading to systematic underestimation of this parameter.

1458 Are high doses of intracoronary adenosine an alternative to standard intraveneous adenosine for the assessment of fractional flow reserve?

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Background: Fractional flow reserve (FFR) is a measure of coronary stenosis severity based on pressure measurements obtained at maximal hyperemia. Therefore, achieving maximal vasodilatation is a prerequisite for determining FFR. All validation studies were performed with intravenous adenosine (Ado-iv). However, compared to intracoronary adenosine (Ado-ic), Ado-iv is more expensive, more time consuming and possibly associated with more side effects. The present study was designed to compare high doses of Ado-ic with Ado-iv.
Methods: 57 lesions (LAD,n=27; LCx, n=15; RCA, n=15) were studied in 54 pts. FFR was assessed five times in every pt, with 4 bolus injections of Ado-ic (60, 90, 120 and 150 μg) and standard Ado-iv (140μg/kg/min) in a randomized changing sequence.
Results: No adverse events occurred with Ado-ic injections into the LCA. Transient AV-blocks were observed with Ado-ic into the RCA (4/15). With Ado-iv, minor side effects (angina, dyspnoe) were noted in 21/54 pts (39%). At rest hemodynamics were not different. Mean FFR was 0.79, 0.80, 0,78 and 0,77 with 60 μg, 90 μg, 120 μg and 150 μg Ado-ic. The lowest FFR of 0.76 was achieved with Ado-iv.
Conclusions: High doses of intracoronary adenosine (150 μg) are safe, but compared to Ado-iv, the effect on coronary resistance vessels is less pronounced. Minor side effects were common with Ado-iv, but were tolerated by all pts. Thus, Ado-iv should be the preferred mode of administration not only in pts with diffuse disease, but also for the assessment of circumscript coronary lesions.

SYNCOPE: THE CONTINUING CLINICAL CHALLENGE

1459 Natural history of 312 consecutive patients with syncope and abnormal head-up tilt test

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Objectives: After abnormal head-up tilt test (HUT), several trials have evaluated treatment strategies. However, few unequivocal results have been obtained. Aim of the study was to prospectively analyze the natural history of patients with vasovagal syncope (VVS) who did not received specific treatment but education after an abnormal (HUT).
Methods and Results: From 1996, 312 consecutive patients with VVS and abnormal HUT result were followed. All received education for avoiding syncope as single therapy. During 37.9±21.9 months, there were no cardiac deaths. However, 89 patients (28.5%) had recurrences (one n=52; >1 n=37), which were not influenced by the type of response during HUT or by age. Mean recurrence-free time was of 49.08 months (95% CI: 45.3-52.8) and the cumulative probability of no recurrence of 71.5%. However, there were significant (p=.004) differences in the recurrence rate between patients with <5 or > 5 previous syncopes (23.4% vs. 39.2%, respectively). In addition, the mean recurrence-free time of patients with <5 syncopes was significantly (Log rank 7.94; p=.004) longer (51.7 months; 95% CI: 47.3-56) than in patients with >5 syncopes (41.9 months; 95% CI: 31.1-58.4). Multivariate logistic regression identified the previous number of syncopes as an independent risk marker of recurrences (RR: 3.06; p=0.0001; 95% CI: 1.7-5.5).
Conclusions: Survival of patients with VVS presenting an abnormal HUT is excellent. Although the broad majority of those patients do not suffer recurrences after education, the number of previous syncopal spells critically influences the recurrence rate.

1460 Clinical characteristics of patients with diagnosis of syncope: results from the GIFA study

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Background and Aims: Syncope (S) is a serious event in older people, because it is directly related to a great risk of falling and fractures. Physicians often suspect a iatrogenic cause of S, but few studies exist about this topic, in particular in the older patient. The aim of the study is to evaluate the prevalence of S in the population of the GIFA study (Gruppo Italiano di Farmacovigilanza nell'Anziano) and to analyse the clinical characteristics of patients with diagnosis of S at discharge.
Methods: From the GIFA database (a multicentric epidemiologic study conducted in Italian departments of geriatrics and internal medicine), 28896 patients enrolled in 1988, 1993, 1995, 1997 and 1998 (mean age 70,4±15,5 years, 50,2% males) were studied. Patients were divided in two groups, according to the diagnosis of S (ICD9 code: 780.2): no-S (N=28339), and S (N=557). The drugs were coded according to ATC codes. Continuous variables were transformed in dichotomic or ordinal variables, and we used McNemar and chi-squared tests to study the differences between groups.
Results: The prevalence of S was 1.9% (557 patients); in this group the number of subjects with more than 85 years was higher (18.7% vs. 12.5% in no-S group, $p<0.001$). After correcting by age, there were no differences between the two groups in terms of hypertension, myocardial infarction, ischemic heart diseases, congestive heart failure, peripheral arteriopathy, cerebro-vascular diseases, and total comorbidity. Nevertheless, the subjects with S took a greater number of calcium-channel blockers (15.8% vs. 10.8% in no-S group, $p>0,001$) and ace-inhibitors (12.2% vs. 8.5% in no-S group, $p>0.001$); in patients with more than 85 years the prescription of nitrates (32.0% vs 27.7%, $p>0.001$) and beta-blockers (1.9% vs. 0.6%, $p<0.001$) was higher with respect to patients without S.
Conclusions: Despite the lack of differences in cardiovascular diseases and comorbidity, patients with S took a greater number of antihypertensive and vasodilator drugs, most of all if they were very old.
These results suggest a more frequent iatrogenic etiology of S in elderly patients. To demonstrate this finding, prospective studies are needed with the specific aim to identify modifiable causes of loss of consciousness in older patients.

1461 Response to repeated tilt testing in different haemodynamic types of neurally mediated syncope

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Medical treatment of syncope (pharmacological and pacemaker therapy) is insufficient in many cases with a high recurrence rate of syncope. In our department we use tilt training as a standard therapy for neurally mediated syncope. The aim of the present study was to analyse whether the number of tilt training sessions required to obtain negativation differs between different types of syncope. Patients start the tilt training program in the hospital and are instructed to continue this therapy at home: per day 1 or 2 sessions of 30 min upright standing against a wall.
In this study we have included 179 patients (92 males and 87 females) with recurrent syncope and with a positive tilt test. 1163 tilt training sessions were performed. Mean age was 33.4 ± 21.3 (SD) years. They were tilted daily (60° inclination) until syncope or until a maximum of 45 min. For classification of positive responses to tilt training we have adopted the new classification of the ESC Task Force on Syncope: Type 1: mixed type (MX) with a decrease of blood pressure and heart rate (HR) to > = 40 bpm; Type 2A CI: cardioinhibitory with a decrease of HR to < 40 bpm; Type 2B CI: cardioinhibitory with asystole > 3 sec; Type 3: vasodepressor (VD) with a decrease of blood pressure without a decrease of HR of more than 10%.
The first negative tilt test was obtained at session 2 in 98 patients (55%), at session 3 in 35 (20%), at session 4 in 24 (13%), at session 5 in 12 (7%), at session 6 in 6 (3%), at session 7 in 2 patients and at session 8 in another 2.

Response to repeated tilt testing

Type of syncope	Number of pts	Diagnostic tilt (min°)	First negative tilt
1 MX	59	20.2 ± 11.6	2.8 ± 1.2
2A CI	5	26.4 ± 14.6	2.8 ± 1.3
2B CI	54	15.7 ± 11.8*	2.8 ± 1.2
3 VD	61	22.8 ± 11.12	3.1 ± 1.5

Data are expressed as mean ± standard deviation of the mean; N = number; * P < 0.001 vs other types of syncope; ° time until syncope (mean ± SD)

Conclusion: In about half of the patients with neurally mediated syncope already the second consecutive tilt test became negative. Patients with a 2B CI (cardioinhibitory and asystole) response did not require more training sessions than patients with type 1, type 2A and type 3 of syncope.

1462 Tilt training program influences the renin-angiotensin-aldosterone system activity in patients with vasovagal syncope

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Orthostatic stress caused during head-up tilt test (HUTT) leads to the activation of sympathetic nervous system and secondary to RAAS activation lasting in patients with vasovagal syncope up to 10 minutes after the procedure. The tilt training program is one of the therapeutic approaches in patients with vasovagal syncope. It is unknown if the training influences the neurohumoral reactions involved in the mechanism of syncope. The aim of present study was to assess the influence of short- and long-lasting tilt training program on RAAS activity in patients with vasovagal syncope.
Material and Method: The study population consisted of 15 pts (11F, 4M, mean age 38,9 ± 17,2 years) with the history of syncope of unknown origin and vasovagal reaction during HUTT. The blood for determination of plasma renin activity and aldosterone concentration was drawn after 30 minutes supine rest, immediately before HUTT and 10 min after HUTT. The study was performed at three times: the first time during the diagnostic HUTT, the second one after achieving two negative HUTT and after tilt training program lasting 1 to 3 months. Plasma renin activity (PRA) was assessed using radioenzymatic assay and aldosterone was measured using radioimmunologic assay.
Results: 12 patients remained free from syncope during study period. In the diagnostic HUTT PRA increased significantly when syncope occurred and stayed elevated up to 10 minutes after the test. In short- and long-term control HUTT after the training PRA rose significantly immediately after test and then decreased. Aldosterone level rose significantly after the HUTT induced syncope and increased to the highest values 10 minutes after diagnostic test. After the both control tests the aldosterone level increased immediately after the procedure but there was no further increase 10 minutes later.
Conclusions: 1. The observed differences in PRA and aldosterone concentrations during tilt training program indicate on changing pattern of sympathetic nervous system activation. 2. The meaning of the neurohumoral reaction observed during tilt training program is not ascertained, in could be either the marker of improvement or mechanism preventing the syncope. 3. Not parallel changes in PRA and aldosterone concentration indicate on existing different control mechanisms of this two parts of RAAS.

1463 CLS pacing in vasovagal syncope: final outcomes of the INASY study

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Permanent cardiac pacing is an ACC/AHA/NASPE Class IIa indication to prevent recurrent and invalidant cardioinhibitory vasovagal syncope (VVS). Aim of the INVASY (INotropy controlled pacing in VAsovagal SYncope) multicenter, prospective study was to investigate whether DDD-Closed Loop Stimulation (CLS), which is sensitive to changes in myocardial contractility, may prevents recurrence of VVS.
Between 1997 and 2002, 80 pts (51 m, mean age 62±15 yrs, range 25 - 79) were enrolled and implanted with a pacemaker mod. INOS2 CLS (Biotronik, Germany). All complied the inclusion criteria: mean of 2.2±1.2 VVSs in the last 6 months before implantation, head up tilt test (HUTT) Type 2A or 2B induced syncope, cause of syncope not related to cardiac or neural pathologies. Primary end point was the recurrence of 2 spontaneous VVSs (confirmed by HUTT) during the 1st year FU. All 80 pts in the study completed the FU. No drug therapy was performed during the observation time. Randomization between DDD-CLS and DDI(back-up @ 40 bpm)pacing, to test the placebo effect of device implantation,was performed only during the first stage of the Study, then it was stopped by the steering committee. The reason was that of the 9 pts randomized in "back up" DDI mode: 4 (44%) had two VVS spells; 3 (33%) had one VVS spell; and only the remaining 2 (22%) had no spell during FU. At the end of the one year FU all these 9 pts were reprogrammed in DDD-CLS (no more spells after mode change).
The remaining 71 pts were all programmed in DDD-CLS mode and the mean FU time was: 27.3±15 months (total observation time 2,187 months). NONE of these pts (100%) reported recurrences of VVS during FU, and the 9 pts reprogrammed in this modality as well. Only 5 pts (6.2%) reported occasional pre-syncopal symptoms, not followed by lost of consciousness.
In conclusion, the results achieved in the INVASY study confirm the efficacy of DDD-CLS pacing in preventing malignant VVS. A positive placebo effect of pacemaker implantation can be expected in no more than 20% of implanted pts. Even in the INVASY Study, the HUTT performed during FU do not showed helpfulness in predicting spontaneous VVS spells.

1464 Are women more susceptible to nytroglicerin-induced syncope during head-up tilt testing?

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The gender does not appear to influence the results of drug-free or isoproterenol-tilt tests. However, the effect of sex on nitroglycerin (NTG)-potentiated HUT has not been thoroughly investigated. The objective of this study is to evaluate the influence of gender on the results of NTG-tilt test in patients with suspected neurally mediated syncope.
Methods: 696 consecutive patients referred for assessment of syncope or presyncope who underwent HUT in our cardiology department were included in the study. Demographic and clinical variables, as well as HUT results were prospectively introduced in a specifically designed database. Patients underwent tilt at a 60° angle for a 20 min drug-free phase followed by 25 min after the administration of 400 μg sublingual NTG spray. A positive response was defined as syncope or near-syncope associated to severe bradicardia, hypotension or both. Patients with a slowly progressive decrease in blood pressure (n=27) were considered to have non-specific responses.
Results: Men (n=412) and women (n=284) did not differ significantly in age (57.3 ± 19.1 vs 54.8 ± 20.6 y.), history of recurrent syncope (75.9% vs 78.9%), frequency of syncopal spells (median=3 for both groups), presyncope as index episode (5.6% for men vs 3.8% for women) or non-specific responses to HUT (4.1% vs. 3.5% respectively). Structural heart disease was more frequent in males (n=136, 33%) than in females (n=51, 18%, $p<0.001$). This variable did not have a significant influence on the results of the test. Positive responses to HUT were observed in 228 men (57.7%) and 204 women (74.5%, $p<0.001$). Sex did not influence the likelihood of a positive HUT during the drug-free phase of the test (33/412, 8.0% for males vs 16/284, 5.6% for females, n.s.). However, tilt-induced syncope was more common in females after the administration of NTG: 188/258 (72.9%) when compared with 195/362 (53.9%) in males ($p<0.001$). Moreover, the time from NTG administration to syncope was significantly shorter in females (4.6 ± 2.3 min) than in males (5.2 ± 2.6 min, $p<0.05$).
Conclusions: Women are more susceptible to the effects of nitroglycerin as a provocation agent in the head-up tilt table test.

DRUG-ELUTING STENTS: THE LATEST NEWS

1493 The European multicentre, randomized, double-blind study of the sirolimus-eluting stent in the treatment of patients with de novo coronary artery lesions (E-SIRIUS): 1-year clinical outcomes

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The E-SIRIUS study is a multicenter (35 investigational sites in Europe) randomized, double-blind trial examining the safety and efficacy of the sirolimus-eluting stent vs. a control (uncoated) stent in a projected 350 patients with de novo native coronary artery lesions between 15 and 32 mm in length and 2.50 mm to 3.00 mm in diameter (by visual estimate). The protocol called for a maximum of 2 stents to be implanted; direct stenting (DS) or predilation (P) was left to the investigator's discretion. The primary endpoint was in-stent minimum lumen diameter (MLD) at 8-month follow-up. Among the secondary endpoints were major adverse cardiac events (MACE) at 1, 6, 9 and 12 months - and annually up to 5 years thereafter -, as well as target lesion revascularization, target vessel revascularization and target vessel failure at 9 months. By February 15, 2002, 353 patients were enrolled, with 1 patient subsequently deregistered. Of the 352 patients, 177 were randomized to group A and 175 to group B. A total of 92 patients (26.1%) underwent direct stenting (47 in group A, 45 in group B). Clinical characteristics were not different between group A and B patients, nor between DS and P patients. Device success (< 50% residual stenosis with assigned stent and no in-hospital MACE) was achieved in 99.4% of group A patients and 100% of group B patients. At 30 days, MACE - predominantly non-Q-wave myocardial infarctions - were observed in 8 patients (2.3%). Nine-month and 1-year clinical follow-up was completed in December 2002 and March 2003, respectively. The unblinded 1-year clinical outcomes data will be available for presentation.

1494 Positive remodelling with reduced neointimal formation in response to paclitaxel-eluting stents: a serial intravascular ultrasound analysis

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Background: In the TAXUS II trial, polymer controlled paclitaxel-eluting stents have shown a remarkable reduction in restenosis rates compared to bare metal stents. The aim of this substudy was to characterize local arterial responses to paclitaxel using a serial quantitative intravascular ultrasound (IVUS) analysis.
Methods: The TAXUS II was a randomized, double-blind study with 536 patients in 2 consecutive cohorts comparing slow release (SR) and moderate release (MR) TAXUS NIRx™ paclitaxel-eluting stents to bare stents. There is an 8-fold higher release rate of paclitaxel in the first 48 hours in MR compared to SR. This IVUS substudy included all patients treated with one study stent who underwent serial IVUS examination post-procedure and at 6-month follow-up (control n=152, SR n=81, MR n=81). Quantitative analysis was performed by an independent core laboratory. The stented segment (15mm) was divided into 5 subsegments. In each subsegment mean vessel area (VA), neointimal hyperplasia area (NIHA), lumen area (LA), and plaque behind stent area (PBSA) were measured. Results are present as mean of all subsegments per group.
Results: A total of 1570 subsegments were analyzed post-procedure and at follow-up. At 6-month, the degree of in-stent restenosis was significantly reduced in SR (NIHA 0.7±1.1 mm^2, $p<0.0001$) and MR (0.6±0.9mm^2, $p<0.0001$) compared to control (1.9±1.7mm^2) with no dose-dependent differences between the two paclitaxel-eluting formulations. This reduction in in-stent restenosis coincided with an increase in plaque behind the stent in SR (1.0±1.8 mm^2, $p<0.0001$) and MR (1.4±2.0 mm^2, $p<0.0001$) when compared to control (0.5±1.7mm^2). This increase in plaque burden correlated with an increase in vessel area (SR 1.1±2.3mm^2, MR 1.5±2.5mm^2, control 0.6±1.9mm^2), indicative of positive remodeling in all groups. In contrast to the reduction in in-stent restenosis, this effect on vascular remodeling occurred in dose-dependent manner being more pronounced in MR than SR (PBSA p=0.0006, VA p=0.007).
Conclusions: Both slow and moderate release paclitaxel-eluting stents inhibit neointimal growth to the same degree when compared with bare stents. Positive remodeling occurs after stenting irrespective of paclitaxel elution, however the release profile affects the extent.

1495 Everolimus stent coating: promising procedural and 6-month angiographic and intravascular ultrasound follow-up results of the FUTURE I and II trial

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Background: The FUTURE I trial has been conducted to evaluate both safety and efficacy of the new Challenge-Stent, coated with a bio-erodable polymer carrying the agent Everolimus. Everolimus is a new anti-proliferative agent binding to cytosolic immunophyllin FKBP12 and inhibiting growth factor-driven cell proliferation with promising results in animal studies demonstrating a 50% reduction of neointimal proliferation compared with a bare metal stent.
Methods: FUTURE I was a prospective, single blinded, randomized trial including 24 and 12 patients with native de-novo coronary lesions allocated for drug and control groups respectively. Primary endpoint was 30-day MACE free survival. Angiographic and IVUS follow-up was scheduled 6 months after index procedure to evaluate acute gain and lumen late loss due to neointimal proliferation. The ongoing FUTURE II is the efficacy trial including 90 patients in a prospective randomized fashion. Endpoints are late loss at 6 month as well as freedom from MACE at 1 month, 6 months and 1 year. QCA and QCU analyses of both FUTURE I and II were done by independent core laboratories.
Results: The periprocedural success rate of FUTURE I was 100% in both arms. At 30 days post procedure, no MACE were reported in either group. To date, the interim 6 month follow-up QCA analysis in the first 13 out of 36 patients of FUTURE I revealed an in-stent restenosis rate of 0% vs. 33% in the drug eluting stent (DES) and control group, respectively. The MLD at 6 month follow-up was significantly improved in the DES group as compared to the control (2.96 mm vs. 1.56 mm, $p<0.01$) with a late loss of 0.07 mm vs. 1.11 mm ($p<0.01$), respectively. The in-segment restenosis rate in the DES group was 0%. The IVUS analysis revealed a significant reduction of %neointimal volume from 24.3 ± 16.0% in the control to 2.6 ± 2.6% in the DES group ($p<0.01$). At time of presentation, we will demonstrate the complete procedural and 30 days results as well as 6 month follow-up angiographic and IVUS data of both FUTURE I and the efficacy study FUTURE II.
Conclusions: The FUTURE I trial represents a pioneer experience demonstrating safety and feasibility of the new Everolimus coated Challenge-Stent. In addition, the preliminary long-term follow-up results suggested the efficacy of this Everolimus eluting stent in reduction of neointimal proliferation and therefore, reducing the incidence of in-stent restenoses.

1496 Batimastat (BB94) anti-restenosis trial utilizing the biodivysio local drug delivery PC-stent (BRILLIANT-EU-trial)

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Background: Matrix metalloproteinases (MMPs) are involved in the vascular smooth muscle cell (SMC) migration, and therefore their inhibition can be an interesting approach to control the migratory capabilities of the SMC and, consequently, control restenosis following balloon angioplasty and stenting. Preclinical studies have shown that matrix metalloproteinases inhibitors (MMPIs) have beneficial effects on restenosis. The aim of this study was to evaluate the safety and efficacy of the BiodivYsio Batimastat OC stent (2.0μg batimastat per mm^2 of stent surface area) implanted in patients with a single, de novo coronary vessel disease. **Methods:** This was a multi-center, prospective, non-controlled, European-based pilot trial performed at 8 interventional cardiovascular sites in Belgium, 10 sites in France and 2 sites in the Netherlands. 173 symptomatic patients with stable or unstable angina pectoris or documented ischaemia were included in the study. All patients received a single BiodivYsio DD OC coated coronary stent pre-loaded with Batimastat of 11mm, 15mm, 18mm, 22mm or 28mm in length to treat a de novo coronary stenosis. The primary end point was the occurrence of MACE (death, recurrent myocardial infarction or clinically driven target lesion revascularisation) 30 days post-procedure. The secondary end points were the binary restenosis rate determined by QCA at 6 months, incidence of (sub)acute stent thrombosis at 30 days follow-up, MACE at 6 and 12 months. **Results:** The mean age was 61 years. Hypercholesterolemia (62%), hypertension (46%) and family coronary history (43%) were the most frequently reported risk factors. Lesion length was 11.5 ± 5.0 mm (range from 4 to 25 mm). Technical device success rate was 98%. In hospital events (non-Q-wave MI) occurred in two patients. One cardiac death was reported at 24 days after stent implantation. In addition, there were no reported cases of (sub)acute thrombosis. The MACE free rate at 30 days was 98%. No additional death, MI, CABG occurred during the 6m follow-up. Six month angiographic f-up results were obtained in 146 patients (84%). Late loss was 0.88±0.63 and mean loss index was 0.50±0.39. The MACE rate and restenosis rate at 6m was 18% and 23% respectively. **Conclusion:** The 30 days results suggest that the BiodivYsio Batimastat OC Stent is safe during the period of drug elution from the stent. However, the 6 months angiographic data demonstrate that the BiodivYsio Batimastat OC Stent loaded with this dose of Batimastat has no additional beneficial effect on in-stent restenosis.

1497 Long-term follow-up from the STRIDE (anti-restenosis with the biodivysio dexamethasone-eluting stent) clinical study

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Background: Late complications of the drug eluting stent remain a concern. The Study of Anti-Restenosis with the BiodivYsio Dexamethasone Eluting Stent (STRIDE) was designed to evaluate the safety and efficacy of BiodivYsio Matrix Lo dexamethasone (DEX) eluting stent to reduce restenosis. Six-month results showed a beneficial effect on in-stent neointimal hyperplasia especially in the unstable angina patient group. The aim of this study was to evaluate the long-term efficiency of this treatment modality. **Methods:** In the multicenter (from 8 study sites in Belgium) STRIDE trial, an appropriately sized BiodivYsio Matrix Lo stent loaded with a total DEX dose of 0.5μg/mm^2 of stent was used. The primary endpoint of the study was 6m angiographic restenosis rate determined by QCA. The secondary endpoints were 30 days and 6m MACE (death, CABG, myocardial infarction or clinically driven target lesion revascularization). Furthermore, clinical follow-up at 12 month was obtained. **Results:** 71 patients were enrolled in the study, 79% males, Risk factors: 68% had hypercholesterolaemia, 56% had hypertension, 45% had a previous MI, 47% had two or more than two vessel diseases, 33% had lesion type B2 or C, 42% had unstable angina pectoris. At 6 months, late loss was 0.45 ± 0.47 mm and late loss was lower in the unstable angina pectoris pts compared to the stable pts (0.32 ± 0.39 vs. 0.60 ± 0.55 mm, $p< 0.07$). Percent diameter stenosis was significantly lower in the unstable group compared to the stable group (26.86 ± 14 vs. 38.40 ± 16%, $p<0.02$). MACE free rate at 6 months was 96.7%. Between 6 month and 12 months no late thrombosis, nor additional MACE were reported. **Conclusion:** Preliminary results of the 12-month clinical results indicates the DEX-stent efficacy and safety profile seen at 6 months is maintained at 12 months. The final results will be presented.

POSTER DISPLAY III

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

P1502 Prehospital versus periprocedural administration of abciximab in STEMI: early and late results from the randomised REOMOBILE-study

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Background: Pre-treatment of pts with STEMI with abciximab already in the mobile intensive care unit (MICU) is believed to facilitate percutanous coronary intervention (PCI) and improve outcome.
Methods: We randomised 100 pts with STEMI (age <80 yrs, symptom duration <6 hrs) to receive weight adjusted abciximab at the scene (PTx, n=52) or immediately before intervention in the cath lab (HTx, n=48). All pts received 500 mg aspirin and 70 U/kg heparin in the MICU.
Results: Groups were well balanced for sex (19% female), age (median 63 yrs), localisation of MI (39% anterior) and symptom duration until arrival of MICU (median 50 min). Symptom duration until abciximab application was 68 min in pts with PTx and 164 min in pts with HTx. Symptom duration until first visualisation of infarct related artery (Vis-IRA) was 142 min in pts with PTx and 172 min in pts with HTx respectively. ST segment resolution after 60-90 min (before PCI) was <30% in 39%, 30-70% in 37%, and >70% in 24% of pts with PTx, compared to 56%, 14%, and 30% of pts with HTx respectively. In pts with PTx initial TIMI-flow 0/1 was present in 48%, and TIMI-flow 2/3 in 52%, compared to 52% and 48% in pts with HTx respectively. Blush grade before intervention was 0/1 in 63%, and 2/3 in 37% with PTx, compared to 66% and 34% with HTx respectively. Stents were successfully placed in 93% of pts. TIMI flow 3 was achieved in 88% in pts with PTx and 82% in pts with HTx. None of the differences between the groups were signifcant, but tended to be more pronounced in those 50% of pts with PTx, who received abciximab during the first 40 min after syptom onset.
One HTx-pt died on day 4 after prolonged resuscitation, two pts had major bleeds (1 PTx, 1 HTx). Urgent CABG was performend in 7 pts (4 PTx, 3 HTx) until day 5. Until day 180, three pts with PTx had reinfarctions, two within 30 days, one during month 4. Ten pts had ischemia driven re-PCI of IRA (5 PTx, 5 HTx), three of these within the first 30 days after the index event.
Conclusion: Prehospital application of abciximab is safe and feasible. However, in some contrast to the ADMIRAL study we found only minor advantages of early pretreatment with abciximab in pts with STEMI and planned PCI. It may also be considered that fast-track and targeted prehospital therapy in general had added an important part to the excellent short and long term prognosis of the observed pts.

P1503 Infarct related artery patency before percutaneous coronary intervention influences outcome in patients with acute myocardial infarction

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Background: TIMI 3 flow in infarct related artery (IRA) before primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) is associated with better clinical outcome. However frequency of TIMI 3 before primary PCI is very low. We analyzed the influence of IRA patency before PCI on myocardial reperfusion and LV function recovery in patients (pts) with AMI undergoing primary PCI and facilitated PCI (patients pretreated with combined thrombolytic therapy before PCI).
Methods: 476 non shock pts, with AMI <12 hours, treated with primary PCI (n=268) or facilitated PCI (n=208), with TIMI 3 after PCI were enrolled to the study. Patients were divided into two groups according to baseline angiography before PCI: group A (n=224) - occluded IRA (TIMI 0+1); group B (n=252) - patent IRA (TIMI 2+3).
Results: There was no difference between the two groups in 30-days and 6 months clinical outcome. Frequency of myocardial perfusion grade (MPG) after PCI and LV function recovery (EF) after 6 month follow up for both groups are shown in the Table.

TIMI before PCI	TIMI 0+1	TIMI 2+3	p=
MPG 0 after PCI (%)	2,2	3,2	NS
MPG 1 after PCI (%)	33,5	13,5	0,001
MPG 2 after PCI (%)	30,8	25,4	NS
MPG 3 after PCI (%)	33,5	57,9	0,001
EF baseline	49,9 ± 11,6%	54,4 ± 10,8%	0,04
EF 6 month follow up	50,9 ± 14,4%	57,9 ± 12,3%	0,009

Conclusions: Despite of similar epicardial flow after PCI patients with patent IRA before PCI had better myocardial reperfusion and LV systolic function recovery after six month follow up in comparison to pts with occluded IRA at baseline.

P1504 Lack of prognostic significance of normal pre-intervention flow in patients treated with primary angioplasty for acute myocardial infarction in real-life setting with short in-hospital treatment delay

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Background: It has been demonstrated in a metaanalysis of PAMI trials that normal pre-intervention flow in infarct-related artery is an independent predictor of good in-hospital and middle term outcome in patients (pts) with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous intervention (pPCI). We set out to validate this finding in real-life setting.
Methods: A prospective registry of consecutive unselected patients treated with pPCI within 12 hours of STEMI in our tertiary center performing >600 pPCI's yearly was interrogated. In this registry pre- and post-intervention flow grades according to Thrombolysis in Myocardial Infarction (TIMI) group are being entered at the end of the procedure by operators.
Results: Between Feb 2001 and Oct 2002 a total of 1064 STEMI pts were treated with pPCI at our institution including 43 pts in cardiogenic shock on admission and 37 unconscious pts. Median pre-hospital delay was 3,1 hours. Median door-angiography time was 24 minutes and median door-balloon time was 42 minutes. TIMI 3 flow was present at baseline in 9% of pts and post intervention in 84% of pts. Final TIMI 3 flow was achieved in 95% with TIMI 3 flow at baseline and in 82% of pts with TIMI 0-2 flow at baseline. Forty-five pts died in hospital. In-hospital mortality was significantly lower in pts with final TIMI 3 flow than in pts with final TIMI 0-2 flow (2% vs. 15%,p<0,0005) but was the same regardless of pre-intervention flow.
Conclusion: normal pre-intervention flow in infarct related artery does not predict short-term outcome of STEMI patients treated with primary percutaneous intervention in real-life setting with short in-hospital treatment delay.

P1505 The use of glycoprotein IIb/IIIa receptor blockers in primary percutaneous coronary intervention for ST-elevation myocardial infarction: results of the international Shakespeare Registry

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Background: According to current ESC guidelines for the treatment of ST-elevation myocardial infarction (STEMI) primary percutaneous coronary intervention (PCI) is the preferred therapeutic option for reperfusion of STEMI. The data of randomized controlled trials with abciximab as conjunctive antiplatelet treatment support its use during primary PCI whereas the routine administration of abciximab with primary stenting for STEMI is still a matter of debate. Little is known about the use of GP IIb/IIIa receptorblockers (GPIIb/IIIa) during primary PCI in clinical practice in Europe.
Methods: Since February 2002, consecutive patients undergoing PCI have been enrolled in 30 centers in 6 countries of the European Society of Cardiology (France, Germany, Israel, Italy, Portugal, United Kingdom) to document clinical practice of coronary interventions as well as outcome of these patients.
Results: Out of 6327 consecutive PCI 1153 (18.2%) were performed as primary PCI in patients with acute STEMI. A total of 782 patients (68%) received GPIIb/IIIa during primary PCI. Patients with STEMI treated with primary PCI and GPIIb/IIIa did receive stents more often (78.4% vs 72.8% of treated lesions, p<0.01). There was no difference in interventional complications such as severe dissection or acute occlusion between patients treated and not treated with GPIIb/IIIa. Bleeding complications were more frequent in patients treated with GPIIb/IIIa (8.4% vs 4.6%, p<0.01), cerebral bleeding occurred in 2 patients treated with GPIIb/IIIa. After correction of differences in baseline characteristics and adjunctive treatment primary stenting was associated with a significant reduction in hospital and 30-day mortality (OR 0.34, CI 0.17-0.68 and OR 0.31, CI 0.14-0.70). The administration of GPIIb/IIIa showed a non-significant trend for better outcome in addition to stenting (OR 0.56, CI 0.29-1.07 for hospital mortality and OR 0.83, CI 0.40-1.72 for 30-day mortality). In the subgroup of patients who did not receive stents, the treatment with GPIIb/IIIa was associated with a significant reduction of hospital and 30-day mortality (OR 0.18, CI 0.04-0.76 and OR 0.17, CI 0.04-0.76 respectively).
Conclusion: Two thirds of patients undergoing primary PCI for STEMI did receive GPIIb/IIIa as conjunctive therapy in clinical practice in Europe. GPIIb/IIIa significantly improved outcome in patients who did not receive stents. In patients with primary stenting for acute STEMI the use of GP IIb/IIIa was only associated with a nonsignificant trend to a reduction in mortality.

P1506 Clinical and statistical significance of stable reperfusion as determined by continuous ST-segment recovery methods in acute ST-elevation myocardial infarction (STEMI)

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Background: Combination therapy with thrombolytics and anti-platelet or anti-thrombin therapies in STEMI improves infarct-artery patency, but a significant mortality reduction has not been demonstrated in large-scale clinical trials. Analysis of surrogate biomarkers that characterize the timing and stability of reperfusion may clarify the relationship between ST-segment reperfusion biomarkers and clinical outcomes.
Methods: ST-segment recovery analysis parameters provide a noninvasive, quantitative biomarker of the speed and stability of reperfusion. To assess the incremental benefit of adjunctive therapies and correlation to mortality we analyzed time from treatment onset until stable ST reperfusion (STBLST) collected from 1,511 continuous digital 12-lead ST-segment 24-hour recordings. STBLST is calculated as ≥50% recovery from peak ST levels lasting at least 4 hrs. All ST-segment study patients from 10 STEMI trials: TAMI-9 (212), DUCCS-II (33), GUSTO-I (231), IMPACT-I (100), PARADIGM (229), PRIME (174), HERO-I (172), GUSTO-III (35), GUSTO-V (191) and INTEGRITI (134), were analyzed while blinded to treatment group and clinical outcomes. Patients were treated with thrombolytics only (LYT) or combination of lytics and IIb/IIIa inhibitor (PLT) or direct thrombin inhibitor (DTI). STBLST was stratified by drug group and in-hospital mortality.
Results: See table. STBLST significantly correlated to treatment (p<.001) and mortality (p=.01). Logistic regression model predicts a 30-60 minute reduction in STBLST decreases odds of mortality 9%-14%.

Time to Stable ST Reperfusion (Minutes)

	LYT	PLT	DTI	Death=Yes	Death=No
N	836	425	250	48	1463
Median STBLST	124	74	111	164	104
(25th, 75th) %iles	(58, 236)	(8, 128)	(31, 182)	(70, 286)	(40, 186)

Conclusions: (1) Continuous ST-segment monitoring in STEMI studies provides a clinically and statistically significant biomarker (STBLST) to analyze novel treatment regimens and 2) Limited 30-day follow-up suggests the correlation between STBLST and mortality is maintained (p=.06).

P1507 Relation of electrocardiogram subendocardial ischaemia and microcirculation dysfunction by contrast echocardiography

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Left ventricular (LV) hypertrophy (LVH) can be associated with ST-T changes on the 12 lead ECG, which are designated as systolic overload or subendocardial ischemia (SEI). These ECG changes are associated with LVH and a reduction of its coronary flow reserve (CFR). In hypertensive heart disease, the presence of SEI associated to LVH criteria in the ECG, identiphies a high-risk subgroup for cardiovascular events, morbidity and mortality. Using LV myocardial contrast echocardiography (MCE), we evaluated both the perfusion pattern in the anterior wall and its ECG changes. Exclusion criteria were diabetes mellitus, dyslipidemia, hypertrophic cardiomyopathy and coronary artery disease.

We studied by MCE 66 patients (pts), 12 pts without LVH and SEI (N group), 32 pts with LVH and no SEI (G1 group) and 22 pts with LVH and SEI (G2 group), after iv infusion of Optison® (Mallinkrodt, USA), under basal conditions and after coronary vasodilator stress with adenosine, 140 μg/kg/min iv. Using a quantitative software of imaging analysis (MCE2.7 Yabko, LLC 2002, USA), we calculated the maximal values of coronary microcirculation velocity β, myocardial blood volume A, myocardial blood flow (A*β=FM) and the stress/basal MBF ratio, which reflects CFR for each region of interest (ROI), endocardial (Endo) versus meso-epicardial (Meso-Epic) layers (total n=264 ROI). Coronary microcirculation revealed already under basal conditions, a certain degree of dysfunction similar in G1 and G2 groups. Comparing N and G1 groups for the Endo layer, G2 has a clear pattern characterised by a significant reduction of its basal perfusion, which becomes more pronounced after iv overload with adenosine.

Relation of MBF to ECG changes

	Number	MBF stress/ Meso-Epic	Basal Endo	MBF Endo/Meso-Epic
Normal	12	3.20	3.03	0.95
G1 group	32	3.01	2.40	0.80
G2 group	22	3.02	2.02	0.67

Conclusion: We observed a major MCE gradient across the LV wall thickness, with lower values in the Endo layer in G1 compared to N and G2 groups. These ECG changes, described as systolic overload or subendocardial ischemia, reflect a significant reduction of the capillary myocardial perfusion pattern assessed through MCE.

P1508 Primary stenting for acute myocardial infarction in the real world. Zwolle 6 randomized trial

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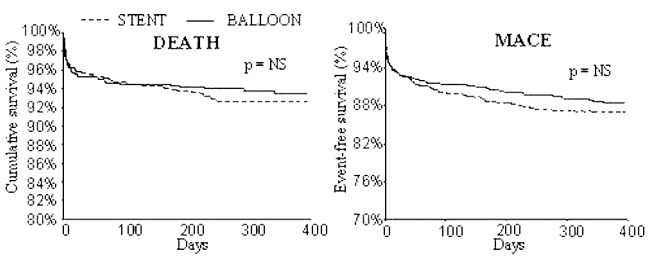
Purpose: Although primary angioplasty has been shown to improve the outcome of patients with ST-elevation myocardial infarction (STEMI), the potential benefits of primary stenting, compared to balloon angioplasty, have yet to be investigated. In fact, all currently available randomized trials have only enrolled highly selected patients, after the initial angiogram. Thus, the aim of the current study was to compare stenting and balloon angioplasty in STEMI with an early randomization strategy (before the angiogram) in unselected, consecutive patients with STEMI.

Methods: A total of 1683 patients with STEMI were randomized before the angiogram to stent (STENT group = 849 patients) or balloon angioplasty (BALLOON group = 834 patients). All angiographic, clinical and 1-year follow-up data were prospectively collected.

Results: A total of 787 patients (92.6%) in the STENT group and 765 patients (91.7%) in the BALLOON group underwent primary angioplasty. The cross-over rate from balloon to stent and stent to balloon were 28% and 14%, respectively. No difference was observed in 1-year mortality and MACE according to intention-to-treat analysis (Figure).



Conclusions: This is the first randomized trial comparing stenting and balloon angioplasty in a large cohort of unselected, consecutive patients ("real world") with STEMI. The results suggest that provisional stenting is perhaps still the best option in the management of patients with STEMI.

P1509 Recurrent ST-elevation in a different territory to the index infarct after fibrinolytic therapy: a manifestation of multiple unstable plaques

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Purpose: In patients with acute coronary syndromes, multiple unstable plaques have been demonstrated by various techniques in both culprit and non-culprit arteries. To evaluate how frequently clinical manifestations of this phenomenon may occur, we studied the electrocardiographic (ECG) patterns in patients suspected of in-hospital reinfarction (reMI) following thrombolytic therapy.

Methods: In the HERO-2 trial, 17073 patients were randomised to 48 hours of either bivalirudin or unfractionated heparin as adjunctive therapy to streptokinase for ST elevation myocardial infarction. The protocol predefined reMI criteria prior to and after 18 hours post randomisation, and associated with revascularisation procedures. In patients with suspected reMI it was protocol recommended that investigators perform serial ECGs and cardiac marker levels, and these were referred to a Clinical Endpoints Committee for adjudication. We studied the ECGs recorded at the time of reMI and compared the territory of ST elevation with that at the time of the index infarction of those patients.

Results: Of 722 patients with suspected reMI, 4% had ST elevation in a different territory to the index infarction whilst recurrent ST elevation in the territory of the index infarction was seen in 67% of cases, 18% had no new ECG changes, 2% had new bundle branch block (BBB) and 9% had other changes, including paced rhythm or technically poor quality ECGs. ST elevation in a new territory occurred at a median of 46 hours after randomisation compared to 67 hours for ST elevation in the index territory (p=0.08). Of patients with ST elevation in a new territory, 50% occurred during the 48 hours of randomised antithrombin treatment, compared to 29% of those with recurrent ST elevation in the index territory (p=0.046). Overall, mortality at 30 days was 27% in those patients with reMI, and 10% for patients without reMI ($p<0.001$). Mortality was highest in those patients with new BBB at 79%, compared with 35% for those with ST elevation in a new territory, 26% for those with ST elevation in the index territory and 21% for those with no new ECG changes ($p<0.001$).

Conclusion: Recurrent ST elevation in a different ECG territory to the index infarction occurred in 4% of in hospital reMIs, but in only 0.2% of all patients enrolled in the HERO-2 trial. As this manifestation of multiple unstable plaques was more likely to occur during antithrombin treatment, more intensive therapies may be required. Early mortality following presumed plaque rupture in a second arterial territory is high.

P1510 The benefits of combined antiplatelet therapy with aspirin and clopidogrel in patients with acute myocardial infarction and ST-segment elevation

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Purpose: Platelets play a major role in the thrombotic response to rupture of a coronary artery plaque. This study aims to assess the effect of combined antiplatelet therapy with aspirin and clopidogrel in the clinical outcome in patients with acute myocardial infarction and ST-segmend elevation.

Methods: This is a prospective randomized study, which included 342 patients (age: 35 – 85 years) with acute myocardial infarction treated with thrombolytic agents. All patients received anti-ischemic and antithrombotic therapy and were divided into two groups regarding antiplatelet therapy. Group I 178pts (52%) were treated with aspirin only (loading dose of 325 mg and then 100mg daily) while group II 164pts (48%) received a combined regimen of aspirin (loading dose of 325 mg and then 100mg daily) and Clopidogrel (loading dose of 300mg and then 75 mg daily. The mean length of hospital stay was 8 days. Both patient groups were followed for 3 months.

Results: During hospitalization mortality and ischemia recurrence rates were1.12% (2pts) and 16.8% (30 pts) respectively in group I versus 0.61% (1pt) (P=NS) and 3.65% (6 pts) (P=0.03) respectively in group II. During the 3-month follow-up period the ischemia recurrence rate was 23.59% (42 pts) in-group I versus 6.09%(10 pts) in-group II (P=0.04).

Conclusion: Combined antiplatelet therapy with aspirin and clopidogrel seems to be superior to aspirin in terms of recurrent ischemia reduction over the first 3 months after acute myocardial infarction.

P1511 Incidence, severity and timing of neurological events after a major myocardial infarction

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Background: Patients with major left ventricular systolic dysfunction (LVSD) or heart failure after a myocardial infarction are at increased risk of stroke. The incidence of stroke and, more importantly, disabling stroke after a myocardial infarction are poorly characterised.
Aims: To describe the incidence and severity of stroke in patients who have survived a myocardial infarction complicated by LVSD or heart failure.
Methods: 5477 patients with MI with evidence suggesting major LVSD were enrolled in the OPTIMAAL trial. Patients were followed-up for a mean of 2.7 years. Strokes were adjudicated by an endpoints adjudication committee. Disability was reported by the investigators and classified as none, minor, and major one month after the event with respect to Self Care, Walking, Vision, and Speech.
Results: The patients' mean age was 67 years. At study end, 441 possible strokes had been reviewed resulting in 300 confirmed strokes in 272 patients. There were additionally 113 events of transient ischemic attack (TIA) reported by investigators. Use of aspirin, presence of atrial fibrillation, age, history of hypertension, and not undergoing angioplasty at baseline were associated with an increased risk of stroke during long-term follow-up. Of the 272 patients with confirmed strokes, sixty-five (24%) occurred within 30 days of the index infarction. Sixty patients (22%) with strokes subsequently died, of which fifteen (6%) occurred within 30 days of randomisation. However, among the 234 patients with stroke-related disability records, only seventy-five (32%) had persistent major disability in one or more of the above categories, whilst eighty-nine (38%) were reported to be alive without any disability. Patients surviving stroke with major disability spent an average of 48 days in hospital versus 22 days for patients with no stroke over 2.7 years of follow-up.
Conclusions: Stroke and TIA are common after a myocardial infarction associated with LVSD or heart failure. However, most survivors of a stroke event recover without major chronic disability.

SYNCOPE: NEW PERSPECTIVES

P1512 How many patients with syncope should be properly hospitalized in 2003?

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Syncope is a frequent clinical manifestation which causes a great impact on hospital organization owing to the high (and frequently inappropriate) hospitalization rate of the patients.
Aim: To evaluate how many patients with syncope should be hospitalized according to the indications of the 2001 European Society of Cardiology (E.S.C.) Guidelines on the management of syncope.
Methods: Starting from August 2002 we prompted a Syncope Unit (S.U.), that is a multidisciplinary functional structure which includes the Emergency Department and the Cardiology and Internal Medicine Divisions. One of the main objectives of the S.U. was the implementation of the 2001 E.S.C. Guidelines on Syncope. According to the latter, criteria for hospitalization were considered: documented cardiogenic syncope, structural heart disease, abnormal electrocardiogram (ECG), severe comorbidities, severe trauma, very frequent recurrences. All the clinical data relative to patients presenting with syncope were prospectively collected and stored in a dedicated data base.
Results: In the period between 01/09/2002 and 31/01/2003, 284 patients were observed for a transitory loss of consciousness, and 235 of them were diagnosed as having syncope. Out of these patients, 9 (4%) had a documented cardiogenic syncope, 49 (21%) were found to have a structural heart disease, 20 (9%) an abnormal ECG, 16 (7%) severe comorbidities, 10 (4%) had a severe trauma, and 1 presented very frequent recurrences. Thus, a total of 105 patients (45%) presented at least one criterion for hospitalization according with the E.S.C. Guidelines. After a 4-hour median observation time, 104 patients (44%) were actually hospitalized, while the remaining 131 (56%) were directly discharged from the Emergency Department (adherence rate to Guidelines: 93% for hospitalization, 95% for hospital discharge).
Conclusions: The implementation of the E.S.C. Guidelines on Syncope is technically feasible. Nevertheless, also when the Guidelines are carefully observed a high percentage of patients with syncope has still to be hospitalized. Our data suggest that new criteria are needed for a safe Emergency Department discharge of the patients with syncope.

P1513 Fluoxetine versus propranolol in the treatment of neurocardiogenic syncope

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Aim: The optimal medical treatment of patients (pts) with neurocardiogenic syncope (NCS) is still controversial. The aim of this study was to prospectively compare the therapeutic efficacy of Fluoxetine (FL) and Propranolol (PR) in pts with NCS.
Methods: Forty-four pts with recurrent NCS were randomly assigned to either treatment with PR or FL. Then, they were followed up for 6 months and reported the number of their syncopal (sync) and presyncopal (presync) spells. Before and during treatment, all pts graded their quality of life (QOL) expressed as well-being, general activities and everyday activities (each scaled from 1= very good to 5=very bad).
Results: Each arm (FL or PR) consisted of 22 pts. Two pts from the PR-group refused follow-up (FU). Ten pts (5 from each group) interrupted therapy due to drug's side effects (interruption group). Seventeen pts from the FL-group and 15 from the PR-group completed the study. Pts with sync and presync were significantly less in the FL-group than in the PR-group (1/17, 6% vs 4/15, 27%, $p<0.05$ and 1/17, 6% vs 7/15, 47%, $p<0.01$, respectively). QOL was significantly improved only in the FL-group (14.5 before vs 12.8 during treatment, $p<0.01$), as shown in the table.

	Pts with sync during FU	Pts with presync during FU	QOL before treatment	QOL during treatment
FL-group	1/17 (6%)	1/17 (6%)	14.5±0.6	12.8±11.3**
PR-group	4/15 (27%)*	7/15 (47%)*	14.8±0.7	14.6±12.9
Interruption group	2/10 (20%)	4/10 (40%)	14.4±0.8	13.4±11.3

*: Kaplan-Meier analysis, $p<0.05$ compared to FL-group **: mean±SD, ANOVA repeated measures, $p<0.01$ compared to QOL before treatment

Conclusion: FL seems to be superior to PR regarding its therapeutic efficacy and pts' QOL. However, a considerable proportion of pts from both groups discontinued treatment due to drug's side effects.

P1514 Nitrate stimulated head up tilt testing potentiates the predictive value of the tilt test on the risk of recurrence in patients with vasovagal syncope

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Background: Nitrate stimulated tilt testing may be used to diagnose vasovagal syncope and to guide therapy. However, to date the predictive value of the test is undetermined. This study analyses the risk of recurrence of syncope in vasovagal patients on the basis of a nitrate stimulated tilt result and other clinical factors.
Methods: We used a combined passive and nitrate stimulated tilt protocol. One year after the test a questionnaire, asking about recurrence of syncope and other demographic factors, was sent to 131 patients.
Results: Passive tilting was found not to be a useful predictor; recurrence rates after a positive and negative test were 26% and 30% respectively, ns. With the addition of sublingual nitrates the test became a significant predictor; recurrence rates of 34 (34%) with a positive tilt test and 4 (13%) with a negative (p= 0.031). Univariate analysis of the clinical factors revealed that gender and pre-test symptomatology were significant predictors of recurrence. (Table 1)

Table 1

	recurrence	no recurrence	p value
pos. passive test n=23	6 (26%)	17 (74%)	ns
neg. passive test n= 108	32 (30%)	76 (70%)	
pos. nitrate test n= 78	28 (36%)	50 (64%)	0.031
neg. nitrate test n= 30	4 (13%)	26 (87%)	
1 syncope n= 49	9 (18%)	40 (82%)	0.027
> 2 syncope n=79	29 (37%)	50 (63%)	
female n=62	27 (44%)	35 (56%)	< 0.001
male n= 69	11 (16%)	58 (84%)	

Tilt test and baseline characteristics related to outcome

Conclusion: In patients with suspected vasovagal syncope, a positive tilt test with sublingual nitrates together with the clinical factors gender and symptomatology, are predictors for recurrence of syncope during one year follow-up. Without specific t herapy the prognosis of vasovagal syncope is good.

P1515 Correlation of cardio-inhibitory responses in head-up tilt tests and ATP tests with spontaneous syncope recurrence documented by implantable loop recorders

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The type of response observed during a positive head-up tilt test (HUT) or adenosine triphosphate test (ATP test) is sometimes used to select therapy in vasovagal syncope (VVS) patients (pts). However, a strict correlation between spontaneous syncope and HUT or ATP response has never been demonstrated.

Purpose: The aim of this study was to compare the heart rhythm observed during a positive HUT or ATP test and during the first spontaneous syncopal recurrence in VVS pts equipped with an implantable loop recorder (ILR).

Methods: All VVS pts included in this study presented with no heart disease, had no treatment and a history of at least 2 syncopes within the last year. In addition, they recorded a positive HUT at baseline or after nitroglycerin or isoproterenol provocation. Westminster protocol was used for the HUT, with continuous ECG recording and finger blood pressure monitoring. HUT-responses were classified according to the VASIS classification. In addition, all the patient underwent a ATP test (intravenous bolus injection of 20 mg ATP). A positive test was defined as the induction of atrioventricular block with a ventricular pause longer than 6 sec.

Pts did not receive any treatment for VVS and were equipped with an ILR (Reveal, Medtronic). The ILR was analyzed after the first syncopal recurrence: bradycardia was defined as a ventricular rate lower than 40 bpm and asystole as a ventricular pause longer than 3 sec.

Results: Twenty pts (age: 59.0 $\pm$ 16.0 years, 6.6 $\pm$ 5.0 VVS per year, 12 females) were included in the study. HUT responses were vasodepressor in 13 cases (65%) and cardioinhibitory in 7 (35%). The mean follow-up was 14.1 $\pm$ 7.2 months. Thirteen pts (65%) had syncope recurrence, 5.0 $\pm$ 4.9 months after ILR implant. During the event, the ILR memory showed slow heart rates in 9 pts (bradycardia in 2, asystole in 7) and normal sinus rhythms in 4 pts. Among the 9 pts with slow heart rates, 7 had either cardioinhibitory HUT-response (n=3), a positive ATP test (n=3) or both (n=1). No significant correlation was found between a slow heart rate at the ILR interrogation and a cardioinhibitory HUT-response (chi2, p = 0.39, Fisher exact test) or a positive ATP test (chi2, p = 0.39, Fisher exact test).

Conclusion: In this prospective study of highly symptomatic VVS pts equipped with an implantable loop recorder, a cardioinhibitory HUT-response or a positive ATP test were not statistically associated with the presence of slow heart rate during the first spontaneous syncopal recurrence.

P1516 The influence of the tilt training program on sympathetic nervous system activity to the head-up tilt test

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Orthostatic stress during head-up tilt test (HUTT) produces changes in autonomic nervous system activity. Either overactivity of the sympathetic nervous system or insufficient peripheral sympathetic discharge (lack of appropriate venoconstriction) may predispose to inappropriate reflex reaction leading to vasovagal syncope. Tilt training program is a treatment method for vasovagal syncope. The aim of the study is to assess the activation of the sympathetic nervous system during HUTT before and after tilt training program.

Material and method: The study group consisted of 15 pts (11F, 4M, mean age 38,9 $\pm$ 17,2 years) with the history of syncope of unknown origin and vasovagal reaction during HUTT. The blood for determination of plasma concentration of neuropeptide Y (NPY) was drawn after 30 minutes supine rest, immediately before HUTT and 10 min after HUTT. The study was performed twice: the first time during the diagnostic HUTT and the second one after tilt training program lasting 1 to 3 months. Neuropeptide Y concentration was measured using radioimmunologic assay.

Results: The first HUTT according to VASIS investigators was cardiodepressive in 11 pts and mixed in 4 pts; syncope occurred in passive phase of the HUTT in 6 pts and after provocation with nitroglycerine in 9 pts. During the control HUTT in 3 pts presyncope was observed and the test was stopped after 4, 14 and 36 minutes. During the diagnostic HUTT there was no change in the NPY concentration (26,3 $\pm$ 27,3 vs 31,6 $\pm$ 30,0 pg/ml, p= ns). After the period of tilt training program there was statistically significant increase in NPY concentration (18,7 $\pm$ 14,2 vs 38,9 $\pm$ 41,5 pg/ml, $p<0,05$).

Conclusions: 1. The activation of sympathetic nervous system during diagnostic HUTT in patients with vasovagal syncope is not correlated with NPY concentration changes. 2. Orthostatic stress during tilt training program probably change the mode of sympathetic nervous system activation in comparison to this observed before the treatment. 3. The increase of the NPY concentration may be a defense reaction against vasodilatation and therefore a mechanism preventing the syncope.

P1517 Comparison between a short nitroglycerin sensitized tilt test and a conventional isoproterenol sensitized tilt test in patients with unexplained syncope

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Background: Conventional tilt test protocols are time consuming and furthermore, there is not agreement on the optimal duration of the test and provocative drug to be used. Nitroglycerin protocols are being used widely for the evaluation of syncope, however its diagnostic value in comparison with isoproterenol test is still under debate. We investigated the usefulness of a short nitroglycerin sensitized protocol as compared with a conventional isoproterenol sensitized protocol.

Methods and Results: Sixty-four consecutive patients underwent a tilt test with a protocol that included a 15 min passive phase followed by 400 μg nitroglycerin spray sublingually administered as a provocative drug. The control group included 64 randomly chosen patients tilted with a conventional protocol (30 minutes passive phase and 20 min of Intravenous isoproterenol infusion); all patients were referred to our center for unexplained syncope. There were no statistically significant differences in age, sex and clinical variables. There were 39(60.9%) positive tests in the short nitroglycerin protocol compared to 27(42%) in the isoproterenol protocol, P=0.034. The mean duration of the isoproterenol protocol was 41.2$\pm$15 and in the nitroglycerin protocol 23.26$\pm$0.9 (P=0.001). There were more vasodepressor responses in the nitroglycerin protocol (51.3%) as compared to the isoproterenol protocol (18.5%), and more mixed responses on the isoproterenol protocol (59.3%) in comparison to the nitroglycerin protocol (38.5%), (P=0.001). No differences were observed in the cardioinhibitory responses.

Conclusions: Short nitroglycerin sensitized tilt test protocol has a higher percentage of positive responses than a conventional isoproterenol sensitized protocol for the diagnosis of vasovagal syncope, and is less time consuming. Differences in responses can be attributed to the different mechanism of action of the drugs.

P1518 Effect of carotid sinus massage and tilt table testing in a normal, healthy older population

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Introduction: Experience from dedicated "syncope in older people" clinics suggests that carotid sinus syndrome and vasodepressor vasovagal syncope account for >50% of cases of syncope in this group. Tilt table testing (TTT) combined with carotid sinus massage (CSM) is required to establish these diagnoses. There has been increasing enthusiasm for the use of CSM and TTT. The response of "healthy" older subjects to these maneuvres has not been clearly delineated. We have investigated normal cardiovascular responses, in particular the spectrum of responses to CSM and TTT in a carefully defined group of healthy, older subjects.

Methods: 100 subjects aged 60 to 80 years were identified from local databases. Volunteers were excluded if they provided a history of syncope or falls, cardiovascular or cerebrovascular disease, orthostatic hypotension, diabetes mellitus or had a carotid bruit, abnormal resting ECG, anaemia, renal dysfunction, or were using medications known to influence cardiovascular responses to CSM or tilt table testing. Volunteers with abnormal findings on echocardiography, carotid ultrasonography and ambulatory ECG assessment were also excluded.

CSM and TTT with continuous non-invasive beat-to-beat finger arterial pressure and ECG monitoring were performed on those volunteers not excluded by the criteria specified.

Results: 32 subjects (mean age 70 $\pm$ 5 years, median 70 years, range 61-79 years, 22 female) completed all components of the study protocol, culminating in CSM and TTT. 20 subjects (62.5%) completed CSM and 40 minutes of TTT without syncope or presyncope. There were 13 positive responses in 12 subjects. 4 (12.5%) subjects had a positive response to CSM, 2 each with cardioinhibitory and vasodepressor responses. 9 subjects had a positive response to TTT, including 1 subject who had a cardioinhibitory response to CSM. With respect to the VASIS classification, 3 of the positive outcomes were type 1 (33%), 2 were type 2A (22%), 1 was type 2B (11%) and 3 were type 3 (33%). The mean time to syncope was 22 $\pm$ 11 minutes. There were no differences in the age (p=0.473) or sex (p=0.170) distributions of the positive and negative outcomes.

Conclusion: The combined specificity of CSM and TTT is low at 62.5% in healthy, older people. We advise caution when interpreting positive results of these investigations in older people. Consideration should be given to additional clinical and other data before diagnosing carotid sinus hypersensitivity or vasovagal syncope as the mechanism of syncope in this age group.

P1519 Long-term follow-up in patients with neurocardiogenic syncope

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Aim: The aim of our study was to access the long term clinical outcome in patients (pts) with VVS.
Patients and Method: Between July 1993 and September 2002, 124 consecutive pts with a positive history of VVS (73 F and 63 M, mean age 47.6±18.5 yrs) were followed-up at our outpatient clinic for a mean of 58.5±28.9 months (range 14 to 113 months). Our pts had a mean of 8.36±11.68 (2.88±4.49/year) syncopal and 4.54±8.87 (1.86±3.85/year) presyncopal episodes. Ninety pts (72.5%) had a positive clomipramine or isoproterenol head-up tilt-test (HUT). Eighty pts were treated with drug therapy (b-blocker in 58 pts for a mean 27±31.4 months and fluoxetine in 22 pts for a mean 27±31.4 months). In 6 pts a DDI pacemaker was implanted.
Results: During follow-up, syncope recurred in 40 pts (32.2%). In 28 of them, syncopal episodes were associated with psychological stress (death of a close relative, divorce, loss of job, etc.). The number (1.06±3.27) and frequency (0.25±0.95/year) of syncope were significant reduced during FU compared to those prior to inital evaluation ($p<0.001$). Presyncope recurred in 64 pts (51.6%). A significant reduction in the frequency (0.67±1.14/year) of presyncopal attacks during FU was also observed, compared to that before the initial evaluation ($p<0.001$). Pts' probability of remaining free of syncope after 58 months was 68%. Pts with less than 6 episodes within 2 years had a higher probability to remaining free of symptoms during the following 15 months (80%), compared to those with > than 6 episodes within 2 years (40%). Additionally, fluoxetine seems to be superior to any other treatment regarding time to the first recurrence of syncope, during FU as it was assessed in multivariable analysis.
Conclusion: During FU, the number of syncopal attacks was reduced in pts with VVS regardless their treatment. However, fluoxetine-treatment pts had a longer time to the first recurrence of syncope compared to any other group.

P1520 Should the tilt-table test be performed as soon as possible after the spontaneous syncopal episode?

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Objectives: The propensity for spontaneous and tilt induced neurocardiogenic syncope may exhibit temporal variations. Therefore it has been suggested that the sensitivity of the head-up tilt test (HUT) could be improved if it is performed soon after the occurrence of spontaneous syncope. The objective of this study is to assess whether the time interval between the last syncopal episode and the HUT has an influence on the outcome of the test.
Method: Three hundred and fifteen consecutive patients (178 men, age 55.1 ± 20.2 y) undergoing a diagnostic HUT potentiated with sublingual nitroglycerin for suspected neurocardiogenic syncope were included in the study. The time interval between the last spontaneous syncope and the HUT (T-ST) was recorded and its relationship with the results of the test were analyzed in the whole population and in different subsets.
Results: The HUT gave a positive result in 211 patients (67.0%), in most of them during the pharmacologic phase (n=186, 88.2%). The T-ST was similar for patients with positive and negative HUT results: median 28, range [1-500] days vs. 32 [2-700] days, n.s. No significant relationship was observed between the results of the test and the ocurrence of spontaneous syncope within the week previous to the procedure: 48/73 (65.8%) positive tests vs. 163/242 (67.4%) in patients with the last syncope prior to the last week. Similar results were obtained for the whole population considering two weeks, one month or three months previous to the HUT. However, a higher rate of positive tests was observed in men with a T-ST interval lower than one month (72/108, 66.7%) when compared to men with a T-ST > 1 month (34/70, 48.6%, $p<0.05$). Patients older than 50 years showed as well more positive tests if their last spontaneous syncope had occurred within the month previous to the HUT. When both criteria were combined the rate of positive tests for men over 50 years of age fell from 50/79 (63.3%) for patients with T-ST < 1 month to 13/37 (35.1%) for the rest.
Conclusions: The T-ST does not have a significant impact on the outcome of the head up tilt testing in the whole population with suspected neurocardiogenic syncope. However, the sensitivity of the test may be reduced in men and patients older than 50 years if it is performed beyond one month after the ocurrence of the spontaneous syncopal episode.

P1521 Time to first recurrence of syncope in patients with syncope

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Purpose: The European recommendations for driving restrictions due to heart diseases suggest in case of syncope a licensing in case of satisfactory results after 3 months. The aim of the investigation was to assess how often und when occurs the first recurrence in patients with syncope.
Methods: The study included 161 consecutive patients with syncope at the time of their clinical evaluation with a head-up tilt test. Patients with cardiac syncope or neurological or psychiatric syncope were excluded. Each patient completed a follow-up of 12 months. The patients with a recurrent syncope and the time interval until the first recurrence were determined. The time interval was divided from 0 to 3, from 3 to 6, from 6 to 9, and from 9 to 12 months after the evaluation. Patients with one syncope were compared to patients with more than one syncope within the last 6 months.
Results: One syncope in the last 6 months had 72 (54 ± 17 years, male n =39, positive head-up tilt test n = 32 (44%)) and more than 1 syncope 75 patients (51 ± 17 years, male n =33; positive head-up tilt test n = 25 (33%)). There were 2 deaths during the 12 months follow-up. At least one recurrent syncope reported 10 (14%; positive head-up tilt test n = 7 (70%)) patients with one and 18 (24%; positive head-up tilt test n = 4 (22%)) patients with more than one syncope within the last 6 months. No syncope occurred during driving. The first recurrence occurred in the group with one syncope within the last 6 months between 0 and 3 months in 4, between 3 and to 6 months in 2, between 6 and 9 months in 2 and between 9 and 12 month in 2 patients. In the group with more than one syncope within the last 6 months the time of the first recurrence was 13 (0 – 3 months), 2 (3 – 6 months), 2 (6 – 9 months), and 1 (9 – 12 months). The patients with a recurrence within the first 3 months had a positive head in 3 (75%) cases with one syncope and in 2 (15%) cases with more than one syncope within the last 6 months.
Conclusions: A recurrent syncope was reported in 14% in patients with one and in 24% in patients with more than one syncope within the last 6 months. The first recurrence occurred within the first 3 months after evaluation only in 40% in the first and in 72% of the latter group. A delayed first recurrence of syncope should be considered if driving restrictions are considered in this group of patients.

PACEMAKER AND IMPLANTABLE CARDIOVERTER-DEFRIBRILLATOR TECHNOLOGY II

P1522 Preliminary mid-term safety and efficacy results of cardiac contractility modulation by non-excitatory electrical currents for heart failure

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Background: The concept of enhancing cardiac contractility, by means of non-excitatory currents, applied during the absolute refractory period was extensively tested in preclinical studies. Indeed, after assessment of acute efficacy in human beings, we conducted a treatment-only pilot study to assess mid-term safety and efficacy of cardiac contractility modulation (CCM) by non-excitatory electrical currents for HF.
Methods: Seven patients with NYHA class III HF were implanted with a device (OPTIMIZERTM II) delivering CCM biphasic square-wave pulses (20ms, 5.8 to 7.7V, 30ms after detection of local activation) through two right ventricular leads screwed-in the right aspect of the interventricular septum. CCM signals were delivered 3 hours daily over 8 weeks (3hr phase) and 7 hours daily over the next 16 weeks (7hr phase). Ejection fraction (EF) and NYHA class were assessed, and 6-minute walking test (6-MWT) and Minnesota Living with HF Questionnaire (MLHFQ) performed, at baseline, and at the end of each phase.
Results: During the 3hr phase EF improved from 21.7±8% to 29.1±6% (P=0.01), 6-MWT from 441±97m to 476±91m ($P<0.01$), MLHFQ from 32±22 to 19±9 (P=0.01) and NYHA class from 3 to 1.7 (P=0.01). CCM delivery 7 hours daily caused a further improvement in EF (from 29.1±6% to 34±11.2%, P=0.01), 6-MWT (from 441±97m to 487±101m, P=0.06), MLHFQ from 19±9 to 8±4 ($P<0.01$) and NYHA functional class (from 1.7 to 1.5, P=0.04). Use and dosage of inotropic and diuretic agents were reduced in both phases. Serial 24-h Holter analysis revealed no major arrhythmias nor improper CCM signal delivery in any patients.
Conclusions: CCM gradually and significantly improves systolic performance, symptoms and functional capacity. CCM therapy for 7 hours/d is associated with greater dispersion near the mean, emphasizing the need for individually tailoring CCM delivery duration. Proarrhythmic effects of this novel therapy seem unlikely.

P1523 Do airport metal detectors interfere with implanted pacing devices?

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Background: It is currently unknown whether airport metal detector gates interfere with implantable pacemakers (PM) or cardioverter defibrillators (ICD).
Methods: 200 PM and 148 ICD recipients passed a standard airport metal detector gate (model 02PN10; C.E.I.A., Viciomaggio, Italy) twice as they would do it for routine airport security checks. Then the patients were advised to perform a 360° torsion around the body axis within the metal detector gate and to place the chest side with the implanted device as close as possible towards the transmitter of the metal detector. PM basic rate and/or AV-delay was programmed to achieve either bifocal pacing or atrial triggered ventricular pacing in dual chamber PM. In single chamber PM the basic rate was programmed greater than the intrinsic rhythm. Sensitivity was programmed as clinically required for correct PM function and avoidance of myopotential oversensing. During testing external 6-lead ECG was continuosly recorded. ICD were programmed with detection "on" and therapies "off", maximal sensitivity, detection rate for ventricular tachyarrhythmias >100 bpm, and shortest available detection period. ICD Holter was interrogated before and after testing within the electromagnetic field of the airport metal detector gate.
Results: 203 PM and 151 ICD systems were tested (some patients with testings before and after replacement of the pulse generator for battery depletion). Manufactorer of the PM were (number of PM tested/number of different PM types): Biotronik 14/9, ELA 21/8, Guidant 38/14, Intermedics 27/7, Medtronic 77/23, St. Jude Medical 22/12, and Vitatron 4/4. Manufacturers of ICD were (number of ICD tested/number of different ICD types): Biotronik 10/5, Guidant 58/14, Medtronic 71/13, and St. Jude Medical 12/7. None of the following was observed in the PM group: Atrial or ventricular oversensing, loss of capture, pacing in the magnet mode or spontaneous reprogramming of the device. In the ICD group none of the following occurred: Inappropriate tachyarrhythmia detection, temporary deactivation of ICD therapies due to reed switch mechanism, spontaneous reprogramming.
Conclusion: In vivo testing of 203 PM and 151 ICD systems showed no electromagnetic interference with a standard airport metal detector gate. Clinically relevant interactions between airport metal detector gates and implanted pacing devices seem unlikely.

P1524 Effect of atrial pacing site on left and right haemodynamic function during dual-chamber pacing biventricular pacing

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The SAVER study evaluated the influence of the atrial pacing site on the interatrial conduction delay as well as on the ventricular hemodynamic function during synchronous biventricular pacing on HF patients candidates to Cardiac Resynchronization Therapy (CRT). Two atrial sites are compared: low interatrial septum (LIS) and right atrial appendage (RAA). We showed previously that the shortening of the inter-atrial conduction delay observed when pacing at the LIS was not reflected in a higher LV+dP/dt when compared to pacing at the RAA. In this study, we also evaluated the effect of the atrial pacing site on pulse pressure and RV+dP/dt.
Methods: 15 pts 70±7 years, 67% male, 60% ischemic, NYHA 2.5±0.5, LVEF 29±4%, QRS 184±16 ms, LBBB, PR interval 225±53 ms and P-wave 125±20 ms were enrolled in the study. Two atrial leads were placed at the RAA and LIS. The ventricular leads were placed at the right ventricular apex and LV free wall. A DDD protocol consisted of 50 beats in AAI mode with atrial pacing at the RAA followed by 50 beats in BV DDD mode with atrial pacing at the RAA (DDD_RAA) or at the LIS (DDD_LIS) at 4 different AV delays. The acute hemodynamic response was evaluated by LV+dP/dt, aortic pulse pressure (PP) and RV+dP/dt. The optimal AV delay was determined by both LV+dP/dt and PP.
Results: One pt could not be tested due to a limited dissection of the coronary sinus intima and another pt was excluded due to invalid data. 11 pts had the LV lead in the lateral or postero-lateral vein and 2 pts in the antero-lateral vein. The optimal AV delay during DDD_RAA and DDD_LIS pacing was 202±61 ms and 159±45 ms, respectively ($p<0.01$, paired t-test). The average (±se) %LV dP/dt increase with DDD_RAA and DDD_LIS pacing with respect to the baseline in AAI mode at the optimal AV delay was 22.7±4.3% and 19.5±4.3%, respectively ($p<0.01$). The difference in %PP increase during DDD_RAA and DDD_LIS (12.2±2.0 vs 11.5±1.9%) and the difference in RV+dP/dt increase (0.3±5.7 and 3.3±5.0) were not significant.
Conclusions: The results showed similar hemodynamic change in PP and RV+dP/dt with both DDD_RAA and DDD_LIS pacing. While both pacing configurations improve the contractile function, the increase in LV+dP/dt with DDD_RAA was significantly larger than with DDD_LIS, though the clinical impact of this difference may require further evaluation.

P1525 Two years follow-up performance of a unipolar coronary sinus lead for left-ventricular pacing

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Purpose: Left ventricular pacing improves symptoms of patients with advanced heart failure and bundle branch block. New coronary sinus pacing leads have been developed for the transvenous approach. The objective of the study was to assess the long-term follow-up of a coronary sinus lead for cardiac resynchronization therapy.
Methods: The study included 75 patients (61 ± 18 years, male n = 42) with advanced heart failure and bundle branch block who received the unipolar coronary sinus lead model 1055 K (SJM). The lead was implanted in a side branch of the coronary sinus. After lead fixation the lead was connected to a dual-chamber pacemaker (Affinity) for left ventricular pacing in 8 or to a three-chamber pacemaker (Frontier, SJM) for biventricular pacing in 67 patients. The two groups were analyzed separately. Ventricular pacing threshold was measured at 0.4 ms pulse duration. Pacing impedance and R-wave amplitude was determined at each follow-up. Follow-ups visits were in 3-months intervals during the first two years after lead implantation.
Results: After implantation lead dislodgment occurred in 3 patients. There were no lead infection, 4 deaths and 3 lost to follow-up. There were 3 re-operation due to phrenic stimulation in 1 and high pacing thresholds in 2 patients. At implantation, pacing threshold was 1.7 ± 0.5 V for left ventricular and 1.4 ± 0.9 V for biventricular pacing. The left ventricular pacing threshold was 1.9 ± 1.0 V after 6 months, 1.7 ± 0.9 V after 1 year and 1.9 ± 0.7 V after 2 years. Biventricular pacing threshold was 1.5 ± 1.1 V after 6 months, 1.7 ± 0.6 V after 1 year and 1.9 ± 0.5 V after 2 years. Left ventricular pacing impedance was 687 ± 134 ohms after 6 months, 708 ± 113 ohms after 1 year and 671 ± 119 ohms after 2 years and biventricular pacing impedance 378 ± 75 ohms (6 months), 362 ± 56 ohms (1 year) and 335 ± 89 ohms (2 years)($p < 0.05$ for left ventricular vs. biventricular). R-wave amplitude for left ventricular sensing was 13.2 ± 5.3 mV after 6 months, 12.1 ± 7.4 mV after 1 year and 12.8 ± 7.0 mV after 2 years and for biventricular sensing 10.1 ± 4.2 mV after 6 months, 11.8 ± 5.3 mV after 1 year and 10.9 ± 3.2 mV after 2 years.
Conclusions: The unipolar coronary sinus lead provided stable left ventricular pacing thresholds and high R-wave amplitude, which allowed effective long-term cardiac resynchronization therapy. Biventricular pacing compared to left ventricular pacing was associated with lower pacing impedance.

P1526 Efficacy of implantable defibrillator therapy using the lowest effective energy for treatment of spontaneous ventricular tachyarrhythmias: results of the minimum energy output trial

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Purpose: In patients undergoing defibrillator implantation (ICD) the recommendations for appropriate defibrillation safety margins based on several studies handling with submaximal shocks for treating induced and spontaneous ventricular tachyarrhythmias (VTA). The "minimum energy output trial" (MINT-study), a prospective nonrandomized clinical multicenter study, investigated the conversion rate for spontaneous fast VTA as well as spontaneous VTA accelerated by preceding antitachycardia pacing therapies (ATP) with a first shock set at intraoperatively and twice confirmed defibrillation threshold (DFT++).
Methods: 133 pts with a mean age of 62.2±12.1 years, 113 Males, met the inclusion criteria requiring an intraoperative DFT++ of = 15 J on a dual coil defibrillation lead (Kainox-SL electrode; Biotronik). All pts had a class I indication for ICD therapy and an active can ICD-system was implanted requiring a special feature of shock optimization (automatically programming of higher first shock energy for next shock-trial after assessment of failure). The DFT and DFT++ were measured using a modified step-down protocol. The first shock was programmed to the DFT++.
Results: The mean DFT++ for all pts was 10.2±3.7 Joule. During a mean follow up of 24±8.4 month there was a total of 131 shock treated spontaneous arrhythmia episodes with a mean cycles length of 268±44 ms. The first shock conversion probability for all episodes was 90.1% (118/131 episodes) with a 95% confidence interval of (83.5-94.6%). The first shock conversion rate was not significant different between fast VTA and VTA accelerated by preceding ATP (90.8% vs. 87.9%). VTA of failed episodes were successfully converted with subsequent shocks from the same therapy sequence.
Conclusions: The first-shock conversion rate for spontaneous VTA using the DFT++ energy output without safety margin is relatively high and independent from preceding ATP-trials.

P1527 Atrial sensing performance of a recently developed defibrillation lead with a free-floating atrial dipole connected to a single chamber defibrillator with enhanced atrial sensing characteristics

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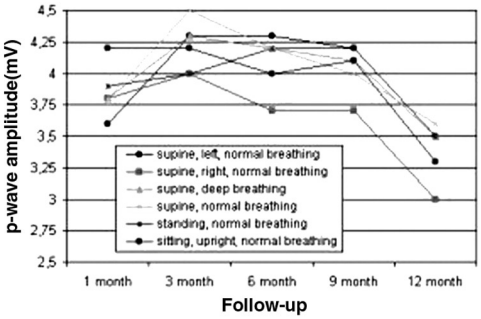
Introduction: Despite the wide use of VDD-leads in pacemaker dependent patients the sequential atrioventricular pacing fails in 40% because of decreased long term atrial sensing performance. First results of an ongoing study with a recently developed VDD-defibrillation lead (Kainox® VDD-lead, Biotronik, Berlin) connected to a dual chamber defibrillator with enhanced (4-times) atrial sensing characteristics (Deikos A+®, Biotronik, Berlin) promise besides the excellent detection quality of ventricular tachyarrhythmias enhanced VDD-pacing characteristics.
Methods: The examined group consisted on 106 patients (62±10 years) with standard ICD-indication. 59 patients completed 6 months, 39 patients 9 months and 39 patients 12 months follow-up. Atrial sensing measurements were performed at 6 different body positions/breathing conditions (supine normal breathing, supine deep breathing, supine left sided, supine right sided, sitting upright normal breathing, standing normal breathing).
Results: The filtered average P-wave amplitude at implant was 4,6±1,7 mV. During the 12 month follow-up no significant change of measured P-waves independent of body position and breathing condition was observed (figure).



Conclusion: The enhanced atrial sensing performance of the new VDD-ICD-system provides stable P-wave detection over a long term period. These findings enable the use of this system as a dual chamber defibrillator in pace-dependent patients and in combination with a coronary sinus lead as a multisite pacing system for heart failure.

P1528 Clinical importance of the initiation pattern of monomorphic ventricular tachycardia

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Introduction: Analysis of the stored electrograms of the implantable cardioverter defibrillators (ICD) allowed to study the initiation patterns (IP) of ventricular tachycardia (VT) onsets. It is not clearly defined whether there is a dependence of the VT onset on the drug or electrical therapy applied for their termination. We aimed to investigate the electrophysiological features of monomorphic VT (MVT) with different IP in patients with ICD and to assess whether there is a relationship of the IP of sustained MVT with clinical characteristics, efficacy of antiarrhythmic and electrical therapy.
Methods: Fifty-five stored IECGs in 22 patients (mean age of 67.4±3.5 years) with MVT were evaluated. Cardiovascular diagnosis included coronary artery disease in 81.9% of the patients. All MVT episodes were classified as those initiating with ventricular premature beats (non sudden onset MVT) and those without ventricular ectopy preceding tachycardia (sudden onset MVT)
Results: Non-sudden onset initiation was the most common pattern of MVT initiation. No distinct differences in the type of the class III antiarrhythmic drug therapy were observed in both patterns of arrhythmias. Other results are presented in the table.
Conclusions: Non-sudden onset MVT was characterized by shorter cycle length(CL), higher rate of different 1 st beat morphology, and required higher shock energy for termination. Sudden onset MVT was precipitated by shortening of sinus CL before tachycardia. It was more common with relatively better preserved systolic function.

Parameters	Sudden Onset MVT (n=20)	Non-sudden Onset MVT (n=35)	p
CL-SR (ms)	792.2±87.1	883.8±94.3	p<0.001
CL-MVT (ms)	383.0±51.9	345.9±46.2	p<0.001
Equal 1 st MVT beat morphology, (%,n)	65.0 (13)	37.1 (13)	p<0.05
LVEF (%)	39.6±4.9	34.8±3.8	p<0.03
Mean shock energy (J)	12.2±2.6	16.2±4.0	p<0.001
Terminated by ATP (%,n)	30.0 (6)	22.9 (8)	ns
Terminated by single shock (%,n)	50.0 (10)	54.3 (19)	ns
Terminated by multiple shocks (%,n)	20.0 (4)	22.9 (8)	ns

MVT: Monomorphic ventricular tachycardia, CL-SR: Cycle length in sinus rhythm, CL-MVT: Cycle length of MVT, ATP: Anti-tachycardia pacing, LVEF: Left ventricular ejection fraction, ns:non significant

P1529 Reducing implantable cardioverter-defibrillator-implantation length including DFT determination by using the upper limit of vulnerability – the TULIP study

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Introduction: Previous studies have shown that the ULV is a reliable predictor of the defibrillation threshold (DFT). The purpose of this study is to validate the intraoperative TULIP test protcol for ICD implantation independent of patient specific conditions.
Methods: 80 pts are to be included in the study in order to show a successful intraoperative TULIP testing with a success rate better than 80%.
At the interim analysis 52 pts (mean age 65±11 years) with a LV ejection fraction of 41±17% were prospectively enrolled. Testing was performed according to a defined protocol. The protocol started at 13J induction energy. When failing the induction, further attempts were done with 11, 9 or 6J shock deliveries. In case of successful induction, an 18, 15, 13 or 9J biphasic shock was delivered to terminate VF. If a 6J shock failed to induce VF, lower energy shocks or other forms of induction were allowed. In this case termination was attempted using a 9J shock. When the termination was succesful the lowest delivered energy terminating VF was confirmed.
Results: 42 pts (81%) with an implanted single or dual chamber ICD (Biotronik) were successfully tested. In 5 pts the first and in 5 pts the confirmation shock failed to terminate VF. The lowest conversion energy was determined at 11,9±3,5 J, requiring only two induced VF episodes. The mean induction energy was 7.2±4.5J. According to the test protocol we assume that the mean average of the ULV is 10J. With reference to published data, the programming of the ICD first shock energy equal to the ULV +5J will lead to a 99% success rate in termination of spontaneous VF. Based on our data the ICD first shock energy would be 15J.
This value is significantly below the ICD first shock energy of 30J as programmed by the widely used function test. By programming a lower ICD first shock a reduction of the charging time up to 50% is possible. Performing the TULIP protocol takes 2,6±2,2min from the first induction attempt to effective induction, representing a clinically well acceptable time for this intraoperative test procedure.
Conclusion: The TULIP test protocol is a highly effective procedure for intraoperative DFT-testing dependent on the ULV. It can be applied clinically during ICD implantations to reduce the programmed first shock energy.

P1530 False negative detections of ventricular arrhythmias in implantable cardioverter-defibrillator

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False negative detections (FND) of ventricular arrhythmias in patients with ICD are usually difficult to reveal based on ICD holter memory.
The aim of this study was to evaluate frequency and reasons of FND of ICDs and consequences of this disturbances.
Study population consisted of 193 patients (pts), (51 F, 141 M) with a mean age of 56±15 years with implanted ICD (234 devices: 229 Biotronik, 5 Medtronic). The mean follow-up was 24±18 months. Intracardiac electrograms registered by the holter memory of ICD were analysed.
Results: In 106 (55%) pts during follow-up occurred 2773 episodes (epi) detected by devices as ventricular tachyarrhythmias and treated. Two thousands forty eight (73.9%) epi were detected appropriately, the remaining 725 (26.1%) epi in 61 pts were recognised inappropriately. FND included no or delayed detection were observed in 59 epi in 14 pts. No serious complication of FND were observed. Six times ICD did not detect slow VT (CL= 430-600 ms). Fifty three times ventricular arrhythmias (51 VT, 2 VF) were delayed. VF detection delay was 18 and 20 s. and was caused by R-wave undersensing. VT detection delay vary from 30 s. to over 27 minutes. To asses the correlation to proarrhythmia in case of delayed VT detection the number of proarrhythmia due to ICD therapy were compare between epi with delayed detection (51 epi), appropriate detection of VT (1541 epi) and epi of false positive detection (caused by SVT - 390 epi). The number of epi with proarrhythmic effect in these groups was 7, 129 and 7 respectively. The frequency of proarrhythmia was 13,5%, 1,8%, 8,3% respectively (p=0,00001).
Conclusions: 1) The most frequent cause of FND is slow VT. 2) FND do not cause any serious consequences for the ICD patients but are associated with higher risk of proarrhythmia.

P1531 Should implantable cardioverter defibrillators rather than permanent pacemakers be used for medically refractory long QT syndrome?

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Background: Although pacemaker (ppm) implantation may reduce the incidence of symptoms in congenital long QT syndrome (LQTS) patients, the long-term benefit remains to be determined. ICD implantation remains a class II, IIb indication (ESC, ACC/AHA/NASPE 2002) in patients (pts) with medically refractory LQTS. We therefore evaluated clinical outcomes in medically refractory LQTS pts who underwent ppm implantation at our institution.
Methods: Patients with LQTS who underwent implantation of ppm for medically refractory LQTS were followed in pacemaker clinic and clinical events were recorded.
Results: 9 pts (2M: 7F) aged 21yrs (1-57yrs) with diagnosed congenital LQTS underwent pacemaker implantation at our institution from 1989 onwards. All patients were paced at a lower rate of at least 70 bpm and beta blockers were standard therapy. Mean followup was 4.9 yrs (0.5-13.5). This therapy failed in a total of 7 (77%) pts. 2 pts (22%) aged 7, 8 yrs died suddenly. These deaths occurred at 6, and 18 mths post device implantation. 3 (33%) pts had sudden cardiac death episodes and 2 (22%) had recurrent syncope. In these 5 patients the ppm was upgraded to an ICD, all but 1 were transvenous. This epicardial ICD developed an epicardial lead fracture and pocket infection and the patient died in the context of recurrent VT storms. 2 of the 5 had tachyarrythmias requiring ICD therapy. In 1 child (age 1 yr) the ICD was removed because of recurrent erosions. 1 pt (57yr) had cardiac perforation requiring surgical drainage at the time of implant. The devices were otherwise well tolerated.
Conclusion: PPM implantation for refractory LQTS is associated with a significant failure rate both in terms of morbidity and mortality. ICD implantation has previously been logistically problematic but with ongoing advances in ICD technology it may merit consideration as first line therapy.

CLINICAL ASPECTS OF DEVICE THERAPY I

P1532 Predictors of low treatment satisfaction in patients with automatic implantable cardioverter defibrillators

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Purpose: A trustful attitude towards an automatic implantable cardioverter defibrillator (AICD) is crucial because the rejection of the device may have fatal consequences. Thus, we aimed to identify predictors of low treatment satisfaction (LTS) in AICD patients.
Methods: Of 178 AICD patients (median 62 yr, IQR 52-69) enrolled into the study, 152 (85%) were male and 26 (15%) female. We measured anxiety, helplessness and depression with standardised instruments and LTS with 11 dichotomous items (range 0-11) concerning a mistrustful attitude, a negative body image and low assessment of the device. A total of 42 (24%) patients were labeled as LTS patients.
Results: In a logistic regression model, the experience of ≥ 5 shocks exhibited a 9-fold risk for LTS (Odds ratio 9.0, 95% CI 3.4-23.8, p=0.001), female gender an OR of 3.8 (95% CI 1.4-10.4, p=0.009), being employed an OR of 3.1 (95% CI 1.3-7.4, p=0.010), anxiety an OR of 4.0 (95% CI 1.4-11.2, p=0.009). Age, educational status and depression were not significant in the multivariate model. Substantially more LTS patients required psychotherapeutic counselling (p=0.015) and more information about living with the AICD (p= 0.01).
Conclusions: Female gender, the experience of ≥ shocks and being currently employed combined with high anxiety levels constitutes high risk for low treatment satisfaction with the AICD. These LTS patients deserve special attention and support for coping to reach higher levels of acceptance. Clinicians may be advised from these data to identify LTS patients and to consider psychotherapeutic counselling or support groups for them.

P1533 Influence of bundle branch block or cardiac disease regarding the results of implantable loop recorder in patients with recurrent syncopes

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Recurrent syncopes remain unexplained in about 30% of cases whereas the prognosis of cardiac syncopes is poor. The implantable loop recorder (ILR) is a useful tool which allows a diagnosis in 50% of cases. We assessed if these results depend on the presence of bundle branch block (BBB) or underlying cardiac disease which exposed patients to paroxysmal atrioventricular block or severe arrhythmias.
ILR was implanted in 42 consecutively patients (66 ± 18 years, 26 males) suffering from reccurent syncopes (n=5.4 ± 4.8). Twenty patients had abnormal resting ECG: rigth BBB n=12, left BBB n=8. Twenty patients had cardiac diseases: coronary artery disease n= 11, arterial hypertension n=8, aortic stenosis n=1). Before the implantation of ILR, all patients previously underwent a 24 hours ambulatory ECG, a tilt test and an electrophysiological study which were normal.
During the follow up (5.9 ± 4.8 months) 18 patients developed a new syncope. IRL was normal in 10 (55%) and demonstrated a cardiac origin in 8 patients (45%): complete atrioventricular block n=2, sinus arrest > 4 secondes n=4, fast atrial fibrillation n=1, non sustained ventricular tachycardia n= 1. The cardiac syncope was not more frequent in the subgroup of patients with BBB (60% versus 53.8%, NS) nor in the subgroup of patients with cardiac diseases (45% versus 40.9%, NS). Six patients (14%)underwent the implantation of a pacemaker: only three of them had BBB on resting ECG. Likewise in the subgroup of patients with cardiac diseases only three patients had paroxysmal bradycardia or tachycardia during syncope.
In conclusion: Non cardiac aetiology is frequent in patients with recurrent syncopes (55%) whatever the clinical profile of patients. When electrophysiological study is normal, ILR is very useful to exclude a cardiac origin in the sugroups of patients with BBB or cardiac diseases thus preventing unnecessary implantations of pace maker in theses patients.

P1534 Evaluation of myocardial damage, neurohormonal activation, inflammation and ventricular dysfunction prior to, and following internal atrial defibrillation

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Purpose: Myocardial injury and neurohormonal activation may occur following transthoracic atrial cardioversion (CV). The aim of this study was to assess whether myocardial damage, neurohormonal activation, left ventricular dysfunction and inflammation occurs following a single internal atrial shock delivered by the atrial defibrillator.
Methods: Ten patients aged 57 $\pm$ 14 years (range 40 to 71) were implanted with either Jewel AF 7250 or Gem III AT implantable atrial defibrillators (IAD) (Medtronic Inc.). for drug refractory symptomatic persistent atrial fibrillation (AF). All patients had maximum defibrillation energy programmed to achieve first shock success. Patients were implanted for $>$ 1 month (mean 35 months; range 1- 54 mo). CK-MB, troponin T, cortisol, catecholamines, C-reactive protein (CRP) and brain natriuretic peptide (BNP) were measured on a control day when patients were in sinus rhythm, 8 hours after spontaneously occurring AF before cardioversion, and 8 hours following successful cardioversion with oral midazolam for sedation.
Results: In all patients CK-MB, troponin T, cortisol, and CRP did not change during AF or following internal cardioversion. BNP levels rose significantly during AF (from a mean basal value of 49 $\pm$ 37 to 168 $\pm$ 198 pg/ml, p = 0.02) then decreased after CV (mean 82 $\pm$ 88 pg/ml, p $<$ 0.001). There were significant increases in serum adrenaline and noradrenaline levels during AF (from 0.4 $\pm$ 0.3 to 0.6 $\pm$ 0.4 nmol/l, p$<$0.01; and from 2.1 $\pm$ 0.5 to 3.1 $\pm$ 1.0 nmol/l, p$<$0.05 respectively), which decreased 8 hours post shock to baseline levels. The increases in BNP and catecholamines were not correlated.
Conclusions: A single internal atrial shock delivered by the atrial defibrillator does not result in myocardial damage, inflammation, or significant adrenocortical secretion 8 hours post shock. Atrial fibrillation resulted in significant sympathetic activation and left ventricular systolic dysfunction, as indicated by elevated catecholamine and BNP levels, that resolved after restoration of sinus rhythm. Thus the atrial ICD is a safe and effective modality of treatment for persistent AF.

P1535 Pacemaker leads infection in young patients

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Transvenous pacing has become widespread in the pediatric population, but related pacemaker lead infection in young patients has rarely been reported. In order to determine prevalence and optimal management of pacemaker lead infection in children and young adults, we reviewed our pacing database including 4476 patients having had pacemaker implantations from 1975-2001. A pacemaker was implanted in 304 patients under the age of 40, 217 of them had congenital heart disease: 108 with structural defect, 109 without (mainly complete AV blocks). Among patients with congenital heart disease, 12 developed a pacemaker lead infection (5.5%, 6 patients with structural defect, 6 without). This incidence was significantly higher than in patients $<$ 40 years at first implantation without congenital heart disease (2.3%) and in $>$ 40 year-old patients (1.2%, p$<$0.001). However, the number of reinterventions at the pulse generator site was higher in patients having had their first implantation before the age of 40. In patients with structural cardiac defect: 2 died after surgical lead extraction and 1 died before the scheduled lead extraction. The 3 remaining patients had successful surgical (1 patient) or percutaneous (2 patients) lead extractions. In patients without structural cardiac defect: successful percutaneous extraction (5/6) or surgical extraction (1/6 with vegetation $>$ 25 mm) was performed. One patient with percutaneous extraction developed chronic cor pulmonale during follow-up. One infection recurred in one patient with structural cardiac defect although complete removal of the pacing material had been performed. Conclusion: The prevalence of pacemaker lead infection is higher in younger patients, perhaps in part due to a higher number of procedures at the pacemaker site than in the general population of patients with a pacemaker. Patients with structural cardiac defect who underwent surgical lead removal were at high risk for death. Patients with percutaneous lead extraction may develop cor pulmonale.

P1536 Effectiveness of systemic antibiotic prophylaxis given at implantation of permanent pacemaker systems

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Purpose: Infections after permanent pacemaker implantation (PPI) remain a serious and potentially life threatening complication with a reported incidence varying from 0.5 to 5.1%. At present there are no available results from controlled studies concerning the impact of antibiotic prophylaxis on the infection rates. The aim of this study was to assess the effectiveness of antibiotic prophylaxis against the infective complications (IC) after PPI.
Methods: Our study included 600 consecutive patients (pts) scheduled for PPI between 1998 and 2001. The aforementioned pts were randomly assigned to either to receive (group A) or not receive (group B) a systemic antibiotic prophylaxis. All procedures were undertaken in the operating room and the skin was assiduously disinfected with povidone iodine. The antibiotic used was Vancomycin given the high resistance of staphylococci to methycillin in our hospital. Vancomycin was administered at a dose of 1gr IV given in one hour infusion 1 hour before PPI and followed by 500 mg at 6, 12 and 18 hours after the procedure. All pts were followed for at least 12 months and the eventual infective complications were recorded. Patients with previous insertion of a temporary pacemaker in an emergency basis out of the operating room and those with creatinine serum levels above 2.0 mg/dL were excluded.
Results: There was a total of 567 pts (282 from group A and 285 from group B) who met the criteria of the study. No clinical and demographic differences were found between the 2 groups. During the follow up period there was a total of 11 IC (i.e: 1.9%), 2 of which in group A pts (i.e: 0.7%) and 9 in group B ones (i.e: 3%, p=0.035). The IC consisted of 9 cases of pacemaker pocket infections and 2 cases of pacemaker lead related endocarditis (both in group B). The time delay from PPI to the infection was 109 $\pm$ 83 days (range from 25 to 300 days). No preexisting disorders likely to predispose to infection were identified. Moreover, no adverse reactions requiring vancomycin discontinuation were recorded.
Conclusions: Our results showed that routine antibiotic prophylaxis given at implantation of permanent pacemaker systems protect against infective complications.

P1537 First description of cardiac troponin elevation after sustained tachycardia and without evidence of acute coronary disease

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Elevations of troponins T and I (TnT and TnI) reflect irreversible myocardial cell necrosis. This usually occurs in acute coronary artery disease (myocardial infarction with or without ST-segment elevation). However, abnormal values have been described in various conditions not related to infarction, like pulmonary embolism, acute heart failure, myocarditis, septic shock, and after therapeutic procedures like electrical cardioversion or ablation. We describe the elevation of TnI after sustained tachycardias (T) which has to our knowledge not been reported before.
In 16 consecutive patients who presented to the emergency department with various types of sustained T. TnI was measured (Abbott Axsym, Illinois, USA). None of the patients had any ECG evidence of an acute coronary event and none had a significant elevation of CK/CK-MB. None had any evidence of reduced renal function. The following types of T (rate 130-190 beats per min.) were encountered: ventricular T (VT), AV-node-reentry T (AVNRT), AV-reentry T (AVRT), tachyarrhythmia with atrial fibrillation or atrial flutter (TAA), and pacemaker mediated T (PMT). The maximum TnI values during the clinical course ranged between 2.7 and 11.5 ng/ml. All patients with TnI elevation and 4/7 of those without underwent coronary angiography. The only significant difference between patients with and without a rise of TnI was the duration of the T (p= 0.025).

Patient characteristics

	n	Age (SD)	CAD	Chest pain	Tachycardia	Duration of T (SD)
TnI $>$ 0.4 ng/ml	9	48 (12)	1/9 (11%)	5/9 (55%)	1 VT, 2 TAA, 4 AVNRT, 1 AVRT, 1 PMT	14 hrs (8)
TnI $<$ 0,5 ng/ml	7	51 (14)	1/7 (14%)	4/7 (57%)	3 TAA, 1 AVRT, 3 AVNRT	2 hrs (3)

CAD=coronary artery disease; SD=standard deviation; chest pain during T

Sustained tachycardia is a hitherto not reported reason for TnI elevation in the absence of acute coronary disease and other conditions known to induce myocardial cell necrosis with subsequent troponin rise. The duration of the tachycardia seems to be related to the extent of myocardial injury. Since chest pain during tachycardia despite normal coronary arteries is a common complaint, risk stratification is likely to be difficult in these patients with an elevated troponin level after sustained tachycardias.

P1538 Is implantable cardioverter-defribrillator prescription sexist?

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Background The TRACE investigators have reported the male (M):female (F) risk ratio of sudden death (SD) in coronary disease (CD) to be 1.3:1.1 Contrary to popular belief, F with CD are not SD low risk. The rate of CD is 2-3:1 in M:F but the published rate of ICD implantation is 4:1. We investigated whether there was discrimination against F at ICD implant by reviewing our large single centre database. All subjects underwent prior coronary angiography. We hypothesised that if discrimination was taking place at implant, then M and F would differ with respect to their risk factors for arrhythmia, subsequent arrhythmic events or survival.
Results 514 implants (406 subjects; 302 with CD) were performed between 08/1986 and 10/2002 (13,904 patient month follow-up). 12% of CD (16% all aetiology) was F. No differences were found between M (n=267) and F (n=35) receiving ICDs in age (65(1) vs 64(2) years), ejection fraction (32(1) v 32(7) %),ECG implant indication (VF/VT or primary prevention-PP) or electrophysiology study result (performed in 64% M and 77% F). Importantly F were no more likely to receive appropriate device therapy or VT-storm on Kaplan-Meier analysis. Interestingly F had significantly fewer diseased arteries and a trend towards improved survival.

	Female	Male	p value
EP study (%VF/VT/not inducuble)	88/6/6	89/0/11	0.68
ECG indication (%VF/VT/PP)	73/24/3	70/25/5	0.55
% appropriate therapy	54	48	0.34
% VT storm	19	20	0.57
% Dead	11	22	0.09
Mean (SEM) no. diseased coronary arteries	2.2 (0.1)	1.6 (0.2)	<0.005

PP-primary prevention

Conclusion The proportion of ICDs implanted in F is low compared with the risk of SD in M:F with CD. No M:F differences were observed at ICD implant in risk factors for SCD or subsequent device therapy. This suggests that bias was taking place prior to referral. The less severe CD observed in F ICDs together with the trend towards lower subsequent F mortality suggests that a sub-group of F with more severe CD was not being referred. The reason for this is unclear.

P1539 Implantable cardioverter-defibrillator in children and young adolescents: potential benefit and complications

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Purpose: Implantable cardioverter-defibrillators (ICD) have developed to first line therapy in patients with life-threatening ventricular arrhythmias. The purpose of this study was to investigate whether children and young adolescents also derive a benefit from ICD therapy as assessed from data stored in the memory of ICDs.
Methods: Between 1989 and 2001, 25 children and young adolescents (median age 15.3 years [9 to 18 years], median size 168 cm [125 to 187 cm], median weight 55 kg [22 to 85 kg]), with congenital heart disease [3x], dilated cardiomyopathy [3x], hypertrophic cardiomyopathy [4x], arrhythmogenic right ventricular cardiomyopathy [4x], long QT syndrome [3x], or idiopathic ventricular tachycardias/fibrillation [4x] received an ICD with extended memory function (storage of electrograms and/or RR intervals from treated episodes). The potential benefit of ICD therapy was estimated as the difference between the overall mortality and the combined endpoint overall mortality and recurrence rate of presumably fatal tachycardias had the device not been implanted. Presumably fatal tachycardias were defined as fast highly symptomatic polymorphic ventricular tachycardias or ventricular fibrillation ($>$ 240 bpm with pre-syncope or syncope).
Results: Two patients died during a mean follow-up of 4.3$\pm$3.3 years. The total mortality rate was 4.2%, 4.2%, and 4.2% after 1, 3, and 5 years of follow up, respectively. The recurrence rate of fast highly symptomatic polymorphic ventricular tachycardias or ventricular fibrillation was 12.5%, 35.9%, and 35.9% after 1, 3, and 5 years, respectively. As a result, the calculated potential benefit of ICD therapy was 12.5%, 34.8%, and 34.8% after 1, 3, and 5 years, respectively (p=0.007). The rate of inappropriate therapy was 28.4%, 38.3%, and 48.6% after 1, 3, and 5 years, respectively.
Conclusions: The outcome of children and young adolescents treated with an implantable cardioverter-defibrillator is excellent. Analysis of stored EGM data suggests that ICD therapy may lead to a survival benefit and prolongation of life in children and young adolescents with the history of life-threatening ventricular arrhythmias or at high risk for a sudden cardiac death. However, ICDs may contribute significant to morbidity mainly due to inappropriate shock delivery and to occasional mortality in children and young adolescents.

P1540 Implantable cardioverter-defibrillator therapy for primary and secondary prevention of sudden death in patients with arrhythmogenic right-ventricular cardiomyopathy/dysplasia

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Background: Arrhythmogenic right ventricular cardiomyopathy/dysplasia is an inherited condition associated with the risk of sudden death.
Methods: We conducted a retrospective multicenter study of the impact of implantable defibrillator therapy on the prevention of sudden death in high risk patients affected with this disease.
Results: The study population consisted of 132 patients (93 males, 39 females, aged 15-72 years, mean 40$\pm$15). In 95 patients (78 percent), indications for defibrillator implant were a history of either cardiac arrest or sustained ventricular tachycardia (secondary-prevention group); the other 37 (22 percent) had one or more risk factors for sudden death in the absence of spontaneous ventricular tachyarrhythmias (primary-prevention group). During a mean follow-up of 39$\pm$25 months, there were 3 deaths due to congestive heart failure, acute endocarditis and ventricular tachycardia "storm", respectively. Sixty-four patients (48 percent) had at least one appropriate defibrillator intervention, although 83 percent of them received concomitant antiarrhythmic therapy. A total of 15 (12 percent) patients had inappropriate interventions and 21 (16 percent) had defibrillator-related complications. Analysis of the stored electrograms showed that 32 patients (24 percent) experienced ventricular fibrillation or flutter which would have been fatal in the absence of the device. The projected sudden death-free survival (i.e. freedom from ventricular fibrillation/flutter) was 72 percent at 36 months as compared with the actual patient survival of 98 percent ($p<0.0001$). The incidence of ventricular fibrillation/flutter was similar in both primary- and secondary-prevention groups (7.0 vs 7.4 percent per year). Patients implanted because of hemodynamically stable ventricular tachycardia had a significantly lower incidence of ventricular fibrillation/flutter (log rank=0.017). Younger age, history of cardiac arrest or hemodynamically unstable ventricular tachycardia, and left ventricular involvement were independent predictors of ventricular fibrillation/flutter.
Conclusions: Defibrillator therapy provided lifesaving protection by effectively terminating life-threatening arrhythmias in high risk patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia who were trated for both primary and secondary prevention of sudden death.

P1541 Single sheath lead extraction

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The center is serving the whole country of Norway for lead extractions, and we have adopted a single sheath technique (originally devised by Dr. Bongiorni, Pisa), which we believe is more effective and gentle than the original double sheath technique.
Material and Methods: We started the service in 1997, and have treated 90 patients per January first 2003, median age 66,5 years (range 7 - 97 years) with 156 electrodes. The last three years we have explanted 36, 34 and 42 leads in 23, 21 and 26 pts. Seventy-four % of the lead extractions are due to infections, the rest are elective extractions. Median age of all leads 7 years, (range 0,1 - 25 years), leads extracted by traction alone median age 1 year (range 0,1 - 9 years) and leads extracted by single sheath technique 10 years (range 0,3 - 25). We most often use a locking wire (Spectranetic or Cook) to secure the lead, and a single Cook sheath mounted with a Cook Pin Vise. The sheath is then gently pushed down the lead with rapid rotation. The single sheath technique was used on 99 (68%) of the leads, traction alone on 33 (23%), iv. "fishing" in 5 (4%), and double sheath technique in (the first) 8 (6%).
Results: For the last three years complete removal has been achieved in 94, 97 and 100%, with a clinical success in 97, 100 and 100%. The median "sheath time" (from the introduction of the sheath to the complete removal of the lead) the last year was 11 minutes, range 1 to 50 minutes. We have seen a marked "learning curve". We have Cook's Electrosurgical Dissection System, but have not needed it so far. Complications: Three patients had a subclavian vein thrombosis, resolved with low molecular heparin and warfarin. One patient had a pericardial bleeding resolved by drainage (after iv. fishing with "Needles eye"). One patient had a fatal tamponade in spite of rapid drainage procedure and thoracotomy, as the lead loosened unintentionally early in the procedure, perforating the right ventricle.
Conclusion: The single sheath technique appears to be effective and gentle, with 100% success for the last 70 patients (including 3 ICD leads). Serious complications in relation to this technique are infrequent.

ATRIAL FIBRILLATION: MECHANISMS AND MANAGEMENT I

P1542 Left atrial volume is a predictor of cardiovascular events in lone atrial fibrillation: a long-term follow-up study

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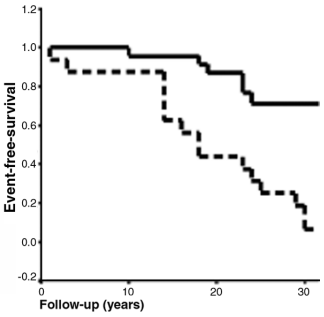
Purpose: To investigate the predictive value of LAV regarding outcome we evaluated a group of patients previously screened to be exclusively lone AF. We sought to evaluate, in these patients without any CV or other life-limiting disease like malignancies, if an enlargement of the LAV was associated with a worse long-term outcome. **Methods:** We retrospectively evaluated the medical records and echocardiography videotapes of an original cohort of 97 patients diagnosed as being lone atrial fibrillation, after a selection from 3623 pts, in the period of 1950-1980. The 38 patients who received at least one echocardiogram during followup were considered and an investigator blindedly assessed off-line LAV indexed for body surface area by using the biplane area-length method. Stroke, myocardial infarction and congestive heart failure were regarded as events. Mean follow-up duration from the onset of AF was 23.5 $\pm$ 8.5 years. Mean age at the end of followup was 75.3 $\pm$ 10.85 years.



Results: The figure shows the Kaplan Meier event-free survival split in two groups for LAV. The dashed line indicates a LAV $>$ 32 ml/m^2, while the solid line indicates LAV $\leq$ 32 ml/m^2. Event-free survival showed a a steeper decline in patients with enlarged LAV (p = 0.0006). A logistic regression with stepwise forward selection showed a trend with age as the only independent predictor of enlarged LAV (p = 0.016), while the duration and type of AF, and clinical risk factors were not significant.
Conclusions: In this highly selected patient population with lone AF, enlarged LAV was associated with a higher incidence of events and the parameters related to AF were not associated with increased LAV. We therefore conclude that LAV independently allows for further risk stratification of patients with AF.

P1543 Antitachycardia pacing for atrial fibrillation in pacemaker patients: a prospective study

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Effectiveness of Antitachycardia pacing (ATP) in patients with paroxysmal atrial fibrillation (AF) is not established. The aim of the study was to analyze the usefulness of ATP in terminating arrhythmic episodes. **Methods:** The population consisted in 35 consecutive patients with class I indication for pacing and documented AF, that received an AT500 (Medtronic Inc). The pacemaker has atrial ATP and electrogram intracavitary (EGM) storage capabilities. The ATP capabilities were enables four months after implant. During three months of follow-up, all recorded episodes of atrial tachyarrhymias (AT) were retrieved and analyzed. Episodes were classified into type I, II or III according to the high, intermediate or low degree of organization, respectively. Efficacy of ATP was established for every episode. Termination was considered "Primary" when it occurs immediately after the ATP and "secondary" AT termination was defined as the arrhythmia termination within 30 s after ATP. The presence of immediate relapse of AF (IRAF) after ATP delivery was also retrieved. **Results:** A total of 1107 recorded episodes were analyzed. There were 561 episodes of type I EGM (50,7%), 453 episodes of type II EGM (40,9%) and 93 episodes (8,4%) of type III EGM organization. ATP was delivered in 93% of episodes, whereas 7% of episodes terminated spontaneously. The global efficacy of ATP was 65%. The efficacy in type I was 68%, in type II 66,8% and in type III 38,4% ($p < 0.01$). From 669 episodes successfully treated with ATP, primary termination occurred in 478 episodes, and secondary termination in191 episodes. IRAF was present in 149 episodes with primary termination (31,2%) and in 138 (72,6%) of episodes with secondary termination ($p<0,01$). In primary termination episodes, IRAF was more frequent in type III (10/17 episodes, 58.8%) and type II (81/194 episodes 41.8%) than type I (58/267 episodes 21.7%) ($p<0,01$).
Conclusion: The organized tachyarrhythmias (type I and II) are the most frequent form of presentation, and ATP was successful in a high percentage of them. The IRAF was less frequent when the episode had primary termination by ATP and a more organized pattern.

P1544 Altered atrial voltage and propagation pattern in patients with idiopathic paroxysmal atrial fibrillation

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Purpose: To evaluate the voltage and propagation pattern on electroanatomic biatrial maps in sinus rhythm, in pts with idiopathic paroxysmal atrial fibrillation (IPAF) as compared to control (C) pts.
Methods: pts with IPAF and no heart disease, nor frequent ectopies triggering the arrhythmia episodes were included in the IPAF group. Pts with similar age, undergoing ablation of a left-sided accessory pathways, no history of atrial arrhythmias and no heart disease were included in the C group. All pts were on stable sinus rhythm and off drugs at the time of evaluation and they signed written informed consent. Electroanatomic mapping (CARTO, Biosense-Webster, Inc) was performed in both atria on sinus rhythm. Analysis of the propagation and of the low voltage areas ($<$0.5 mV) was then performed.
Results: 8 pts (8M, age 40$\pm$11 yrs) and 7 pts (5M, age 37$\pm$11 yrs) were included in the IPAF and C groups, respectively; 110$\pm$18 and 87$\pm$20 sites were acquired in the right (RA) and left (LA), respectively. The average values of the RA propagation, LA propagation, systolic time interval and activation times at the anterior and posterior breakthroughs of interatrial propagation were 15, 27, 30, 33 and 25%, respectively, longer in the IPAF as compared to the C group. A marked prolongation (mean value + 2 standard deviations) of the RA, LA and anterior interatrial propagation was observed in 3, 4 and 4 IPAF pts, respectively. No altered propagation pattern was found in the C group. In the IPAF group, areas of low voltage were found in the sinus node zone (3 pts), posterolateral RA (5 pts), septum (2 pts), anterior LA (1 pt), around the pulmonary veinoses (6 pts) or diffusely in both the RA and LA (1 pt). Conversely, in the C group small areas of low voltage were found only around the right pulmonary veins in 5 pts.
Conclusions: Electroanatomic mapping identifies an altered voltage and propagation pattern in a subset of patients with IPAF as compared to C patients. The altered pattern may be observed both in the RA and LA; the pattern of interatrial propagation may also be delayed.

P1545 Clinical value of echocardiographic markers for the prediction of sinus rhythm maintenance at 30-day and 1-year follow-up in patients with non-valvular atrial fibrillation

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Background: Atrial Fibrillation (AF) is the most common sustained arrhythmia and is associated with a high risk of thromboembolic complications. Both clinical and echocardiographic markers have been related to embolic risk in these patients. However, there are little data related to the echocardiographic parameters which may be related to long-term maintenance of sinus rhythm (SR).
Aims: To determine echocardiographic parameters related to short and long-term maintenance of SR in non-valvular AF patients.
Methods and Results: We prospectively studied 131 patients with non-valvular AF (80 with paroxysmal and 51 with chronic AF) who were not receiving antithrombotic therapy at admission. Transthoracic and transesophageal echocardiography (TEE) were performed during the first 24 hours of admission. Mean age of the group was 67 $\pm$ 13 years old, 70 males. Forty-six percent of the patients were $>$ 70 years old, 59% were hypertensives, 15% diabetics and 34% had an associated cardiomyophaty. TEE showed 54% of the patients with an enlarged left atrium (LA $>$45 mm), 52% with LA echo contrast and/or thrombus, and 15% with systolic left ventricular (LV) dysfunction. At the 30-day follow-up, 58% of the patients were in SR (85% of paroxysmal AF) and 46% at 1 year (63% of paroxysmal AF). Univariate predictors of SR at 30-day and 1-year follow-up were age, LA diameter, left atrial appendage (LAA) fractional shortening (by planimetry) and LV systolic and diastolic function. On multivariate logistic regression analysis the echocardiographic predictors of maintenance of sinus rhythm at the 30-day follow-up were LA size $<$ 45 mm (OR = 4.1, 95% CI = 1.83-9.9), LV diastolic dimension $<$56 mm (OR = 6.1, CI=1.9-23.2), LAA peak emptying velocity $>$40 cm/s (OR = 4.3, 95% CI = 1.7-12.9), LAA fractional shortening (OR=1.024, 95% CI = 1.0-1.04) and isovolumic relaxation time (OR = 1.005, CI = 1.0-1.01). At 1-year follow-up, the predictors of SR were LA size $<$ 45 mm (OR = 3.3, 95% CI = 1.23-9.2), LV diastolic dimension $<$56 mm (OR = 12.8, 95% CI = 2.5-114.4), LAA shortening (OR = 1.028, 95% CI = 1.0-1.05) and isovolumic relaxation time (OR = 1.008, 95% CI = 1.0-1.01).
Conclusions: The echocardiographic parameters predicting SR maintenance are similar during the short and long term follow-up. Both normal LA and LAA size and function and LV diastolic and systolic function identify patients with a higher probability to maintain sinus rhythm. These findings are important to guide treatment in patients with non-valvular AF.

P1546 Can mechanical function of the left atrial appendage in patients with persistent non-valvular atrial fibrillation predict early recurrence after successful biphasic waveform cardioversion?

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Introduction: After successful cardioversion different pathogenetic factors are involved in early recurrence of atrial fibrillation (AF). The purpose of this study was to assess whether mechanical function of the left atrial appendage (LAA) is valuable to predict early recurrence of new-onset AF after a successful biphasic waveform cardioversion.
Methods: In this study were enrolled 62 patients (age 55-86 years, 42% female) with a first episode of persistent non-valvular AF (time from onset >72 hours) treated with successful electrical cardioversion. After onset, oral anticoagulation treatment was performed for at least 30 days. All patients were subjected to transesophageal echocardiography; LAA filling and emptying flow velocities were assessed and LAA maximal and minimal areas were measured. Electrical cardioversion was performed and conversion to sinus rhythm was obtained with biphasic waveform shocks. After 7 day follow-up, ECG evidenced incidence of AF recurrence and PW-Doppler transthoracic echocardiography evaluated "A wave" flow velocity. For statistical analysis, t-Student test, logistic univariate analysis and univariate regression analysis were performed.
Results: After electrical conversion to sinus rhythm, in 25 patients (40% of total, 36% female) AF recurrence was evidenced at follow-up. In these subjects lower LAA filling (25.3 vs 46.4 p=0.003) and emptying (21.4 vs 45.1 p=0.015) mean flow velocity were evaluated before cardioversion and similarly LAA per cent emptying fraction was reduced (20.4% vs 36.5% p=0.015). In univariate logistic regression LAA emptying flow velocity <30 cm/second (odds ratio 3.86 CI95% 1.25 - 11.92 p=0.0131) and LAA filling flow velocity <30 cm/second (odds ratio 3.27 CI95% 1.09 - 9.78 p=0.0271) were related with lower incidence of sinus rhythm after 7 days, especially when combined (odds ratio 6.00 CI95% 1.38 - 26.10 p=0.0086 specificity 91% sensitivity 36%). Furthermore, in patients with AF recurrence arrhythmia duration was superior (75 vs 48 days p=0.034), while in patients with persistent sinus rhythm at follow-up, "A wave" flow velocity was related with duration of AF (R=0.361 p=0.040). No association with age, antiarrhythmic drugs, sex or the number and energy of biphasic waveform shocks was evidenced.
Conclusion: Our data indicate that in patients with persistent non-valvular atrial fibrillation, the mechanical dysfunction of the left atrial appendage may predict early recurrence of atrial fibrillation after successful biphasic waveform cardioversion.

P1547 Warfarin utilization following implantation of a pacemaker with advanced atrial arrhythmia detection features

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Purpose: To assess the impact of advanced atrial fibrillation (AF) diagnostic data contained in pacemakers on the utilization of warfarin anticoagulation in patients with AF and risk factors for stroke.
Methods: The Vitatron Selection AFm Registry, a multi-center, prospective data set of patients with a Class I or II indication for pacing with either known or suspected paroxysmal AF, was queried for patients not on warfarin anticoagulation at the time of pacemaker implantation and with at least one risk factor for stroke. All patients received the Vitatron Selection AFm pacemaker, a device with advanced atrial arrhythmia recording features. AF burden, defined as the mean amount of time spent in AF during follow-up, was assessed in patients with 6 months of clinical follow-up data.
Results: Data on 118 patients (mean age 78 ± 9 years; 56 men and 62 women) were identified. AF burden was divided into 3 groups and the mean AF burden quantified per group (table). Of the 77/118 (65%) patients with AF detected, only 12/77 (16%) were started on warfarin. All 12 of these patients had known paroxysmal AF at enrollment. High AF burden (>20%; mean burden 53%) as determined by pacemaker diagnostics was more likely to result in warfarin initiation (6/12 patients; 50%) whereas low or no AF burden did not prompt warfarin therapy. Intermediate amounts of AF burden (<20%; mean burden 7%) were associated with some warfarin initiations (6/65 patients; 9%).

AF Burden

AF Burden Group	0% (mean AF)	<20% (mean AF)	>/- 20% (mean AF)
Overall (n = 118)	41 (0%)	65 (2.2 ± 4.3%)	12 (51.3 ± 25.3%)
Known AF (n = 84)	26 (0%)	47 (2.5 ± 4.6%)	11 (54.1 ± 24.6%)
Suspected AF (n = 34)	15 (0%)	18 (1.4 ± 3.5%)	1 (20.3%)

Conclusions: The quantification of AF burden by a pacemaker with advanced atrial arrhythmia recording features appears to have an impact on the decision to initiate warfarin therapy. The definition of a significant AF burden level and it's relationship to stroke risk and clinical decision making warrant further investigation.

P1548 Usefulness of ibutitilide in combination with propafenone for the conversion of atrial fibrillation

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Purpose: To examine the safety and efficacy of ibutilide in combination with propafenone for both converting symptomatic paroxysmal (PAF) and chronic atrial fibrillation (CAF), and maintaining normal sinus rhythm (SR).
Methods: The study included 148 consecutive patients (aged 60.6 ± 15.2 years) without left ventricular dysfunction. For PAF (n=106), patients should have nonself-terminating arrhythmia episodes of < 36 hours duration, and for CAF (n=42), patients should have sustained arrhythmia of < 6 months duration. For patients with PAF (17.5 ± 9.4 hours) propafenone was given as an oral loading dose of 600 mg, and if SR was not restored within 6 hours, a second single dose of 150 mg was repeated before ibutilide administration. Patients with CAF (50 ± 45.3 days) were under continuous therapy with oral propafenone 450 mg daily. In both groups ibutilide was infused at two doses of 1 mg over 10-min, 10 minutes apart. Arrhythmias and heart rate variability indexes to assess the patterns of ventricular rate (standard deviation of RR intervals, SDRR and root mean square of successive differences, RMSSD) were determined by 24-hour Holter monitor applied before ibutilide.
Results: Propafenone was successful in 74 patients (69.8%) with PAF. A total of 74 patients received ibutilide, 32 patients with PAF and 42 patients with CAF. Ibutilide restored SR in a total of 46 patients (62.1%), in 19 patients (59.3%) with PAF and in 27 patients (64.3%) with CAF (p=NS). Electrical cardioversion successfully converted 25 of 28 patients (92.8%) in whom ibutilide failed. Overall, 69 of the 74 ibutilide treated patients (97%) preserved SR during the in-hospital stay. Ibutilide resulted in a further prolongation of QT and QTc intervals ($p<0.0001$), and increase in SDNN and RMSSD values ($p<0.05$). Converters with ibutilide had decreased QT intervals, and reduced SDNN and RMSSD values, compared with nonconverters ($p<0.05$). There were 1 episode of non-sustained torsade de pointes (1.3%), 2 episodes of ventricular tachycardia runs and 4 episodes of transient benign atrioventricular disturbances.
Conclusions: The concomitant use of ibutilide in patients receiving propafenone therapy is a safe and practical approach to fast restore and maintain SR for selected patients with both PAF and CAF.

P1549 Indirect markers of atrial stretching in patients with paroxistic atrial fibrillation

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Purpose: Haemodinamics parameters in patients (pts) with drug resistant paroxistic atrial fibrillation (pAF) have not been completely investigated. Global myocardial index (GMI) is a sensitive echocardiographic indicator of overall cardiac function and has been significantly related to left ventricular filling pressure. We hypothesized that GMI and other indicators of atrial dilatation were significantly different in patients with pAF compared to normal patients.
Methods: 33 consecutive pts without structural heart disease, aged 52 ± 10 years (19 males) with pAF, referred to electrophysiological study were compared with 29 control pts aged 46 ± 12 years (16 males) witch underwent ablation for junctional tachycardias. The following parameters were assessed in all pts: P-wave duration (Pd), GMI, left atrial dimension (LAd), surface (LAs), and ejection fraction (LA EF); interatrial conduction time (ia-CT) between high right atrium and the distal part of coronary sinus.
Results: there was no difference between the 2 groups concerning Pd (p=0.06), and LA EF (p=0.08) while LAd (p=0.028), LAs was founded increased in pAF pts (20.3 ± 4.5 cm^2 vs 16.3 ± 2.1 cm^2, p=0.01); GMI was significantly higher in pAF pts (0.5 ± 0.17 vs 0.36 ± 0.06, p= 0.0001); average value of ia-CT in pts pAF was 70.6 ± 24 ms, significantly higher than in control group (53 ± 14 ms, p= 0.0001).
Conclusions: LAd, LAs, GMI and ia-CT is significantly increased in pts pAF. Although apparently without structural heart disease, the pts with pAF presented evidence of increased filling pressions in left ventricle and indirect markers of atrial stretching. The role of increased intra-atrial pressure in pts pFA and the predictive value of these parameters need to be evaluated in a larger number of pts.

P1550 Atrial fibrillation of unknown duration: characteristics and outcome after electrical cardioversion

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There is a numerous group of patients with persistent atrial fibrillation who are referred to cardiological evaluation in which we can not fix the duration of the present episode.
We carried out a randomized, prospective study of a population of 268 patients with persistent atrial fibrillation who were submitted to our clinic. They were divided in three groups in the basis of atrial fibrillation duration: Group I duration <3 months (n=70); Group II <1 year (n=68); Group III unknown duration (n=130). Each patient was randomly assigned to receive treatment before cardioversion with Amiodarone or Amiodarone plus Irbesartan (150 mg or 300 mg) and 4 weeks later electrical cardioversion scheduled.
93 patients (34.7%) recovered sinus rhythm after anticoagulation and treatment with antiarrhythmics drugs. We performed scheduled electrical cardioversion in 178 patients with a respective efficiency of 93%,92% and 96%. There were no statistically significant differences in the groups composition about demographics, clinical, ECG nor left atrium size. Event-free survival (AF recurrence) was compared with use of Kaplan-Meier curves, and the results at 2 months were 81% in group I, 75.8% in group II and 75.6% in group III (p value =ns). At 12 months, survival was 80%,70.9% and 69.5% respectively (p=ns).
After using logistic regression analysis, we noticed how treatment with Irbesartan reduced in a significant way the recurrences of AF at 2(p=0.004) and 12 months (p=0.02) in the three groups of duration studied.
Conclusions: 1.Patients with persistent atrial fibrillation of unknown duration share most of the clinical features with patients of known duration 2. Preventive treatment with Irbesartan reduces recurrences independently of the duration atrial fibrillation.

P1551 Transthoracic two-dimensional echocardiographic features of inferior isthmus: the thickness of the vestibule predicts the complexity of ablation procedure in patients with atrial flutter

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Linear ablation of the inferior cavo-tricuspid isthmus (CTI) combined with confirmation of bi-directional isthmus conduction block has proved to be curative for typical atrial flutter (AF). An increased myocardial thickness may influence for conduction persistence at the ablation areas and for fluoroscopic and procedure time. The present study was designed to investigate the anatomy and wall thickness of the CTI by means of 2D echocardiographic (2D-echo) exam and its potential contribution for radiofrequency (RF) ablation of patients with AF.
Methods: A transthoracic 2D-echo exam implemented with tissue harmonic imaging was performed in 16 patients (12 men; 67.6±10 years) who underwent successful bi-directional isthmus ablation for common AF. A 8 mm tip ablation catheter was used and right atrial angiography was performed during the procedure in all patients. The echographic visualization of the CTI and their elements were obtained by means of a modified apical and posterior view from the conventional 4-chambers apical view. Echographic findings were compared with those obtained from the angiographic display of the right atrium and CTI. A cut value of 20 minutes of RF-ablation time to achieve bi-directional isthmus block divided simple and complex procedures. Anatomical variables of simple and complex groups were compared
Results: Transtoracic 2D-echo exam enabled us to visualized and distinguished the two components of the CTI: the posterior recess and the vestibule of the tricuspid valve (TV). We found a significant correlation between echographic and angiographic linear measurements of the CTI (r: 0.92; p<0.0001). A novel 2D-echo feature, the wall thickness of the TV vestibule, disclosed a greater value in the complex group (13.6±1.9 vs. 10.0±2.3; p=0.01). Vestibular thickness equal or greater than 11.5 mm predicted complex procedure with a sensitivity of 83.3% and a specificity of 80%.
Conclusions: a) Transtoracic 2D-Echo is a feasible non-invasive approach to study the morphology of the inferior CTI; b) A novel 2D-Echo feature, the thickness of the TV vestibule, predicts the complexity of the ablation procedure.

HEART RATE VARIABILTY AND MAPPING TECHNIQUES I

P1552 Heart rate harmony-based frequency analysis is superior to standard frequency analysis

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Introduction: Heart Rate Harmony (HRH) is a novel signal processing algorithm which is more sensitive in the detection of periodic elements if the analysed signal is characterised by a 1/f behaviour (as many biological signals e.g. human heart beat do). Therefore, the aim of this study was to test the hypothesis that high and low frequency components (HF and LF) assessed by HRH would predict mortality better than HF and LF assessed by standard frequency analysis.
Methods: This study enrolled 1,455 consecutive patients with recent myocardial infarction and presenting with sinus rhythm. During mean follow-up of 22 months (minimum 12 months), 70 patients died. Holter tapes were recorded in the second week after index infarction. High frequency (HF) and low frequency (LF) were calculated by HRH and by standard frequency analysis.
Results: With both methods, HF and LF were significantly associated with mortality. In multivariate cox regression analysis (adjusted for age, history of previous myocardial infarction, diabetes mellitus, mean heart rate, heart rate variability index, arrhythmia count, LVEF), HRH-based measures of HF and LF were superior to the standard measures of HF and LF (table)

Multivariate Analysis

	Relative Risk	p-value
HF (Standard)		n.s.
LF (Standard)		n.s.
HF (HRH)	2.8 (1.1-6.3)	<0.05
LF (HRH)	2.7 (1.1-7.0)	<0.05

LF=Low Frequency; HF=High Frequency; HRH=Heart Rate Harmony

Conclusion: In post-infarction patients, HRH-based frequency analysis is superior to standard frequency analysis.

P1553 Depolarisation and repolarisation heterogeneity in arrhythmogenic right-ventricular cardiomyopathy

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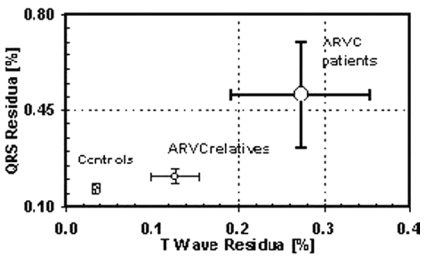
Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) leads to abnormalities of both conduction and refractoriness. We studied heterogeneity of ventricular depolarisation and repolarisation in patients (pts) and relatives of pts with ARVC by measuring the non-dipolar components (i.e. components not due to projections of the heart vector) of the QRS and T wave (QRS and T wave residua, QRSR, TWR) of 12-lead ECGs.
Methods: 10 consecutive digital 12-lead ECGs (500 Hz, MAC 5000, GE Marquette) were recorded in each of 16 symptomatic ARVC pts (12 men, 45±13 years), 27 asymptomatic first-degree relatives of ARVC pts with normal 12-lead ECGs (8 men, age 32±14 years), and in 27 age- and sex-matched healthy controls. QRSR and TWR were measured using singular value decomposition and expressed as proportion [%] of the whole QRS and T wave energy (i.e. dipolar + non-dipolar components).
Results: (mean±SEM): TWR were significantly increased (signifying increased repolarisation heterogeneity) in ARVC relatives compared to controls and were further significantly increased in ARVC pts (0.27±0.09, 0.13±0.03, 0.03±0.005% in pts, relatives and controls, respectively, p=0.0009, ANOVA). QRSR were significantly higher (i.e. depolarisation heterogeneity was increased) in pts compared to relatives and controls, but did not differ significantly between relatives and controls (0.51±0.19%, 0.21±0.02%, 0.17±0.02%, p=0.013).



Conclusions: Heterogeneity of depolarisation and repolarisation is increased in symptomatic pts with ARVC. Heterogeneity of repolarisation rather than depolarisation is likely to be increased among asymptomatic relatives of ARVC pts (i.e. possible carriers of latent gene mutations).

P1554 Heart rate turbulence slope: its relation to conventional autonomic markers and left-ventricular function in patients with dilated cardiomyopathy

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Background: Noninvasive risk stratification by means of autonomic markers in pts with non-ischemic dilated cardiomyopathy (DCM) is controversial. Heart rate turbulence (HRT), a recently introduced autonomic marker, is based on fluctuations of sinus cycle lengths following a ventricular premature beat (VPB) as assessed from 24-hour Holter recordings. It has been demonstrated that HRT is baroreflex-mediated. Its correlation to more conventional autonomic markers such as heart rate variability (HRV – a marker of autonomic tone) and baroreflex sensitivity (BRS – a marker of vagal reflex activity) has not been examined in pts with DCM.
Methods: Noninvasive risk assessment was done in 114 consecutive pts with DCM and symptomatic heart failure (age 56±12 years; 76% males; LVEV 28±11%; β-blocker therapy in 69%; ICD therapy in 23%) including baroreflex sensitivity (BRS; phenylephrine method), heart rate variability (HRV; SDNN from 24 hour recordings), and HRT. Left ventricular ejection fraction (LVEF) was determined echocardiographically. For further analysis, only pts with VPB during Holter recording were considered.
Results: HRT was assessd in 86 pts. HRT onset showed a weak correlation to mean heart rate but to none of the other risk markers. In contrast, HRT slope showed a significant correlation to all autonomic markers, in particular to BRS ($r=0.45$, $p<0.001$), as well as to LVEF ($r=0.31$;$p<0.05$).
Conclusion: HRT can be measured in 75% of pts with DCM and symptomatic heart failure. This methodological study demonstrates a significant correlation between HRT slope, BRS, and HRV in pts with DCM. Similar to HRV, HRT correlates well with LV-function. Whether the predictive value of HRT is superior to that of conventional autonomic risk markers, needs to be evaluated prospectively.

P1555 Thyroid hormones direct regulate the sinoatrial node function in the thyrotoxic subjects

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Clinical signs of thyrotoxicosis are similar with those of hyperadrenergic state. The aim of the study was to assess the contributions of both components of the sympathetic system: beta-adrenergic receptor density and plasma concentration of catecholamines and thyroid hormones in the regulation of the heart rate in the patients with thyrotoxicosis.
Material and Method: The study was performed in 24 patients (18 women and 6 men, mean age 49 ± 13 years) with thyrotoxicosis (17 cases due to Graves' disease, 5 cases due to toxic goitre 2 due to complication of amiodarone treatment) and 30 healthy individuals matched for age, sex. beta-adrenergic receptor density was assessed using 131iodocyjanopindolol. Plasma concentration of catecholamines was assessed by radioenzymatic assay. Holter monitoring was performed.
Results are shown as means ± SD in the table:

	TSH	fT3	fT4	b-adrenergic receptors	total catecholamines
	mIU/l	pg/ml	ng%	fmol/mg	pmol/ml
Patients	0,16 ± 0,1	10,2 ± 6,1	3,7 ± 1,6	37,3 ± 21,7	1,5 ± 0,89
Controls	2,5 ± 0,76			37,2 ± 18,1	1,9 ± 0,73

The maximum, minimum and mean heart rate was significantly greater in the patients with thyrotoxicosis then in the control subjects. No significant differences in beta-adrenergic receptor density between the groups were shown, but plasma concentration of catecholamines was significantly lower in the thyrotoxic patients than in the control group ($p<0,05$). There was no correlation between density of the beta-adrenergic receptor and minimal heart rate in thyrotoxic subjects, the negative correlation between plasma concentration of catecholamines and serum concentration of free triiodothyronine ($r= -0,38$, $p<0,05$), the negative correlation between minimal heart rate and plasma concentration of catecholamines ($r= -0,49$, $p<0,05$), high positive correlation between minimal heart rate and concentration of free triiodothyronine ($r= 0,79$, $p<0,01$)
Conclusions: 1. The plasma concentrations of catecholamines is decreased and beta-adrenergic receptor density is in the normal range in the patients with thyrotoxicosis. 2. Studies on correlation between minimal heart rate and serum concentration of thyroid hormones indicate on direct influence of thyroid hormones on sinoatrial node in regulating the heart rate.

P1556 Can we use heart rate turbulence for risk stratification equally in men and women?

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Purpose: A reduction of postextrasystolic acceleration of the heart rate (heart rate turbulence, HRT) is associated with an increased mortality in patients suffering from coronary artery disease. Physiological properties of this acceleration and the influence of gender and age on HRT have not been evaluated yet.
Methods: In 43 women and 52 men, all healthy individuals, HRT parameters onset (TO) and slope (TS) were calculated per analysis of 24 hour Holter ECGs (sampling rate: 1024 Hz). Furthermore, the exact block number (ranging from #1 to#16) in which the maximum increase of heart rate after ventricular premature contracture (VPC) occurs was analyzed. The gender specific differences of TO and TS were compared using a simple, linear, weighted regression model. Using a multiple linear regression model we analyzed the influence of age on HRT.
Results: The median of the maximum acceleration of heart rate after VPC is present in block #5. In 13 persons the maximum slope occurred in the last three blocks, i.e. blocks #14, #15, and #16. Men and women showed no significant difference in the timing of maximum postextrasystolic acceleration. We evaluated that TO decreases as basic heart rate increases ($p<0.01$). No gender related difference was found. On the contrary, analysis of TS displayed an interesting dissimilarity: in men, TS decreased as basic heart rate increases. Whereas, basic heart rate was not able to influence TS in women at all. This difference in women and men proved to be highly significant ($p<0.003$). A multiple, linear regression model negates any influence of age on TS and TO in men.
Conclusion: Physiological acceleration of the heart rate after ventricular premature complex occurs among more than 75% of our healthy individuals within the first 7 blocks. An increased preceding heart rate affects heart rate turbulence in men. On the contrary, turbulence slope in women could not be influenced by basic heart rate. Age has no effect on HRT in men. These results emphasize to be conscious about physiological properties of HRT when using heart rate turbulence for risk stratification.

P1557 Ventricular arrhythmia, Cheyne-Stokes respiration and death: observations from implantable cardioverter-defribrillator patients

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Background and Methods: Cheyne-Stokes respiration (CSR) is an independent marker of death in heart failure. It has been proposed that the mechanism behind this is nocturnal hypoxaemia related ventricular arrhythmia. No previous study has investigated this. We prospectively investigated patients with documented serious, life threatening ventricular arrhythmia being fitted with a cardiac defibrillator (ICD). All patients were studied at baseline for CSR during sleep. Arrhythmia requiring device therapy (defibrillation or anti-tachycardia pacing) was used as a surrogate marker for sudden cardiac death.
Results: 63 subjects (32 with CSR-51%) were followed for a total of 346 months. Mean (SD) age was 68 (9) years with an ejection fraction-EF of 35 (14) % and a NYHA class of 2.2 (0.8). Subjects with and without CSR were matched for age and EF. CSR subjects had greater symptoms (NYHA). 250 episodes of serious ventricular arrhythmia requiring ICD therapy were observed in 17 subjects. The rate and likelihood of device therapy was not increased in subjects with CSR. Only 18/250 (7%) device therapies occurred between 00:00-08:00. Expressed as the average % of all individual events, CSR vs non-CSR (respectively 4.2 (3.5)% vs 6.2 (4.4)%; p=0.79) did not increase nocturnal therapies.

Results Table

	CSR	No CSR	p value
Age-years	66 (2)	69 (2)	0.27
EF %	32 (2)	37 (3)	0.07
NYHA class	2.5 (0.1)	1.9 (0.2)	0.01
Proportion with an ICD therapy	7/32	10/31	0.35
Therapies/patient/month	1.1 (0.8)	2.4 (1.5)	0.32
Number 4% dips in overnight SaO2/hour	27 (4)	7 (1)	0.001
Average minimum SaO2%	79 (3)	88 (2)	0.01
% of night with SaO2 <90%	15 (5)	2 (1)	0.001

Values are means (SED)

Conclusion: We have clearly shown that there is no evidence that CSR leads to ventricular arrhythmia (and therefore death) via the proposed mechanism of apnoea related hypoxaemia.

P1558 Independent predictive accuracy of classical electrocardiographic criteria in the diagnosis of paroxysmal junctional tachycardias in patients without preexcitation

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In patients (Pt) without preexcitation, the differential diagnosis of paroxysmal junctional tachycardias mainly consists of atrioventricular nodal reentry tachycardias (AVNRT) and orthodromic reciprocating tachycardias (ORT) through a concealed accessory pathway. We assessed the independent accuracy of classical electrocardiographic (ECG) criteria in that diagnosis.
We included 203 consecutive Pt (mean age: 45.7±18 yrs; 130 females, 73 males) who underwent an electrophysiologic (EP) study for paroxysmal, regular, narrow-QRS complex tachycardias without preexcitation. Atrial tachycardias were excluded. The ECG recordings during tachycardia were reviewed in a blinded fashion for the presence of the following criteria: a) pseudo r' deflection in V1, b) P wave separate from the QRS complex, c) QRS alternans, and d) ST segment depression and/or T wave inversion.
Results: EP study demonstrates AVNRT in 131 Pt and ORT in 72 Pt. The prevalence of each ECG criterion for AVNRT Pt was: 41%, 24%, 12%, and 38%, respectively. Similarly, these prevalences for ORT Pt were: 4%, 64%, 25%, and 55%, respectively. The presence of pseudo r' deflection in V1 (adjusted OR: 15, Wald Chi-square: 18; p=0.0001), a P wave separate from the QRS (adjusted OR: 0.21; Wald Chi-square: 20.3; p= 0.0001) and QRS alternans (adjusted OR: 0.31; Wald Chi-square: 5.8; p=0.0158) were selected by stepwise multiple logistic regression analysis as independent significant predictors for the diagnosis of AVNRT (versus ORT). Sensitivity and specificity of the logistic model for the detection of AVNRT were 80% and 72.2%, respectively (overall correct classification rate: 78%).
Conclusions: In Pt without preexcitation, nearly 20% of paroxysmal junctional tachycardias may be incorrectly classified on the basis of a multivariate analysis of classical ECG criteria. The presence of repolarization changes during tachycardia do not maintain significant independent predictive power for the differential diagnosis of the tachycardia mechanism in these Pt.

P1559 Characterization of the excitable gap in typical atrial flutter

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Introduction: Previous studies have shown that typical atrial flutter (AFL) is due to a large right atrial (RA) reentry circuit with anatomic and functional components. Slow conduction has been described by some authors at the low RA isthmus (IS), but the properties of other parts of the circuit are not well known.
Objective: To characterize the excitable gap in AFL by observing changes in conduction throughout the circuit, induced by conduction delays in the IS due to radiofrequency application before AFL interruption.
Patients: 24 patients aged 49-81 y, with typical AFL (21 counterclockwise, 3 clockwise). Cardiac disease in 12 (6 coronary, 4 cardiomyopathy, 1 corrected congenital disease, 1 valvular). Three patients were on class IC antiarrhythmic drugs for previous atrial fibrillation, and 1 on sotalol for ventricular tachycardia.
Methods: Conduction throughout the circuit was recorded basely and during radiofrequency ablation just before the last radiofrequency pulse that interrupted the flutter, by means of a multipolar catheter covering septal, superior and anterior RA with 8-10 bipolar recordings (2 mm separation). The increase in IS conduction time (interval between both low septal and low anterior RA electrograms) was compared to the increase in AFL cycle length (CL).
Results: Eleven patients had no increase in IS conduction time before flutter interruption while in the remaining thirteen patients, the increase in IS conduction was 19-67 ms (mean 36±15 ms). In 7 of these cases IS conduction change was similar to the AFL CL change; in the other 6 cases, all with counterclockwise AFL, the increase in IS conduction time was a mean of 40 ms (19-44 ms) longer than the mean of AFL CL increase (12 ms, range 0-35 ms) due to shortening of conduction through other parts of the AFL circuit. One of these patients had undergone repeated valvular surgery, 2 had coronary disease with mild left ventricular dysfunction, 1 with a dilated cardiomyopathy, and 2 was on class Ic antiarrhythmic drugs.
Conclusions: This small series suggests that rate dependent slow conduction may be present in typical AFL outside the IS in patients with organic heart disease or in the presence of class I antiarrhythmic drugs.

P1560 The application of mental stress to detect impaired myocardial repolarization reserve

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Background: Silent gene carriers of the long QT-syndromes (LQTS) and patients with acquired myocardial repolarization reserve impairement (RRI) often present little or no QT prolongation at baseline. The application of mental stress to induce neurohormonal responses may help to identify affected individuals.
Methods: 31 patients (mean age 74±9 yrs,18 males) went through a simple verbal mental arithmetic (MA). Subjects were asked for serial subtractions for 3 minutes, while an auditory stimulus was used for distraction. ECGs were recorded at baseline and at he end. QT intervals were measured in lead V3 using a digitising board and computer. The Bazett (QTc) and Sagie (QTLc=QT+0.154[1-RR]) methods were used to adjust the QT interval for heart rate.
Results: MA elicited a significant increase in heart rate (HR) and blood pressure (BP), and a significant decrease of the uncorrected QT interval duration. The mean QTc and QTLc did not change significantly (see table). QTc and QTLc highly correlated at baseline and also at the end (r=0,94, p<0,0001 and r=0,95, p<0,0001). In 14 subjects QTc and QTLc increased (17±10 ms and 12±8 ms), in 17 decreased (10±10 ms and 12±9 ms). Multiple regression analysis performed on age, ejection fraction, baseline QT values, HR and BP data revealed no predictor for QTc and QTLc prolongation or shortening.

Comparison of variables

Variable	0 min	3 min	p Value
HR (beats/min)	70 (14)	73 (15)	<0,05
SBP (mmHg)	132 (19)	137 (17)	<0,05
DBP (mmHg)	79 (11)	84 (11)	<0,05
QT (ms)	432 (65)	425 (64)	<0,05
QTc (ms)	460 (53)	462 (50)	ns
QTLc (ms)	449 (52)	448 (50)	ns

Paired t-tests. Data are expressed as mean (SD). HR=heart rate; SBP=systolic blood pressure; DPB=diastolic blood pressure; QTc=Bazett corrected QT time; QTLc=Sagie corrected QT time

Conclusion: (1) MA induced a significant overall HR and BP response. (2) Though in our sample the mean QTc and QTLc did not change, the individual QT values increased or decreased. (3) QTc and QTLc correlated closely. (4) MA is a simple and validated method that may help to diagnose LQTS and RRI if the resting ECG is normal, but further study is needed.

P1561 Reproducibility of ventricular tachycardia inducibility during repeated electrophysiological study in patients with arrhythmogenic right-ventricular cardiomyopathy

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Background: In patients with arrhythmogenic right ventricular cardiomyopathy (ARVC), reproducibility of the induction of sustained ventricular tachycardias (sVT) during the electrophysiological study (EPS) is unknown. However, this is important when treatment strategies are guided by EPS results.
Methods: In 30 patients with ARVC (mean age 47±15years) and ventricular tachyarrhythmias, two baseline EPS (EPS-1; EPS-2; median time interval: 1.03 months) were performed according to a standardized protocol.
Results: During EPS-1, monomorphic VT were inducible in 17 patients (57%; 14 sVT (82%), 3 nonsustained VT (18%)). In 14 of 17 patients (82%), the clinical VT morphology was identical with the induced VT morphology. More than one VT morphology were inducible in 8 of 17 patients (median 2; range 2 to 4 morphologies). During EPS-2, the results of EPS-1 were reproducible in 26 of 30 patients (86%). All patients with noninducible VT during EPS-1 remained noninducible. Only in one patient (6%), in whom a nsVT was inducible during EPS-1, no VT were inducible during EPS-2. A concordance of the clinically documented VT morphology with the morphologies induced during EPS-1 and EPS-2 was observed in 12 of 16 patients (75%). However, in seven patients VT-induction during EPS-2 required one extrastimulus more (n=4) or less (n=3). A change in cycle length >50ms in induced VT was seen in five patients (31%).
Conclusions: In patients with ARVC and documented VT, the reproducibility of VT induction during EPS is high. This has major implications for diagnostic and therapeutic strategies in these patients with regard to EP-guided arrhythmia management.

P1562 Heart rate variability modification induced by weight

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Obese patients are considered at high risk of sudden cardiac death. This risk is often associated to comorbidities such as hypertension, diabetes or heart failure. Information remain scarce about the risk of sudden cardiac death in patient with only obesity.
Our aim was to assess heart rate variability modification in these patients to explain this increased risk.
Methods: We prospectively enrolled 78 obese patients (Body mass index: BMI>30 kg/m^2) and 30 healthy volunteers matched for age and sex. All subjects underwent a physical examination, an EKG and a 24-Holter EKG, a 24 hours recording of their blood pressure, a chest X Ray and a cardiac transthoracic echography. We also looked at glucose and insulin levels as at the lipid profile. The aim was to exclude all obese patients with a cardiac or metabolic disease associated to obesity and able to modify heart rate variability (i.e. hypertension, diabetes or heart failure).
Results: Out of the 78 patients we included 32 obese subjects (19 female and 13 male), mean age 37 $\pm$ 6, BMI of 39.5 $\pm$ 4, mean systolic and diastolic pressure (11.8 $\pm$ 0.8: 7.7 $\pm$ 0.7) without left ventricular hypertrophy or diastolic failure and with a normal glucidic and lipidic profile. Results are depicted in the table below.

	Obese patients	Healthy volunteers	p value
SDNN	65 $\pm$ 11	76 $\pm$ 14	NS
rmssd	39 $\pm$ 8	39 $\pm$ 8	NS
VLF	7.2 $\pm$ 1.3	7.3 $\pm$ 0.3	NS
HF	9.3 $\pm$ 4	9 $\pm$ 2	NS
LF	18 $\pm$ 5	42 $\pm$ 7	0.001

Conclusion: Patient with solely obesity have a higher sympathetic tone. This modification is more marked during day than during nightime. These abnormalities could partly explain the higher incidence of sudden cardiac death in obese patients with no other comobidity. Moreover this increased sympathetic tone could induce hypertension or hyperinsulinemia associated to obesity.

BASIC ASPECTS OF ARRHYTHMIAS I

P1563 Prevalence of haemochromatosis gene mutations in idiopathic atrial arrhythmias

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Introduction: Hereditary haemochromatosis (HH) (autosomal recessive inheritance, mutations in the HFE gene encoded on chromosome 6 {wild type HHCC}) is arrhythmogenic. Two prevalent mutations are: cysteine to tyrosine substitution at position 282 - C282Y (heterozygotes for this mutation HHCY, homozygotes HHYY); histidine to aspartic acid substitution at position 63 - H63D (heterozygotes for this mutation HDCC, homozygotes DDYY). Homozygosity for C282Y (HHYY) and compound heterozygosity (HDCY) are responsible for up to 90% of HH cases in Northern Europeans. Homozygosity for these mutations is common (1:300 for C282Y and 1:30 for H63D) but prevalence of clinically recognised HH is only 1 in 20,000.
Methods: A case-control study comparing patients with structurally normal hearts and idiopathic arrhythmias with control samples from a randomly selected population. HFE genotyping was performed by ARMS-PCR. Cases were analysed by arrhythmia type and HFE mutation. Chi-squared tests were used to determine statistical significance.
Results: 69% of patients who presented with lone atrial fibrillation or flutter had the H63D mutation, compared with only 29% of controls (p<0.002). However, there was no excess of the C282Y mutation in the arrhythmia group (7%) compared with controls (7%).
Conclusions: The H63D mutation is very common and may be a major cause of atrial arrhythmogenesis, often occurring in patients without other features of cardiomyopathy. The C282Y mutation seems not to convey any additional arrhythmogenic risk which is surprising as the C282Y mutation is more strongly associated with iron overload which is postulated to be the main arrhythmogenic trigger. It may be iron distribution within or between cells or factors other than iron overload that truly contribute to the arrhythmogenic substrate.

P1564 Protective role of heat shock proteins in human and experimental atrial fibrillation

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Background: Atrial fibrillation (AF) becomes more persistent in time and is accompanied by electrical, contractile and structural remodeling, which explain maintenance of the disease. Heat shock proteins (Hsps) are chaperones with cytoprotective properties against a variety of cellular stresses. We investigated whether Hsps play a protective role in human AF and in HL-1 atrial myocytes as in vitro model for atrial tachycardia.
Methods and Results: Right and left atrial appendages were obtained from patients with paroxysmal (n=7) or chronic (n=8) lone AF and compared to controls (n=8) in sinus rhythm. Hsp27 and Hsp72 expression (SDS-PAGE and Western blotting) was significantly increased only in patients with paroxysmal AF (+41%, p<0.001 and +59%, p=0.03, respectively) compared to control patients. No changes in expression of Hsps were found in patients with chronic AF. Hsp expression correlated inversely with absence (6%) of hibernative (myolytic) myocytes in paroxysmal AF and presence (30%) in chronic AF. Using a cellular model in which HL-1 atrial myocytes were subjected to a ten times rate increase (5Hz), it was found that induction of Hsps prior to tachycardia protected these myocytes against myolysis.
Conclusions: The data demonstrate that Hsps can protect myocytes from tachycardia induced myolysis and suggest that the elevated Hsp expression, as observed in patients with paroxysmal AF, reflect a cellular defense mechanism to protect tachycardia-stressed cells to go into a hibernative state. Upregulation of Hsp may therefore be a therapeutic goal to prevent or delay progression of paroxysmal AF to chronic AF.

P1565 Temporal changes in 12-lead electrocardiogram T-wave morphology indices during long-term follow-up

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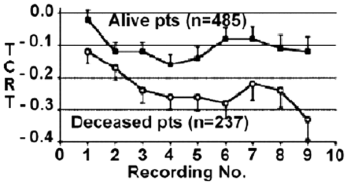
Background: Novel variables of T wave morphology from the digital 12-lead ECG are prognostically useful in different patient populations. It is not known how these indices change over time.
Purpose: To assess temporal changes of various T wave morphology variables.
Methods: In 722 US veterans 9.1 $\pm$ 1.8 serial ECGs were recorded digitally during a mean follow-up (FU) of 11.9 years. In 6250 ECGs, the total cosine R-to-T (TCRT), T wave loop dispersion (LD), T wave morphology dispersion (TMD), normalized T wave loop area (TLA), absolute and relative T wave residua (TWR), and complexity ratio (CR) were calculated using fully automatic software recently described. Sequential ECGs were compared using one-way ANOVA. Deceased patients and survivors were compared using a non-parametric Mann-Whitney test.
Results: LD, TMD, TLA, the TWR and CR exhibited remarkable stability in all patients (p=NS over complete FU). TCRT demonstrated slowly declining and lower values in patients that subsequently died (n=237, p < 0.0001 for decline among all recordings, p < 0.0002 for comparison between surviving and deceased patients) while no temporal change was noted in survivors (p=NS, see figure with SE).



TCRT during FU.

Conclusion: Due to their good stability, novel T wave morphology variables for repolarization assessment from a single-beat ECG maintain their prognostic usefulness long-term.

P1566 Tissue discontinuities delay conduction velocity restitution promoting ventricular fibrillation

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Background: Restitution properties of action potential duration and conduction velocity (CVR) are important determinants for the stability of reentrant ventricular tachycardia (VT) and deterioration to ventricular fibrillation (VF). Structural barriers provide anchors for stable reentry promoting VT rather than VF. However, VF often occurs in the presence of structural heart disease, where fibrotic strands intermingle with myocardial tissue, an architecture that gives rise to tissue discontinuities (TD).
Hypothesis: TD delay CVR, increasing VF susceptibility.
Methods: TD were simulated in patterned, 2-dimensional, cultures of neonatal rat cardiomyocytes with a star shaped structure having 8 arms (n=12). Activation across sites of discontinuities (transition from arm to star center) was determined during basic and premature stimulation. Extra- and intracellular recordings were made in the stimulated arm and at the discontinuity. Voltage clamp recordings of single cells and computer simulations for propagation of the electrical impulse were used to determine depolarizing ionic currents and (in)activation parameters for myocardial cells at the discontinuity.
Results: Progressive increase of activation delay after premature stimulation occurred at sites distal from the discontinuity. Action potentials at the discontinuity revealed double phased upstrokes during premature stimulation. The activating ionic current was biphasic at this site. Computer simulations for cells at the discontinuities revealed similar results and showed a biphasic activation and delayed inactivation of the sodium current.
Conclusion: These data show that CVR is delayed at TD and may explain increased VF susceptibility in structurally abnormal hearts. A biphasic activation together with delayed inactivation of the activating ionic current are responsible for the progressive increase of delay.

P1567 Simulation of cardiac electrophysiology using mathematical models and computer based processing of digital image data

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Purpose: The purpose of this study is to develop a computer model based planning environment for therapeutical cardiac interventions, i.e. surgical or catheter ablation procedures. Existing mathematical models are used to simulate the electrophysiology on an anatomical pig model during a heart cycle. The results of these models were validated in a domestic pig animal experiment.
Methods: The mathematical model that is used describes on one hand the electrophysiology of each single cell with a rule based system depending on tissue type, stimulus frequency and refractory period. On the other hand the model couples cells to a multi cellular environment. This model is called "cellular automaton". It includes tissue heterogeneities, fiber orientation and specific properties of the cardiac conduction system. The anatomical model is created based on CT data. After excluding artifacts the digital image data were processed using advanced algorithms for segmentation of the tissue. During a classification process, the segmented tissue was matched with the properties of the specific tissue region. The simulation results were validated in an animal model using a Langendorff preparation of a domestic pig heart. While performing a spiral CT scan, a balloon catheter for endocardial mapping was sequentially introduced into all four heart chambers to record the electrical excitation propagation in the beating heart. Because of a roentgen opaque triangle at the balloon catheter, the position of the electrodes and the corresponding points of the heart chamber could be matched with the CT-scan. The data acquired in the Langendorff models were compared with the calculated potentials based on the computer simulations.
Results: Eight hearts were studied in sinus rhythm, five of these hearts were studied with induced atrial fibrillation, without humoral or nervous influences. We found that the cellular automaton enables us to simulate the electrical behavior of the heart in real time and reproduces the properties of the heart in sinus rhythm and atrial fibrillation.
Conclusions: This model of cardiac electrophysiology enables us to simulate the effects of therapeutic interventions, i.e. ablation lines to terminate atrial fibrillation, pre-interventional. We further aim at the integration of force development and deformation of the cardiac walls, metabolic and hemodynamic influences and flow dynamics in this models.

P1568 Effects of candesartan and enalapril on atrial endocardial nitric oxide synthase expression in an animal model of pacing-induced atrial remodelling

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It has been recently demonstrated a downregulation of endocardial Nitric Oxide Synthase (eNOS) expression in an animal model of atrial fibrillation. The present study was designed to assess the effects of enalapril and candesartan on atrial tissue eNOS expression in the early stages of atrial remodeling in a canine model of prolonged rapid atrial pacing.
Methods: Sixteen halothane-anesthetized adult beagle dogs underwent insertion of a transvenous lead at the right atrial appendage. Twelve dogs were continuously paced at 400 bpm for 3 days in the presence of candesartan (4 dogs) (2mg/kg/day), enalapril (4 dogs) (2 mg/kg/day) and without drugs (4 dogs). Four dogs in sinus rhythm served as control group. Right atrial effective refractory period (ERP) was measured at either baseline and after 3 days in all groups. Right atrial tissue eNOS expression was determined by Western-blot analysis.
Results: After continuous pacing the atrial ERP was significantly (p=0.046) shorter in untreated paced dogs than control group. Table shows right atrial eNOS expression (percentage of mean of the control group) and the atrial ERP measured after 3 days. We found a basal tisular eNOS expression in the right atrial myocardium and endocardium in all dogs. Atrial tissue eNOS expression decreased significantly (p=0.02) in paced dogs associated with an atrial electrophysiological remodeling. Both candesartan and enalapril prevented the downregulation of atrial eNOS expression, however enalapril attenuated more significantly the effects on atrial ERP.

	Control	Paced-untreated	Paced-candesartan	Paced-Enalapril
ERP (day 3)	137 ± 11.5 ms	80 ± 30 ms	93 ± 36 ms	142 ± 22 ms
eNOS	100 ± 14%	67 ± 16.5%	97 ± 18%	110 ± 11.5%

Right atrial electrical remodeling and eNOS expression.

Conclusions: a) Pacing induced atrial remodeling is associated with an early downregulation of atrial tissue eNOS expression; b) angiotensin-converting enzyme inhibitors prevents the changes on atrial eNOs expression and the early atrial electrical remodeling.

P1569 The ventricular electrical remodelling in rat experimental autoimmune myocarditis. The difference between acute inflammatory phase and dilated cardiomyopathy-like phase

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Background: The EAM in rat reached its peak around 3 weeks after the immunization, gradually subsides, and is followed by DCM-like phase. We have previously documented the electrical remodeling and enhanced arrhythmogenicity in acute phase. In this study, we evaluated the electrophysiologic parameters and the expressions of the ion channels or the transporter along the time course of EAM.
Methods: 14, 21, 35 and 60 days after the myosin injection to Lewis rats, heart to body weight ratio (HW/BW), heart rate, effective refractory period (ERP), monophasic action potential duration (MAPD) and PVC inducibility were evaluated in comparison with control rats. Kv4.2 expression was examined by quantative real time RT-PCR and Western blot. mRNA levels of Na/Ca exchanger (NCX), L-type Ca channel (L-Ca) and Kv1.4 were quantified by real time RT-PCR.
Results: The HW/BW was increased in EAM rats maximally on day 14. The heart rate was not significantly different in EAM and control rats throughout the course. ERP and MAPD were prolonged in EAM rats, but MAP90 recovered slightly on day 60 (111 plusminus 02, day 21 vs. 85 plusminus 16 ms, day 60, p = 0.039). The PVC inducibility was highest in day-21 EAM. The Kv4.2 expression reduced in EAM rats in comparison with control rats, showing the lowest level on day 21, but recovered slightly on day 60. In contrast, mRNA levels of L-Ca and Kv1.4 were the lowest on day 60 in EAM rats. The mRNA level of NCX was not significantly different in both groups.
Conclusions: Although the ventricular electrical remodeling was observed along the whole time-course in rat EAM, the degree of the electrical remodeling and PVC inducibility were highest in acute inflammatory phase. The expressions of ion channels showed the different manners between in acute phase and DCM-like phase. The additional pathogenesis might contribute to the arrhythmogenicity in acute phase of EAM.

P1570 HERG K897T polymorphism and sudden arrhythmic death due to acute coronary event

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Purpose: Arrhythmic death caused by an acute ischemic event is more common in subjects with a family history of sudden cardiac death, suggesting to a genetic background. The nucleotide 2690A>C variation corresponding to the K897T amino acid polymorphism of the HERG gene was recently found, and has been shown to have gender-related effects on cardiac repolarization. The purpose of the study was to test the hypothesis that HERG K897T polymorphism may also be associated with the occurrence of ischemic arrhythmic death either in males or females.
Methods: The cases of this case-control study were comprised of 202 consecutive victims of sudden cardiac death with an evidence of an acute ischemic event at autopsy plus 27 patients with an aborted cardiac arrest caused by an acute coronary event (total number of cases =229). Consecutive patients with an acute myocardial infarction (AMI) without a cardiac arrest or life-threatening arrhythmias during the acute ischemic event (n=644) served as a control group.
Results: The allele frequencies of the whole study group were 0.83 (A) and 0.17 (C). The alleles AC or CC of the HERG K897T polymorphism were more common in females with an ischemic arrhythmia event than in females of the control group (22/47 (47%) vs 31/120 (26%), p=0.008, OR 2.52, 95% CI 1.25-5.11). However, similar association between the HERG K897T polymorphism and ischemic arrhythmia event was not found in males.
Conclusions: The genotypes AC and CC of the K897T polymorphism of the HERG gene coding for the alpha subunit of the rapidly activating delayed rectifier K^+ channel are associated with an increased risk of sudden arrhythmic death during the acute coronary event in females.

P1571 Inhibition of cloned HERG potassium channels by the antioestrogen tamoxifen

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Tamoxifen is a nonsteroidal antiestrogen that is commonly used in the treatment of breast cancer. Although antiestrogen drugs are generally believed not to cause acquired long QT syndrome (LQTS), concerns have been raised by recent reports of QT interval prolongation associated with tamoxifen treatment. Since blockade of human ether-a-go-go-related gene (HERG) potassium channels is critical in the development of acquired LQTS, we investigated the effects of tamoxifen on cloned HERG potassium channels to determine the electrophysiological basis for the arrhythmogenic potential of this drug.
HERG channels were heterologously expressed in Xenopus laevis oocytes, and currents were measured using the two-microelectrode voltage clamp technique.
Tamoxifen blocked HERG potassium channels with an IC50 value of 45.3 μM. Inhibition required channel opening, and unblocking occurred very slowly. Analysis of the voltage-dependence of block revealed loss of inhibition at positive membrane potentials, indicating that strong channel inactivation prevented block by tamoxifen. No marked changes in electrophysiological parameters such as voltage-dependence of activation or inactivation, or changes in the inactivation time constant could be observed, and block was not frequency-dependent.
This study demonstrates that HERG potassium channels are blocked by the antiestrogen drug tamoxifen. We conclude that HERG current inhibition might be an explanation for the QT interval prolongation associated with this drug.

P1572 In the fibrillating atria the mitochondrial sublimons are significantly correlated with both left atrial diameter and atrial fibrillation duration

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Background: Mitochondrial DNA (mtDNA) has a critical role in supporting energy pathways in cardiac cells. Low abundance somatic mtDNA rearrangements (sublimons) have been assumed to contribute to the ageing process and to the pathogenesis of some diseases. However, no role was found for the prevalent class sublimons (PCS) in cardiac pathology (Kajander et al 2002). Therefore, we investigated the PCS in atrial fibrillation (AF).
Methods: Right atrial appendage biopsies were collected from 38 patients in AF and 35 control patients with sinus rhythm (SR) at the time of elective cardiac surgery. The left atrial diameter (LAD) was measured by transthoracic echocardiogram prior to surgery. All tissue samples were cut into slices and total DNA was extracted by standard methods. The break point regions of the two most prevalent classes of sublimon were amplified by PCR using fluorescent oligonucleotides for the 3.75 kb partial duplication, which is the (PCS), and the 2.83 kb deletion. Multiplex reactions included additional primers to amplify an internal genomic standard for semi-quantitative analysis. Fluorescent products were analysed by capillary electrophoresis using GeneScan software on an Applied Biosystems 310 Genetic Analyzer. Reaction products were quantified as peak areas in the electrophoretogram and ratios computed of the sublimon abundance relative to the genomic standard. Correlation of sublimon number to age, LAD, AF duration, and presence or absence of AF was performed.
Results: PCSs were detected in 60 patients (82.19%), in 33 of AF (86.84%) and in 27 (77.14%) of SR patients. The mean sublimon copy number (SCN) ranged variably up to 142.084 copies/cell (mean 14.85 + 3.13). (PCS) did not accumulate with age. There was no difference in PCS abundance between AF and SR patients (19.09 + 28.29 vs 10.25 + 24.68, p = 0.158). There was a significant difference in SCN between pts with AF of 12 months duration and those with AF > 24 months (3.47 + 6.64 vs 17.98 + 21.07, p = 0.02). The correlation between LAD and SCN was significant when LAD reached 5 cm (p= 0.01, r = 0.39, n = 38). This significance continued, but weak, until the LAD reached 6 cm (p= 0.02, r = 0.31, n = 14). This significance was lost in the remaining 14 patients when LAD exceeded 6 cm (p= 0.96, r = 0.01).
Conclusion: This study suggests that mtDNA deletions are part of the pathophysiology of sustaining the substrate for AF in vivo.

SYSTOLIC FUNCTION

P1573 Towards a new strategy in the diagnosis of left-ventricular dysfunction in Chagas disease

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Background: Left ventricular dysfunction (LVd) is the main predictor of mortality in Chagas disease (ChD). ECG and Chest X-ray are recomended as first-line methods in the recognition of LVd in ChD. Although ECG has been recognized as a high sensitivity test, Chest X-ray diagnostic accuracy is considered poor. Otherwise, BNP measurement is an accurate predictor of LVd in ChD (Ribeiro et al. Lancet 2002 460:361-2). We compared the diagnostic performance of abnormalities in ECG or Chest X-ray in the recognition of LVd (conventional approach) with a new strategy, in which BNP is measured in patients with abnormal ECG.
Methods: 166 ChD patients were recruited at an Outpatient Reference Center in 1998-99 and studied by ECG, Chest X-ray, BNP measurement (RIA) and echodopplercardiography. LVd was defined as ejection fraction $\leq$ 0.4. The BNP cut-off value was chosen based on the analysis of the ROC curve. Procedures were prospectively repeated in a validation sample (70 ChD) studied in 2001-02. All investigators were blinded to the results of other tests.
Results: BNP strategy was significantly better than conventional approach (table) in accuracy, specificity, + predictive value (PV) and + likelihood ratio (LR). Sensitivity was higher using conventional strategy, although both strategies showed (-) PV < 95% and (-) LR < 0.3. Considering the LR obtained at the original sample and an estimated prevalence of LVd in the Outpatient ChD population of 15%, an elevated BNP in the presence of abnormal ECG indicates a post-test probability of LVd of 78%; conventional approach, 26%.

Diagnostic performance

Strategies	Sample	Sn	Sp	+ PV	- PV	+ LR	- LR	Ac
ECG + X-ray	Original	100	28	15	100	1.39	0	36
	Validation	100	40	21	100	1.66	0	48
BNP-based	Original	75	95	63	97	15.0	0.26	93
	Validation	75	91	64	95	8.72	0.27	89

Sn: sensitivity; Sp: specificity; PV: predicitive value; LR: likelihood ratio; Ac: accuracy

Conclusion: BNP-based strategy was more accurate than the conventional approach in the detection of LVd in ChD patients. Chagas disease management recomendations should consider BNP/ECG strategy as a first-line option in the evaluation of new Chagas disease patients.
Supported in part by CNPq, CAPES, FAPEMIG and PrPq/UFMG.

P1574 Effects of aortic coarctation on left-ventricular arterial coupling and mechanical efficiency are not baroreflex-mediated

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Objectives: To compare LV response to afterload augmentation when the baroreflex was intact or inhibited by hexamethonium infusion.
Methods: Six pigs, instrumented for aortic pressure and flow, LV pressure and volume measurements were studied under pentobarbital-sufentanil anaesthesia. Vascular properties [input (R1) and peripheral (R2) resistances, compliance (C), arterial elastance (Ea)] were estimated with a windkessel model. LV function was assessed by the slope (Ees) of end-systolic pressure-volume relationship (ESPVR) and stroke work (SW). Ventriculo-arterial coupling was defined as Ees/Ea, and mechanical efficiency as SW/pressure-volume area (PVA). After baseline recordings, LV afterload was increased with an aortic coarctation. Haemodynamic measures were obtained after 30 minutes. The coarctation was lifted, and 30 minutes later, autonomous nervous system (ANS) was inhibited by infusion of hexamethonium. The coarctation was re-installed, and haemodynamic measurements recorded after 30 minutes.
Results: While aortic coarctation increased R1 (from 0.132 $\pm$ 0.010 to 0.352 $\pm$ 0.007 mmHg.sec/ml; $p<0.001$) and decreased C (from 0.57 $\pm$ 0.04 to 0.41 $\pm$ 0.05 ml/mmHg; $p<0.005$) independently of hexamethonium infusion, R2 and heart rate increased (from 1.50 $\pm$ 0.11 to 1.70 $\pm$ 0.06 mmHg.sec/ml and from 115 $\pm$ 5 to 125 $\pm$ 2 beats/min, respectively; $p<0.05$) only when the ANS was intact. Independently of hexamethonium infusion, Ees increased from 2.81 $\pm$ 0.18 to 3.69 $\pm$ 0.20 mmHg/ml, while dead volume Vd decreased from -3.6 $\pm$ 0.2 to -6.8 $\pm$ 0.3 ml ($p<0.01$). Ees/Ea remained unchanged in both conditions. At matched end-diastolic volumes and independently of baroreflex integrity, SW and PVA increased (from 2012 $\pm$ 168 to 2912 $\pm$ 114 mmHg.ml and from 2874 $\pm$ 352 to 4520 $\pm$ 224 mmHg.ml, respectively; $p<0.005$) and SW/PVA decreased (from 0.70 $\pm$ 0.12 to 0.64 $\pm$ 0.10; $p<0.05$).
Conclusions: Our results demonstrate that afterload augmentation has a composite effect on LV function. Ventricular performance is increased (ESPVR leftward shift, increased Ees and SW), but mechanical efficiency is reduced. These changes, observed independently of baroreflex integrity, are of paramount importance in heart transplant patients, which although lacking cardiac innervation, can adapt LV performance without simultaneous changes in HR.

P1575 Influence of cardiac autoantibodies on inotropy, heart rate and coronary blood flow on isolated perfused hearts

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Background: Cardiac autoantibodies may play a functional role in cardiac dysfunction of patients suffering from dilated cardiomyopathy. Therefore, immunoadsorption (IA) which removes antibodies from patients' plasma represents a new therapeutic option for these patients. The mechanisms of IA remain to be elucidated.
Methods and Results: Patients with DCM (n = 9) were treated with IA on 3 consecutive days, with one IA session daily, by application of specific antibody columns directed against human immunoglobulin (Ig). The cardiac index increased from 2.3 $\pm$ 0.1 to 2.9 $\pm$ 0.2 L/min/m^2 ($p < 0.01$) and the systemic vasculary resistance fail from 1373 to 1028 dyne*sec*cm5. IA was also performed with 500 mL of blood taken from 9 healthy donors (controls). After passage of plasma, the IA columns were regenerated. Column eluent (CE) was collected and dialyzed (100 KD). After perfusion of the isolated hearts (Langendorff-perfused rat hearts)with diluted CE (1:30; 1:20: 1:10; 1:5; 1:2) the contractility and the coronary blood flow were analyzed.
Results: CE obtained from controls did not influence contractility and coronary blood flow of the isolated perfused hearts. In contrast, CE of DCM patients (n=9) collected during the first regeneration cycle of IA session no. one caused immediate and dose-related decrease of the inotropy (dLVPdtmax: 1:30 = -9.9 $\pm$ 0.8%; 1:2 = -24.8 $\pm$ 2.5%; $p<0.01$). The coronary blood flow was also reduced by CE received from DCM patients (dilution 1:2: -26.1 $\pm$ 6.0%, $p<0.01$). The heart rate did change significantly in both groups.
Conclusion: IA removes negative inotropic antibodies. Additionally, the coronary blood flow was reduced by the eliminated factors.

P1576 Heat production in human myocardium is inversely related to left-ventricular ejection fraction

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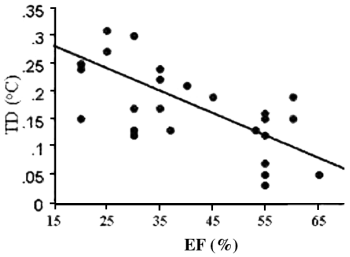
Background: Heat production in the myocardium may be affected by the mechanical deficiency of the left ventricle, leading to increased heat production, which may result in increased coronary sinus (CS) blood temperature. The aim of this study was to investigate whether there was a correlation between left ventricular performance with heat generation from myocardium.
Methods: In the study we included 10 patients (pts) with dilated (DCM) (mean age 54.2$\pm$17 years old), 5 with ischemic (ICM) cardiomyopathy (mean age 64.2$\pm$9 years old) and 12 healthy subjects (mean age 55.5$\pm$10 years old).
Blood temperature measurements were performed by a 7F thermography catheter (Medispes Co., Switzerland), which has a steering arm proximally and by which the distal part can be manipulated to enter the right atrium (RA) and the CS. At the tip of the catheter is attached a thermistor. Temperature difference (TD) was the difference between CS and RA blood temperature.
Results: The procedure was successful and uncomplicated. The left ventricular ejection fraction (EF) was lower in DCM or ICM compared to controls (DCM: 28$\pm$7%; ICM: 29$\pm$7%; control: 55$\pm$4%, $p<0.0001$). EF was similar between DCM and ICM. TD was greater in DCM and ICM compared to controls (DCM: 0.21$\pm$0.06; ICM: 0.24$\pm$0.13; control: 0.12$\pm$0.05oC, $p<0.01$). TD was similar between DCM and ICM (p=0.54). There was an inverse correlation between TD and EF in the whole population (r=0.66, $p<0.0001$)(Figure).



Conclusions: Pts with DCM and ICM have increased blood TD compared to controls, probably due to increased myocardial heat production. Considering the inverse correlation between EF and the increased heat generation, it may be attributed to the mechanical deficiency of the heart independently from the etiology of heart failure.

P1577 Maximising improvements in systolic function during biventricular pacing

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For patients with severe heart failure (HF) and left bundle branch block (LBBB), ensuring maximal improvements in left ventricular (LV) function with biventricular pacing (BVP) is likely to be important in obtaining optimal symptomatic benefits. Using tissue Doppler imaging (TDI), we investigated the effect of different LV lead positions and interventricular pacing intervals (IPIs) on regional systolic function.
Method 17 patients aged 69 $\pm$ 8 years with chronic HF (NYHA III-IV, EF<30%, 9 with ischaemic heart disease) and LBBB (QRS 166 $\pm$ 22) underwent temporary BVP from RV apex and 2 different LV positions (lateral/anterolateral (Lt) n=16 and inferoposterior n=10) at 5 IVPIs ((+80, +40, 0, -40, -80ms referenced to right ventricular (RV) pacing)). LV regional pulsed wave TDI were measured at the level of the mitral valve annulus and from the RV free wall at baseline and during each pacing configuration.
Results RV, lateral and anterior wall mean peak systolic velocities remained unchanged from baseline during any BVP configuration. A stepwise increase in septal, inferior and posterior wall systolic velocities occurred during BVP with earlier LV pacing with greatest velocities at -80ms: septum: baseline 3.2 $\pm$ 0.8, Lt LV site 4.6 $\pm$ 1.4 p= 0.003 and inferoposterior LV site 4.6 $\pm$ 1.1 p=0.015; inferior wall: baseline 4.3 $\pm$ 1.2, Lt LV site 5.3 $\pm$ 1.6 $p<0.01$ and inferoposterior LV site 5.3 $\pm$ 1.3 $p<0.01$; posterior wall: baseline 4.3 $\pm$ 1.2, Lt LV site 5.4 $\pm$ 1.1 p0.002 and inferoposterior LV site 5.2 $\pm$ 1.7 p0.01. At each IVPI there was no significant difference in regional systolic velocity between Lt or inferoposterior LV pacing sites.
(Results in cm/s are expressed as means $\pm$ SD)
Conclusion LV preexcitation during BVP should be considered in order to derive maximal improvements in systolic function. This can be achieved from both Lt and inferoposterior LV pacing sites.

P1578 Prognostic value of left atrium dilatation in patients with left-ventricular systolic dysfunction undergoing coronary artery bypass grafting

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Aim: Assessment of the independent prognostic value of the restrictive mitral pattern and left atrium dilatation (LA) in patients with left ventricular (LV) systolic dysfunction undergoing coronary artery bypass grafting (CABG).
Material and Method: We have taken into study 242 patients (70.2% male, mean age 62±8) with LV ejection fraction (LVEF)<40%(mean LVEF 31±4%) who underwent CABG. Patients were evaluated clinicaly and by echography preoperatively and postoperatively at 10 days, 1, 3, 6, 12, 24 months. The patients were divided into 2 groups regarding the LVEF: 1. Group A-164 patients with LVEF=30-40%. 2. Group B-78 patients with LVEF<30%. The 2 groups were comparable concerning the mean age, gender, LVEF, the mean number of grafts/patient and secondary mitral regurgitation degree. Statistical analysis used SYSTAT and SPSS programs for the simple and multiple linear regression analysis and relative risk calculations.
Results: 1.The index of the LA dimension in group A >28mm/msq and in group B>30mm/msq were found as independent predictors for "fatal outcome" (RR=4.3, respectively RR=5.2, p=0.0012). 2.The restrictive transmitral flow was independently associated with the death or hospitalisation for heart faillure in both groups (p=0.001, respectively p=0.012). 3.The prognostic value of the LA dilatation decreases if there is a concomitantly increase of LV filling pressures or a mitral regurgitation haemodynamic significant. In these patients LA dimension >28mm/m^2 in group A and >30mm/m^2 increases the risk of death by only 1.7 times in group A and by 1.8 respectively in group B. 4. Associated haemodynamic significant mitral regurgitation increases significantly the mortality rate in both groups (RR=6.2, respectively RR=7.1, p=0.0001), but decreases the prognostic value of the LA dimension.
Conclusions: 1.LA dilatation has a independent and incremental prognostic value in patients with left ventricular systolic dysfunction undergoing CABG. 2.Mitral restrictive pattern can predict the fatal outcome and the hospitalisation for heart failure in both groups. 3.The prognostic value of LA dilatation decreases if there is a concomitantly increase of LV filling pressures or a mitral regurgitation haemodynamic significant in these patients.

P1579 Right-ventricular dysfunction in chronic ischaemic heart disease: poor association with right coronary artery disease and inferior left-ventricular wall motion abnormalities

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Background: Previous studies in patients (pts) with chronic ischemic heart disease (IHD) and left ventricular dysfunction (LVD) showed a low frequency of right ventricular dysfunction (RVD) as compared to idiopathic dilated cardiomyopathy. RV infarction is known to occur more frequently in association with inferior wall LV infarction due to right coronary artery (RCA) disease than with any other infarct location. This study investigates whether the association between RVD, inferior wall motion abnormalities (WMA) and RCA occlusion holds true also in chronic IHD.
Methods: Complete hemodynamic and angiographic data of the LV and the RV were obtained in 112 pts with chronic IHD, LVD (defined as a LV ejection fraction -EF- < 45%) and a dominant RCA. Pts were categorized based on a value of RVEF <35% to define RVD. LV WMA were observed by 2 experienced operators in the 30° RAO angiogram, and were defined as: normal; hypo-; a- and dys-kinesia. Five segments were considered according to the CASS classification (antero-basal, antero-anteral, apex, diaphragmatic and postero-basal). Occlusion of the RCA was classified as proximal, mid and distal according to the AHA/ACC nomenclature.
Results: The study cohort had a mean age of 64±10 yrs and included 86% males. Mean LVEF was 33±8% and RVEF 46±11%. A previous myocardial infarction was present in 83 pts (74%) and multivessel disease in 89 (79%). A RVEF<35% was detected in 19 pts (17%) (RVD group) while 93 pts (83%) had preserved RV function (no RVD group). The postero-basal region was abnormal in 79% of RVD group vs 61% in non-RVD group (p=0.23), while the diaphragmatic region was abnormal in 100% of RVD vs 80% of non-RVD (p=0.07). A- or dys-kinetic segments were present in the postero-basal region in 4 pts (21%) and in diafragmatic region in 5 pts (26%) in RVD group compared to 26 (28%) and 37 pts (40%) in non-RVD group, respectively (p=ns). Overall, the number of abnormal segments was significantly higher in RVD compared to non-RVD group (4.2 ± 1.0 vs 3.6 ± 1.1; p=0.03). The average number of diseased vessels was equal in the 2 groups (2.1± 0.6 vs 2.2±0.8). Occlusion of the RCA was present in 53% of pts in RVD group and in 34% in non-RVD (p=0.217). The site of occlusion or the presence of collaterals did not help differentiate the 2 groups.
Conclusions: The present analysis suggests that RVD in chronic IHD is not significantly related to the presence of WMA of the inferior wall, but rather to the extent of WMA. This finding is confirmed by the poor association between RVD and total occlusion of the RCA.

P1580 Beta 2 adrenergic Gln27Glu polymorphism is a protective factor for left-ventricular dysfunction

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BETA2 adrenergic receptors (BETA2 AR) show three main polymorphisms: Glu27Glu characterized by a higher resistance to downregulation phenomenon and Arg16Gly and Thr164Ile characterized by reduced downstream activity and associated with a lower exercise capacity in pts with congestive heart failure
Aim: To test the hypothesis that BETA2 AR polymorphisms are directly related to the presence of LV dysfunction in pts with cardiac diseases.
Methods: Consecutive patients (n=617) referred for cardiac catheterization were genotyped for: Arg16Gly, Gln27Glu and Thr164Ile. LV Ejection Fraction (EF) was assessed by bidimensional echocardiography and left ventriculography in all pts. Pts were divided into 3 groups: Group 1 with normal EF (>50%, n=437), and into groups of mild to moderately reduced EF (Group 2: 36<EF<49%, n=96), and severely reduced EF (Group 3: <35%, n=74) The three groups were matched for age, gender, and cardiac risk factors.
Results: Control group 1 showed following allele frequencies: a)Gly 16: 52% (n=232); b)Glu 27: 47% (n=215); c)Ile-164: 2% (n=19). As shown in Table, allele frequencies for Gly-16 and Ile-164 were similar in both groups with LV dysfunction as compared to Group 1. Of note, frequency of Glu-27 variant was significantly lower in Group 3 pts with severely reduced LV function.

EF<35					36< EF <50			
CI	Odds ratio	P value	Alleles (%)		Alleles (%)	P value	Odds ratio	CI
0.6-1.4	0.9	n.s.	51 (n=53)	Gly 16	47 (n=59)	n.s.	0.8	0.5-1.2
0.4-1	0.6	<0.05	38 (n=40)	Glu 27	44 (n=56)	n.s.	0.8	0.5-1.2
0.1-2.6	0.6	n.s.	1 (n=2)	Ile 164	2 (n=3)	n.s.	0.7	0.2-2.4

Conclusion: The presence of BETA2 adrenergic polymorphisms in codons 16 and 164 do not appear to be directly related to the presence of the LV dysfunction. In contrast, lower incidence of Glu-27 in patients with severe LV dysfunction suggests that Glu-27Glu BETA2 adrenergic polymorphism may play a protective role during the development of congestive heart failure.

P1581 Ventilatory response to early phase of exercise: a novel index useful for the comprehensive assessment of patients with chronic heart failure

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Background: Assessment of ventilatory response to exercise has been applied for the clinical evaluation and risk stratification in patients with chronic heart failure (CHF). However, ventilation is traditionally measured throughout the whole maximal cardiopulmonary exercise testing (CPX). Whether, ventilatory responses to early phase of exercise carries comparable clinical information has not been studied yet.
Methods: We investigated 190 consecutive CHF patients (164 men, age: 60 ± 11 years, NYHA class I/II/III/IV: 26/88/61/15; left ventricular ejection fraction [LVEF]: 32 ± 7%) who underwent CPX. Ventilatory response to exercise, expressed as minute ventilation per unit of CO2 production (VE-VCO2 slope) was calculated from the data obtained during: 1) the whole CPX [VE-VCO2(100%)] and 2) the early phase of exercise, i.e. the first 180 seconds [VE-VCO2(180s)]. Additionally, peak oxygen consumption (peakVO2), baseline (VE-bl) and peak ventilation (VE-peak) were analysed.
Results: CHF patients demonstrated the following metabolic data: peakVO2 - 15.3 ± 4.7 ml/kg/min, VE-VCO2(100%) - 35.5 ± 9.7, VE-VCO2(180s) - 34.1 ± 10.3 (all p<0.0001 vs. reference values in our laboratory). Ventilatory response to early and whole exercise were strongly interrelated (r2=0.73, p<0.0001). Augmented VE-VCO2(180s) identified patients with more compromised exercise tolerance and advanced disease as evidenced by the following relations with: peakVO2 (r=-0.40, p<0.0001), NYHA class (I/II/III/IV: 31.2/32.6/36.5/39.1, p=0.01), VE-bl (r=0.33, p<0.0001), VE-peak (r=0.25, p<0.001), quality of life assessed using Minnesota questionnaire score (r=0.26, p<0.05), serum creatinine (r=0.16, p<0.05). There was no relationship between VE-VCO2(180s) and age, LVEF, CHF aetiology (all r<0.1, p>0.2). In order to investigate the reproducibility of VE-VCO2(180s), in 14 patients CPX was performed twice within 2-7 days, and the mean values of VE-VCO2(180s) were 35.1 ± 10.0 and 34.7 ± 9.0, respectively (variability coefficient=8.5%, r=0.96, p<0.001).
Conclusions: Assessment of ventilatory response to early phase of exercise may become an useful parameter carrying an important clinical message, easily derived from standard CPX data.

A PICTURE OF CHRONIC HEART FAILURE IN THE "REAL WORLD"

P1582 Do disease management programmes improve outcomes for the very elderly with heart failure? Evidence from a hospital-based heart failure clinic

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Background: Disease-management programs are of proven benefit in reducing morbidity associated with heart failure. The effectiveness of such programs in the very elderly remains unclear.
Aim: This report compares the impact of a hospital-based HF clinic in patients $>$ 80 years with those less than 80 years old.
Methods: Eligible patients admitted to hospital with NYHA Class IV HF are assigned to in-hospital cardiology care, nurse-led patient and family education and protocol driven medical care. Following discharge patients attend the HF clinic at 2, 6, 12, 18, 26, and 52 weeks. Weekly telephonic contact with the nurse is maintained on non-clinic weeks until 26 weeks. Patients are advised to contact the clinic outside of these times if they suspect clinical deterioration. All deaths and HF related hospital admissions are recorded.
Results: We report on the first 234 patients to enroll with the HF clinic. Group A (n=38) consisted of patients over 80 years old (mean age of 83.3 $\pm$ 2.8years) and in group B (n=196) were younger patients (mean age of 65.8 $\pm$ 10.8 years). Patients in Group A were significantly more likely to be female, have atrial fibrillation, hypertension and valvular heart disease. Group A patients were significantly less likely to be discharged on beta-blocker therapy (26.3% v. 49.5%, P=0.009) or have a coronary angiogram while in hospital (18.5% v. 66%, P=0.0001). There was no significant difference between the groups in terms of aetiology (76.3% of group A and 85.2% group B were ischaemic, P=0.174) and proportion of patients with LV systolic dysfunction (76.3% group A and 66.3% group B had EF$<$45%, P=0.227). There was no significant difference in percentage of patients who were discharged on an ACEI ($>$88% in both groups). Using Cox's regression analysis, there was no significant difference between groups A and B in probability of death (HR: 1.549 (0.765-3.136), P=0.224) or heart failure related readmission (HR: 1.701 (0.727-3.983), P=0.221) at 1 year following index discharge.
Conclusion: While the numbers are small, these data suggest that the very elderly with HF derive similar benefit to younger patients from DMPs despite some differences in their in-hospital management. Active recruitment of these patients to DMPs should be encouraged.

P1583 Comorbidity and therapy in heart failure in the presence of renal dysfunction

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Renal dysfunction (RD) predicts an adverse outcome and may contribute to the progression of the disease in patients with chronic heart failure (CHF). The prevalence of RD in patients participating in randomised controlled trials ranges between 20-50% and comorbid factors are implicated in its aetiology. Suboptimal pharmacological management of CHF may occur in the presence of RD due to lower doses of angiotensin converting enzyme (ACE) inhibitors being used.
Aims: To determine the prevalence of RD in a representative CHF population and to explore associations with comorbidity and baseline drug treatment in CHF.
Methods: 776 patients with symptoms of CHF and a left ventricular ejection fraction (LVEF) $<$40% on echocardiography were prospectively enrolled in a single community heart failure service. A creatinine clearance (CrCl) $<$60ml/min calculated using the Cockroft-Gault equation [(140-age) x weight(kg)/(Creat(μmol/L) x 0.81) x 0.85 if female] was used to define RD in our cohort. The influences of hypertension, diabetes mellitus (DM), vascular disease (previous peripheral vascular disease, stroke and ischaemic heart disease), use and dosage (expressed as a percentage of maximum recommended daily dose) of ACE inhibitors, use and dosage of loop diuretics, angiotensin receptor blockers, spironolactone, thiazides and beta blockers were explored.
Results: Mean age was 71 (SD 11) years. 438 (56%) patients had CrCl $<$60ml/min of which 248 (32%) were women. Patients with RD were older ($p<0.0001$) and more likely to be male ($p<0.0001$). Hypertension, DM and vascular disease at baseline had no influence on the prevalence of RD in CHF. Patients with RD were more likely to be on diuretic treatment ($p<0.001$) and on higher average daily doses of loop diuretics (61mg v 43mg, p=0.002). There was no difference in the prescription of agents to block the renin-angiotensin-system between the two groups, even if a serum creatinine (SCr) value $>$130μmol/L was used to identify RD. Doses of ACEi were lower in the presence of a SCr$>$130μmol/L (p=0.007). This was not the case when doses were compared with CrCl. There was no difference in the use of other diuretics, beta blockers and aspirin.
Conclusion: Renal dysfunction is more common in patients with CHF than previously reported. Simple factors such as age, sex and diuretic use appear significantly associated with RD. In the presence of a high SCr physicians are hesitant to prescribe optimal doses of ACE inhibitors. Patients with reduced CrCl were on higher doses of diuretics reflecting the need for higher doses to achieve the same response in RD.

P1584 Management of heart failure in hospital in compare to guidelines – any difference between the cardiologists and other specialists?

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Background: Despite the recommendations of the European Society of Cardiology (ESC) results from recent studies suggest that only 50% patients with heart failure (HF) receive such agents as angiotensin-converting enzyme inhibitors (ACE-I) or beta-blockers (BB).
Aim: The aim of this study was to asses how the specialists from different departments think HF should be managed, how they implement their knowledge and whether differences between specialists exist in practice.
Methods: At first, the specialists, cardiologists and diabetologists, answered the questions about the management of different stages of HF. Than we analysed medical documentation of 345 patients aged between 38 and 98 years, hospitalised in Cardiology and Gastroenterology Departments from October 2000 to February 2002 by reason of coronary artery disease, dilated cardiomyopathy and hypertension. Finally we compared the knowledge of HF management from questionnaire and its translation into clinical practice, whether differences in HF treatment exist between cardiologist and diabetologists and if it is consistent with the recommendations of ESC.
Results: ACE-I and BB were prescribed in all NYHA classes of HF. In II, III and IV NYHA class of HF cardiologists more often prescribed ACE-I than diabetologists, respectively 79% vs. 54% (II and III NYHA class), 95% vs. 54% (IV NYHA class), $p < 0.05$.
BB were used more often in Cardiology Dept., respectively 80% vs. 66% (II and III NYHA class), 87% vs. 34% (IV NYHA class), $p < 0.05$. The frequency of prescribing loop diuretics or tiazids increased with the severity of HF. Loop diuretics were more frequently used in the II NYHA class in Gastroenterology Dept. (38% vs. 16%), but in severe HF more often prescribed in Cardiology Dept. (96% vs. 46% in IV NYHA, $p < 0,05$). The patients were additionally treated with digitalis glycoside, spironolactone, started from II NYHA class. Diabetologists more often prescribed digoxin in II NYHA class (27% vs. 8%), but rarely thiazides in II and III NYHA class (7% vs. 33%). The highest compliance between declarations from questionnaire and clinical practice concerned the use of BB and ACE-I combination.
Conclusion: The study indicates that despite the specialists know ESC recommendations of HF management, their knowledge is not sufficiently implemented into the clinical practice. The treatment of patients with HF is less than optimum and there are substantial variations in practice between specialists.

P1585 Improving angiotensin-converting enzyme inhibitor use in patients hospitalised with systolic heart failure: a cluster randomised controlled trial

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Purpose: To evaluate the effect of developing and implementing Clinical Practice Guidelines (CPGs) on the quality of care given to patients receiving Angiotensin-Converting Enzyme (ACE) inhibitors for systolic heart failure.
Methods: Twenty cardiology units in Lorraine (France) were randomised to an experimental group (n=10)or a control group (n=10). In each experimental unit, physicians were involved in drafting and implementing CPGs; those at control units were not. Practice surveys were conducted in all units before and after the intervention; 723 patients with heart failure and less than 75 years old were included. The main outcome was compliance with the CPGs.
Results: Before intervention, clinicians in both groups were already compliant with CPGs relating to indications and contra-indications, adverse effects management, concomitant therapy and monitoring of biologic factors. After intervention, adherence to others CPGs was generally better in the experimental group. Compliance with the CPG relating to ACE inhibitor dose on discharge was higher in the experimental group (p=0.003). Compliance with CPS relating to increasing ACE inhibitors doses ($p<0.0001$) and the contents of discharge letter (p=0.02) improved in all units between the two periods.
Conclusion: These results suggest that physicians involved in drafting and implementing CPGs are more likely to comply with them.

P1586 Relation of gender, age and concomitant diseases to drug prescription for heart failure in primary care in Europe

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Purpose: Previous studies have shown that in patients with heart failure there is evidence for under-utilization of cardiovascular drugs. Current data regarding drug therapy in primary care is limited, and studies assessing the predictors of drug prescription are sparse.
Methods: In a quality of care survey (Improvement of HF study), in 15 European 8256 patients with symptoms of heart failure were enrolled. Among other variables, demographic characteristics, concomitant diseases and drug therapy were recorded. We assessed the role of age, gender and comorbidity for drug prescription with multivariate logistic regression.
Results: Overall prescription rates for ACE-inhibitors/angiotensin receptor blockers (ACE-I/ARB), beta-blockers, digitalis, diuretics and oral anticoagulants were 69%, 30%, 41%, 75% and 18%. There was no evidence for a reduced prescription likelihood for ACE-I/ARB and beta-blockers among women (odds ratio [OR] =0.96 [95% CI 0.87-1.06] and 1.02 [0.92-1.13], respectively), but there was a decreased prescription likelihood for oral anticoagulants (OR=0.74, 95% CI 0.65-0.84). Up to age 85 years, ACE-I/ARB prescription did not materially decline, whereas beta-blocker prescription was already significantly decreased in the category of patients aged 65-74 years. Utilization of diuretics increased with advancing age while prescription of oral anticoagulants declined. There were drug-specific associations of prescription with concomitant diseases. For example utilization of AEC-inhibitors/ARB was higher among diabetic patients, whereas use of beta-blockers was reduced among patients with pulmonary diseases.
Conclusions: Among heart failure patients cared for in the community age and concomitant diseases strongly predict prescription of cardiovascular drugs. Apart from oral anticoagulants among women, there was no evidence for a sex-specific underprescription of cardiovascular drugs.

P1587 Reasons for non-prescription of angiotensin-converting enzyme inhibitors and beta-blockers in ambulatory heart failure: the SONIC survey

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Background: despite guidelines, the use of ACE inhibitors and betablockers remains limited in chronic heart failure (CHF) and the reasons for non prescription are largely unknown. **Aims:** our objective was to evaluate the reasons for non prescription of recommended drugs in a large outpatient population. **Methods:** 1889 outpatients (pts) were enrolled in a national survey among 422 private cardiologists. 75% were pts male, 25% female; NYHA I: 15 pts, II: 66 pts, III: 17 pts, IV: 2 pts. 75% were 61 years or older (mean age: 67 years). Mean ejection fraction was 39%. CHF was ischaemic in 41% and non ischaemic in 59%. **Results:** 86% were treated by a diuretic agent; 76% by an ACE inhibitor at the recommended maintenance dose ranges and 58% by a betablocker with a mean dose of less than 50% of the recommended maintenance dose ranges. Reasons for non prescription of an ACE inhibitor or a betablocker were respectively: adverse reaction = 85% (cough) and 31% (hypotension); contraindication = 3% (renal insufficiency) and 37% (asthma); fear of adverse reaction/compliance = 12% and 32%. **Conclusion:** non prescription of ACE inhibitors in an ambulatory CHF population is mainly related to adverse reactions whereas non prescription of betablockers is equally related to adverse reactions, contraindications or fear of adverse reactions.

P1588 Prescribing for heart failure: a contemporary view

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Background: Betablockers, ACE inhibitors (ACEI) and spironolactone reduce mortality and morbidity in patients with heart failure. There is little contemporary information on the proportions of patients receiving these medications in the community. We, therefore, examined prescribing patterns for heart failure in Scotland. **Methods:** We used the Scottish Continuous Morbidity Record (CMR) Database to study all heart failure patients attending 22 selected general practices in Scotland with a combined list size of 140,246 between 1st April 1999 and 30th March 2000. These practices are broadly representative of the Scottish population in terms of age, sex and social deprivation. **Results:** The prevalence of heart failure in Scotland is 6.4 per 1000 in men and 7.8 per 1000 in women. In men 26.7% were prescribed a betablocker, 15.7% spironolactone and 48.2% an ACEI. The corresponding figures for women were 18.6%, 10.7% and 37.7% ($p=<0.05$). In patients under 75 years 25.3% were prescribed a betablocker, 18.5% spironolactone and 53.9% an ACEI. The corresponding figures for patients over 75, were 16.1%, 9.3% and 34.9% ($p=<0.05$).
Conclusions: Despite the survival benefit of beta-blockers, ACE inhibitors and spironolactone, they are under-prescribed in the community, especially in women and elderly patients.

P1589 Use of digoxin in the treatment of heart failure: How? When? In which patients? Data from the Italian network on congestive heart failure (IN-CHF)

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Purpose: The Dig-study has shown a neutral effect of Digoxin (D) on total mortality of patients (pts) with chronic heart failure (CHF). The impact of the results of this trial on the prescription of D in a community setting of pts with CHF are not known. The aims of this study were to analyse prescription patterns of D in a large group of outpatients with CHF and to analyse the independent predictors of D prescription.
Methods: From 1995 to 2000, 11070 CHF patients (mean age 64±12 yrs, ejection fraction: 35±12%) were enrolled in a large Italian database. Rates of prescription of D were evaluated in two periods: before (1996-1997) and after (1998-1999) the DIG-study pubblication.
Results: Out of 11070 patients, 7198 (65%) were treated with D. The multivariate analysis showed that the following variables were independently associated with D prescription; atrial fibrillation (OR 3.3, 95%IC 2.9-3.8), NYHA class III-IV vs II-III (OR 3.3, 95%IC 2.9-3.8), ejection fraction <30% (OR 1.7, 95%IC 1.5-1.9), third heart sound (OR 1.5, 95%IC 1.3-1.6). After the publication of the Dig-Study, there was a significant reduction in the number of D prescriptions: pts taking D from 1998-1999 fell to 61.7% from 69% in the period 1996-1997 ($p<0.001$).
Conclusions: Over 60% of Italian outpatients with CHF were treated with D; pts with low ejection fraction, atrial fibrillation and in a more advanced stage of CHF are more likely to receive this drug. After the publication of Dig-study, the number of prescriptions for this drug which was given to pts with CHF has significantly decreased.

P1590 Heart failure treatment in the "real world: the Austrian survey of treating heart failure (AUSTRIA)

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Background: In western countries the burden of heart failure is increasing. Therefore, the management of these patients will be a key issue in the future. Although major cardiovascular societies update their guidelines on diagnosis and treatment of heart failure on a regular basis, there are some concerns that this information might not reach those who are responsible for heart failure patients, i.e. the doctors. Furthermore, treating these patients becomes increasingly complicated by introducing new therapeutic regimens for different stages of the disease. Thus, we were interested to reveal how doctors treat heart failure patients in practice.
Methods: A nation-wide survey including general practitioners (GPs), specialists for internal medicine and hospitals with outpatient units for internal medicine was done in Austria between February and May 2002. A simple, two-sided questionnaire asking for demographics, vital signs, concomitant diseases and heart failure therapy was sent to 96 centres. Doctors were asked to report on up to 30 patients from their institution.
Results: A total of 1880 patients were documented, 57% coming from GPs, 27% from specialists and 16% from hospitals. 946 patients were male, 920 female, mean age was 71±11 years, mean systolic blood pressure 144±11 mmHg, mean heart rate 77±12 beats per minute. The majority of patients was in NYHA functional class II (920) and III (565), respectively, 291 were in class I, and 69 in class IV. Aetiology of heart failure was ischemic in 47%, hypertensive in 37% and unknown in 16%.
Blockers of the renin-angiotensin-system (RAS-blockers including ACE inhibitors and angiotensin receptor blockers) were prescribed to 78% of the patients, diuretics (all except spironolactone) were prescribed to 70%, beta-blockers were given to 49%, glycosides to 20%, while spironolactone was prescribed to only 16% of heart failure patients. Most patients were treated with two or three (range 0-7) drugs per day for heart failure.
Conclusion: This nation-wide survey allows a glimpse at the real world of heart failure treatment in Austria. Although treatment is in accordance with current guidelines, our findings indicate that the application of RAS-blockers, beta-blockers and spironolactone should be increased in the heart failure population.

P1591 Impact of diabetes on current in-hospital management of heart failure by cardiologists and internists. Data from the TEMISTOCLE study

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Background Diabetes mellitus affects approximately 15 to 35% of heart failure (HF) patients (pts) and could affect their outcome and clinical management. The aim of the study was to evaluate the impact of diabetes in the clinical profile, use of resource, management and outcome of HF pts.
Methods The study population consisted of 2127 pts, discharged from 167 Italian Cardiology Departments and 250 Internal Medicine Units between 14 and 25 February 2000 with a primary diagnosis of worsening HF. Differences according to the presence of diabetes were assessed comparing clinical characteristics, rate of the use of diagnostic tests during hospital stay, therapy at discharge, in-hospital and 6-month follow-up outcome
Results 603 pts (28.4%) had a clinical diagnosis of diabetes and were admitted in similar rates in Cardiology and in Internal Medicine ward (27.1% vs 29.1%, ns). Mean age was 73±10 yrs among diabetic pts and 75±12 yrs among the non-diabetic pts (p=0.0006). Diabetic pts were more likely to be women (50.9% vs 45.4%, $p<0.0001$), had a more frequent ischemic etiology (50.2% vs 38.5%, $p<0.0001$) and a similar degree of left ventricular dysfunction (mean EF 38.3% vs 37.2%, ns). The rate of atrial fibrillation was lower in diabetic pts (39.3% vs 46.8%, p=0.0075). Diabetes did not influence the rate of diagnostic (invasive and non-invasive) procedures and the lenght of stay (11.2±7.7 vs 11.8±7.4 days, ns). Echocardiography was the most performed procedure in both groups (69.4% in diabetic and 67.6% in non-diabetic pts). At discharge, pts were prescribed ACE-inhibitors, digoxin, furosemide, spironolactone and beta blockers (10.2% vs 12.8%) at the same rate; diabetic pts received less frequently amiodarone and anticoagulants and more frequently nitrates and antiplatelets, according to the higher rate of ischemic aetiology. Among precipitating factors, myocardial ischemia (29.2% vs 22.8%,p=0.0031) and inappropriate dietary factors (10.8% vs 4.9%,$p<.0001$), were more frequent in diabetic pts. Diabetes did not influence in-hospital mortality (5.3% vs 5.7%, ns). After adjusted analysis diabetes didn't result an independent predictor of in hospital and 6 months mortality (OR 1.12 CI 0.72-1.76, OR 0.7 CI 0.47-1.05, respectively) During 6-month follow-up there was a similar rate of re-hospitalization in diabetic comparing with non-diabetic pts (46.1%vs 44.1%, ns).
Conclusion In a "real world " setting diabetes only slightly affects therapeutic choices, use of resource, morbidity and short term mortality of heart failure pts.

P1592 Clinical uncertainty for coronary artery bypass graft surgery: when trials dont have the answer

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Background Lacking or conflicting evidence from trials regarding the appropriateness of coronary bypass grafting (CABG) fuels clinical uncertainty and variations in clinical practice. This study aimed to determine the extent of clinical uncertainty in the decision to perform CABG and its impact on clinical outcomes.
Methods Prospective study of 2552 patients with confirmed coronary artery disease (CAD) participating in the Appropriateness for coronary revascularisation (ACRE) Study. Clinical uncertainty for CABG was defined by expert panel ratings of appropriateness. A combinations of clinical factors was rated on a scale from 1 to 9: 1-3 denoting inappropriate, 4-6 uncertain, 7-9 appropriate use. Patients were matched to these ratings but managed independent of them. Main outcome measures were revascularisation (CABG(n=212),PCI(n=288)) and death (n=81)or non-fatal myocardial infarction(n=27). Patient characteristics were compared to existing trial populations.
Findings The appropriateness of CABG was judged uncertain in 40% of patients with CAD of whom a third subsequently underwent PCI and half were managed medically. The hazard of death or non-fatal myocardial infarction in patients deemed uncertain was greater in patients treated medically compared with patients who received CABG, even after excluding patients with three vessel or left main stem disease (HR 2.94; 95%CI 1.06,8.33). In patients deemed uncertain for CABG 56% had acute coronary syndrome and 30% a high operative risk- both exclusion criteria in the majority of trials. In addition, the most common combined characteristics shared by patients deemed uncertain for CABG were demonstrable ischaemia and one or two vessel disease. While both characteristics were individually well represented in trial populations, the combination of clinical factors as the cause of uncertainty is seldom if ever addressed in trials and by design limited.
Conclusion Uncertainty about the performance of CABG in patients with CAD was considerable. Appropriateness ratings complement trial evidence in guiding decisions when there is uncertainty about the best course of action, because they address individual patient constellations and provide evidence when trial data are lacking. We found that patients who were uncertain for CABG benefited prognostically from CABG despite lack of supporting evidence from randomised controlled trials.

P1593 Anticoagulants for patients with heart failure and atrial fibrillation: myth or reality. A cohort study

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Purpose: All patients diagnosed of heart failure (HF) and concomitant atrial fibrillation (AF) should be anticoagulated unless there are any contraindications. However, often many patients are not treated. The aim of our work was to investigate the magnitude of underuse of anticoagulants and the risk markers of underuse in patients hospitalised with descompensated HF and AF.
Methods: From January 1999 until June 2000, all consecutive patients diagnosed during hospitalisation of descompensated HF were investigated (N=1212) by reviewing the discharge letter, and by a structured telephone interview after a mean follow up of 20±2 months. Data regarding past medical history, clinical data during hospitalisation, and treatments on discharge and follow-up were analysed.
Results: Of 1212 patients included (49.8% males; mean age 76.5±10.5 years old), 653 patients (53.9%) had been diagnosed of AF (51.3% males; mean age 76.7±9.5 years old). On discharge, only 35.4% of patients with descompensated HF and AF were on dicumarinics, 31.7% on low-dose aspirin, 4.4% on triflusal and 1.1% on clopidogrel. After follow-up, 49.4% were on dicumarinics, 36.9% on low-dose aspirin, 1.8% on triflusal and 1.5% on clopidogrel. During follow up 12.2% of patients started dicumarinics therapy, but 2.1% discontinued the treatment. By logistic regression analysis we found that a prosthetic cardiac valve (OR:6.8; IC95%:2.5-18.4), an echocardiographic study (OR:1.8; IC95%:1.1-2.9) and an admission in the Cardiology Service (OR:3.2; IC95%:1.9-5.5) were associated with a higher probability of dicumarinics use on discharge, whereas the higher age (OR:0.89; IC95%:0.87-0.92) and hypertension (OR:0.54; IC95%:0.33-0.87)were associated with lower probability. The only factors promoting the starting dicumarinics during follow up were the ambulatory control of the patient in a cardiology or internal medicine outpatient clinic (OR:5.3; IC95%: 1.9-14.6), and a lower age (OR: 0.97; IC95%: 0.88-0.97). Survival analysis by Kaplan-Meier demonstrated in this population that the use of dicumarinics was associated with a lower risk of death during follow up (log rank p=0.0031).
Conclusions: We have found an unacceptable underuse of anticoagulants in this high-risk population. The use of anticoagulants was significantly associated with lower mortality and hospitalisation rates. The main markers of underuse of anticoagulant therapy were higher age, hypertension, the absence of echocardiography and a hospitalisation outside the Cardiology Service.

ACUTE CORONARY SYNDROME REMAINS A CLINICAL CHALLENGE

P1594 Coronary angioplasty in patients with poor left-ventricular function: procedural and mid-term results

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Objective: Poor left ventricular (LV) function is considered a high risk condition for performing either percutaneous or surgical coronary revascularization. Severely symptomatic patients are often denied appropriate interventional treatment due to fear of procedural failure and are maintained on medications, the fortunate few receiving cardiac transplantation.
Methods and Results: In the present study, we have analyzed the procedural results and mid-term clinical follow-up of 68 consecutive pts, with mean LVEF of 0.25 (8% of patients who underwent percutaneous revascularization the last year).The majority of these pts had multivessel disease (CASS mean 2.3 vessel/pt). Angina Class III or IV was present in 62/68 (92%) and 53/68 (73%) had dyspnea Class III or IV at the time of intervention. Prior revascularization had been performed in 59/68 (87%) of which CABG was done in 18. At the time of the procedure, 5/68 (7.3%) were in cardiogenic shock. IABP was used in 23/68 (34%) patients. Multivessel intervention was performed in41/68 ptients (60%). Of the 160 lesions treated, POBA was done in 37 (23%), stenting in 111(69%), debulking with stent implantation in 6 (3.7%), debulking without stent in 6 (3.7%). Procedural success was achieved in 63 pts (92.6%). The procedural complications included: deaths - one (1.4%), vascular complications - one (1.4%), non-Q MI - 2 (2.9%) and Q wave MI - one (1.4%). All patients received at least a bolo of GP IIb/IIIa antagonists prior to the procedure. At a mean follow-up of 16 $\pm$ 3 months, 55 pts were alive (80.1%). A new interventional procedure was performed in 26 pts. (38.2%) - PTCA in 18 and CABG in 6, and 5(7.3%) had sustained a new myocardial infarction. Improvement in the angina and/or dyspnea status was reported in 24 pts (35.3%).
Conclusion: We conclude that, in high risk patients who are symptomatic despite optimal medical therapy, percutaneous revascularization can be performed with acceptable procedural and mid-term morbidity and mortality rates leading to improvement in the quality of life. Moreover, in this subset of pts, PTCA may have an important role as a bridge to cardiac transplantation.

P1595 Independent and incremental prognostic value of Troponin T kinetics in patients with ST-segment elevation myocardial infarction undergoing percutaneous coronary interventions

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Purpose: The important prognostic of the admission Troponin T (TnT) serum levels in patients (pts) with ST elevation acute myocardial infarction (AMI) is well established from large scale clinical studies. The purpose of this study was to assess if TnT release kinetics could predict a better long-term outcome in pts with AMI treated with successful percutaneous coronary intervention (PCI).
Methods: In 104 pts who underwent successful primary PCI within 4 hours of the symptoms' onset TnT was measured on admission, after PTCA termination, every 6 hours for the first 24 hours and finally at 36, 48, and 72 hours. Cardiac death and the combined end point (CEP) of death, AMI, repeat PCI and CABG were recorded for a minimum period of 2 years. In all pts the relation of the end points with several variables (demographic, clinical, and angiographic) was assessed. Univariate analysis was made with t-test or chi-square, while multivariate analysis was performed using Cox regression.
Results: Cardiac death was significantly related with age ($p<0.001$), time from pain onset to PCI (ischemic time-$p<0.001$), time from pain onset to peak TnT (t-pTnT-p=0.02), TIMI flow grade after PCI ($p<0.001$), number of vessels (p=0.008), diabetes mellitus (DM-p=0.002), and heart failure (HF-p=0.001). Multivariate analysis identified age (p=0.001), HF (p=0.006), and t-pTnT to PCI (p=0.012) as independent predictors of cardiac survival. Kaplan-Mayer analysis revealed a significantly higher incidence of cardiac death in pts with t-pTnT$>$11hours. Incidence of CEP was related with age (p=0.001), t-pTnT ($p<0.001$), TIMI flow grade ($p<0.001$), DM (p=0.001), HF ($p<0.001$) and stents implantation (p=0.005). Multivariate analysis identified age (p=0.032), HF (p=0.001), and t-pTnT (p=0.012) as independent predictors of cardiac event free survival.
Conclusions: Pts with t-pTnT$<$11 hours had better cardiac survival and better cardiac event free survival. In addition, t-pTnT was an independent predictor of cardiac event free survival and consequently it may be used as a marker for the subsequent risk stratification and management of pts with ST segment elevation AMI undergoing PCI.

P1596 Population survival after emergency admission with "chest pain compared to angina and myocardial infarction

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Background: While the prognosis after acute myocardial infarction (AMI) has been widely reported, there are few population data describing outcome following emergency admission to hospital with angina or "chest pain". Though the latter two conditions are often thought to have a benign course (especially "chest pain"), this assumption has not been properly studied. We, therefore, examined short and longer-term case-fatality following emergency admission with AMI, angina and "chest pain" in Scotland between 1986 and 2000.
Methods: Using the Scottish Record Linkage System, we analysed case-fatality for up to ten years following admission. Only patients with a first-ever admission to hospital and a principal discharge diagnosis of one of the three conditions of interest were studied. Patients with "chest pain" had no prior admission with coronary heart disease. We used multivariate modelling to examine the independent prognostic effects of diagnosis, age, sex, socioeconomic deprivation, and co-morbidity.
Results: 161,051 individuals were admitted with AMI, 71,036 with angina and 139,583 with chest pain. 30-day case-fatality was high for AMI (17.9% in men and 26.7% in women) but low for both angina (1.9% and 1.8%) and chest pain (1.2% and 1.1%). However, after excluding deaths within 30 days, the long-term adjusted mortality risk after an emergency admission with chest pain (0.91 in men, 0.78 in women) and angina (0.95 in men, 0.82 in women) approached that of AMI (risk after MI set at 1 in the multivariate analysis).
Conclusions: Emergency admissions with angina or "chest pain" have a low risk of death in the short-term, but have a poor long term prognosis. "Chest pain" or angina leading to an emergency hospital admission should not be regarded as benign. Patients with these conditions merit active investigation and treatment.

P1597 Additional prognostic information of C-reactive protein to TIMI risk score in patients with ST-elevation myocardial infarction

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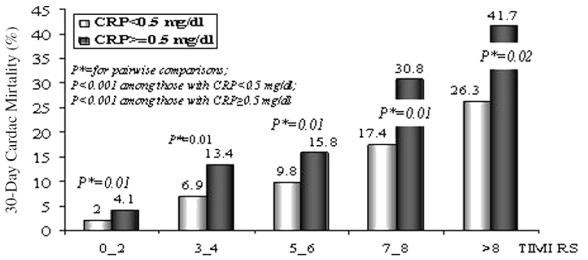
Background: Rapid triage is fundamental for early clinical decision making in the setting of ST-segment elevation myocardial infarction (STEMI). TIMI Risk Score for STEMI (STEMI-TIMI-RS) is a simple, accurate and validated clinical tool for early risk stratification. Additionally, elevated plasma C-reactive protein (CRP) levels have been associated with adverse prognosis in this setting. The present study tested the hypothesis that elevated plasma CRP levels measured early in the course of STEMI may add prognostic information to STEMI-TIMI-RS.
Methods: Among 670 consecutive pts who thrombolysed in the first 6 hours of STEMI were studied. STEMI-TIMI-RS and CRP levels were assessed upon admission. Cardiac death (CD) by 30 days was the primary endpoint.
Results: Total cardiac mortality by 30 days was 8.2%. There was a significant 30-day CD probability with increasing of STEMI-TIMI-RS ($P<0.001$). Moreover plasma CRP levels $\geq$0.5 mg/dl (defined by ROC analysis) was associated with increased 30 days CD probability ($P<0.001$). There was no significant association between plasma CRP with increasing of STEMI-TIMI-RS (P=0.9). Finally, there was significant difference in 30-day CD between the several subgroups of STEMI-TIMI-RS with or without $\geq$0.5 mg/dl (Fig. 1).



Conclusions: The present study implies that CRP, a useful marker of inflammatory response add significant prognostic information beyond that of STEMI-TIMI-RS in pts who thrombolysed in the first 6 hours of STEMI.

P1598 Platelet nitric oxide responsiveness: a novel prognostic indicator for acute coronary syndromes

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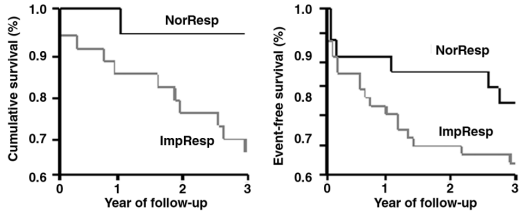
Nitric oxide (NO) is critically important in the regulation of vascular tone and the inhibition of platelet aggregation. We have previously demonstrated that in approximately 60% of patients with acute coronary syndromes (ACS) platelet responsiveness NO donors is impaired (<35% inhibition of ADP-induced aggregation with sodium nitroprusside [SNP; 10uM]). This diminished response to the anti-aggregatory effects of SNP reflects both incremental NO clearance by superoxide and reversible impairment of platelet soluble guanylate cyclase activity. We have now tested the hypotheses that impaired platelet responsiveness to NO is a predictor of (a) mortality or (b) cardiac readmission and/or death in patients with ACS.

Methods: Patients (pts; n=51) with ACS had evaluation of platelet aggregation within 24 hours of coronary care unit (CCU) admission utilizing impedance aggregometry, and were categorized as having normal (NorResp; n=18) or impaired (ImpResp; n=33) NO responses. We then compared the incidence of death and cardiovascular events during 3 years follow-up in these two groups.

Results: During 3-year follow-up, 1 of 18 versus 11 of 33 pts in the NorResp and ImpResp groups died (6% vs. 33% - multivariate adjusted RR 0.10; 95% CI 0.01 – 0.84: P = 0.033). Similarly, 6 versus 21 pts in the NorResp and ImpResp groups had a cardiovascular event or died (33% vs. 64% - adjusted RR 0.26; 95% CI 0.10 – 0.75: P =0.012). The survival curves below (Fig 1) show the increased risk of death and decreased event free survival for patients with initial ImpResp.



Conclusion: Low platelet NO responsiveness is a novel, independent predictor of increased mortality and cardiovascular morbidity in patients with ACS.

P1599 Implications of current definitions on short and long-term outcome of acute coronary syndromes. Results of a large prospective single-hospital registry

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Purpouse To delineate the in-hospital, long-term (first year: 1y) and post-discharge outcome of patients with acute coronary syndromes (ACS) stratified according to the current guidelines.

Methods: After the publication of the new myocardial infarction definition we prospectively analysed 1324 consecutive patients admitted with a diagnosis of ACS to a tertiary hospital. Mean age was 67±12 years and 69% of cases were male. Of these patients 483 (37%) had a ST-elevation myocardial infarction (STEMI), 439 (33%) a non-ST-elevation myocardial infarction (NSTEMI: troponin I >1ng/ml) and 402 (30%) an unstable angina (UA: troponin I <1ng/ml). None of these patients participated in clinical trials. Major events (death or MI) were prospectively registered since arrival to the emergency room and during the first year.

Results: Within one-year follow-up 177 deaths (13.4%), 146 new MI (11%) and 284 first major events (21.5%) were detected. For patients with STEMI, NSTEMI and UA death rates were: in-hospital 13%, 7.1%, 2% (p <.0001), 1y 18.2%, 14.4%, 4.7% (p <.0001) and post-discharge 5.6%, 8.4%, 2.7% (p=.002). MI rates were: in-hospital 3.3%, 4.3%, 2.2% (p=ns), 1y 8.3%, 16.6%, 7.5% (p <.0001) and post-discharge 5.4%, 12.5%, 5.2% (p <.0001). Major events rates were: in-hospital 14.9%, 10.9%, 3.7% (p <.0001), 1y 23.6%, 28%, 10.7% (p <.0001) and post-discharge 9.1%, 17.5% and 7% (p <.0001). In the multivariate analysis of the 922 patients with MI, STEMI was independently related to death in-hospital (odds ratio (OR) 2.8 p <.0001) and 1y (OR 1.9 p=.002) but not post-discharge (p=ns). NSTEMI was related to MI 1y (OR 2 p=.001) and post-discharge (OR 2.5 p=.0005). STEMI was related to in-hospital major events (OR 1.8 p=.007) whereas NSTEMI predicted post-discharge major events (OR 1.9 p=.004). No significant differences in the total rate of major events within the first year were detected between STEMI and NSTEMI.

Conclusions: According to the results of our prospective "real-world" registry the current stratification of ACS seems to be highly adequate. Patients classified as UA exhibit the best prognosis. In the case of STEMI the maximum risk period takes place in-hospital whereas a high rate of post-discharge major events occur in NSTEMI. A wider application of the current management recommendations may improve outcome of MI in each of the critic periods observed.

P1600 Braunwald classification of unstable angina has better prognostic significance than World Health Organization unstable angina classification

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Background: Finding a simple clinical test for stratifying high-risk patients with unstable angina (UA) still represents a challenge. **Method:** The occurrence of non-fatal myocardial infarction, death and recurrent UA was registered in 94 consecutive patients, aged 56 ± 8.65 years, 61 males, with different types of UA, followed for 39 ± 13 months. The exclusion criteria were: clinical signs of heart failure, age less than 70 years, and the possibility of adverse outcome due to concomitant non-cardiac disease. Patients were classified according to the WHO criteria (de novo, crescendo, spontaneous, and early postinfarction angina group was added) as well as according to the Braunwald classification criteria. For the comprehensive analysis the UA scoring system was introduced. Each gradation of the each of the 3 categories of the Braunwald classification was given from 1 to 3 points. Adding the points from all 3 categories resulted in the UA score (minimum 3, maximum 9). Another scoring system based on the severity of angina was introduced for the WHO classification to enable comparison with the Braunwald classification: de novo=1 point; crescendo=2 points (PTS); spontaneous=3 PTS; postinfarction= 4 PTS. The comparison of prognostic significance of the two classifications of UA was performed by the use of the Cox multivariate analysis. **Results:** The frequency of adverse events among the groups formed according to the WHO criteria was as follows: de novo 0/1(0%); crescendo 1/5(20%); spontaneous 16/78(21%); postinfarction 4/10(40%), p=NS. The frequency of adverse events among the groups formed according to the value of the UA score was as follows: score 5 [0/4(0%)]; score 6 [1/25(4%)]; score 7 [4/20(20%)]; score 8 [15/40(37%)]; score 9 [1/5(20%)]; p=0.03. The WHO classification of UA did not show the prognostic significance in Cox multivariate analysis in the model with the UA score. The Braunwald classification, expressed by the UA score, had a significant prognostic value in Cox multivariate analysis in the model with WHO UA classification, p=0.049. **Conclusion:** The Braunwald classification of UA, expressed by the UA score, has better long-term prognostic significance in comparison with the WHO UA classification.

P1601 Neutrophil count, infarct size and cardiovascular mortality in patients with anterior myocardial infarction

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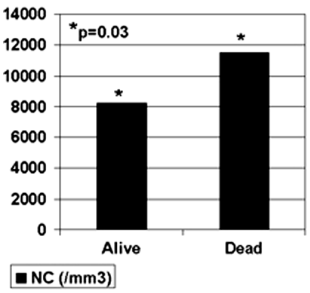
Purpose: Acute myocardial infarction (AMI) is frequently associated with leucocytosis, particularly increased neutrophil count (NC). Elevated NC have been associated with more severe coronary artery disease and with increased risk of myocardial infarction, reinfarction, congestive heart failure and/or in-hospital death. We sought to assess the relationship among NC, infarct size and cardiovascular mortality in patients with anterior AMI.

Methods: We studied 248 consecutive patients admitted to hospital with a first anterior AMI within 12 hours of the onset of symptoms. To minimize confounding factors, we included patients who underwent successful (TIMI 3 flow) primary percutaneous angioplasty. NC was carried out on admission blood samples. AMI size was determined by amount of leads with ST segment elevation, Q wave development after reperfusion, peak creatine phosphokinase level and predischarge left ventricle ejection fraction (LVEF). All patients were followed up during a mean period of 6 months.



Results: Elevated NC correlated positively with longer time elapsed from the onset of symptoms to admission (p<0.0001) and with all variables that determine infarct size, including impaired LVEF. Six month mortality was higher in patients with elevated NC compared to those with lower NC (8.25% versus 3.41%, p=0.08), although did not reach statistical significance. In male patients(n=141), those who died due to a cardiovascular event had higher NC (11513/mm^3 ± 2554 versus 8199/mm^3 ± 3523; P=0.03) than the surviving patients (figure).

Conclusion: 1) High NC on admission in patients with anterior AMI is associated with larger infarct size. 2) High NC on admission is associated to adverse cardiovascular events and 6 month cardiovascular mortality, specially in male patients.

P1602 Effect of angiotensin converting enzyme inhibitor on collagenolysis in acute myocardial infarction patients

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Matrix Metallopreinases (MMPs) and their tissue inhibitors (TIMPs) are key enzymes in myocardial fibrillar collagen degradation and contribute to left ventricular remodelling (LV) after Acute Myocardial Infarction (AMI). Do Angiotensin Converting Enzyme Inhibitors(ACEI) influence collagenase-1 (MMP-1) their tissue inhibitor (TIMP-1) and Complex MMP-1/TIMP-1 (COMP) activity in patients (pts) with AMI?

Methods: We measured MMP-1,TIMP-1 and COMP plasma levels in 24 pts(mean age 58,46±13,9 yrs) with first attack of AMI. Thirteen of them received peridinopril 4 mg/day (group-A) at the time of admission in the hospital, and compared with 11 patients that don't received (group-B). Plasma blood samples were collected at the time of admission (0h) as well as 3h, 6h, 9h, 12h, 18h, 24h, 36h, 48h, 3 days, 4d, 5d, 7d, 15d, 30d, thereafter and analyzed by relevant ELISA kits. All patients did not have previous history of any other disease. For statistical analysis ANOVA rp.m.a and unpaired t-test were used. Data are expressed as mean values±SEM in ng/ml. $p<0.05$ was considered statistical significant.

Results: a) The mean blood values of MMP-1 TIMP-1 and COMP of group-A were found lower average by 34%,18,3% and 40% for total time points respectively compared to corresponding mean values of group-B.

b) A statistically significant difference of mean values between the two groups was found on time points 0h, 3h and 9h for MMP-1 with $p<0,041$, 0,048, 0,039 respectively and for COMP at 9h with $p<0,035$.

c) ANOVA rp.m.a was statistically significant difference within subjects for MMP-1 alone $p<0,0043$ and for combination MMP-1, group A $p<0,046$, while TIMP-1 and COMP within subjects alone were found statistically significant with $p<0,0009$, 0,00013 respectively.

Conclusions: a) A statistically significant decrease of mean blood levels of MMP-1 TIMP-1 and COMP as a consequence of ACEI treatment.

b) These findings may be considered as an alternative mechanism of the beneficial effect of ACEI on the infract expansion and on LV remodeling after AMI.

P1603 Comparison of clinical outcomes, event free survival and repeat enhanced external counterpulsation rates for European and US coronary artery disease patients treated with EECP for angina

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Introduction: EECP is a non-invasive circulatory assist device used in the treatment of patients with refractory angina who are not suitable for further conventional revascularization. Although primarily used in the United States (US) the treatment is now also being used in Europe (EU).This study compares the efficacy, repeat EECP and 1-year major adverse cardiovascular events (MACE: Death/CABG/PCI/MI) free survival rates for patients treated with EECP for angina management in EU with the US.

Methods: The International EECP Patient Registry has enrolled 5000 patients from 90 centers since 1998. Of these 4852 were treated and followed in the US and 168 in EU. Comparisons between groups were analyzed using chi-square tests for categorical parameters and t-tests for continuous variables. Rates of follow-up events were analyzed using survival methods.

Results: EU were younger ($p<0.001$)with a higher proportion of men ($p<0.01$). Duration of coronary artery disease was similar at 11 years and previous revascularization was similar at 82% for EU vs. 86% for US. 38% of EU, 32% of US had congestive heart failure. EU were less likely to have had PCI ($p<0.001$) and more likely to have had CABG ($p<0.01$). 81% of both groups were no longer candidates for further revascularization. EU had less diabetes ($p< 0.001$), hypertension ($p<0.001$), non-cardiac vascular disease ($p<0.001$), hyperlipidemia ($p<0.001$).EU had less Class IV angina ($p<0.001$), less multivessel disease ($p<0.01$),and higher rates of nitroglycerin usage ($p<0.05$). Beta blocker and ARB usage were higher in US.

After a mean treatment course of 34 hours, both groups showed a significant reduction in the severity of angina. Discontinuation of nitroglycerin usage was similar in both groups (83%). MACE during the treatment period were low in both groups (< 2%). Compliance with the treatment course was better in EU, 92% of EU patients completed the treatment as prescribed vs. 83% for US ($p<0.01$). At one year follow up 72% of EU and 77% of US had maintained the improvement in angina class. MACE free survival rate was 94% in EU vs 85% in US (p=0.012). Repeat EECP rates at 1 year follow up were significantly lower in EU (3% vs 13%,$p<0.002$).

Conclusion: Patients presenting for EECP treatment from EU and US populations show very different baseline profiles. Although angina reduction was similar in both groups careful selection of candidates may improve the clinical outcomes, increase the event free survival rates and decrease the need for repeat EECP. Continuing research is needed to determine the best patients for EECP.

ST-ELEVATION ACUTE MYOCARDIAL INFARCTION: PROGNOSTIC MARKERS I

P1604 Angiographical predictors of free wall rupture after primary coronary angioplasty for acute myocardial infarction

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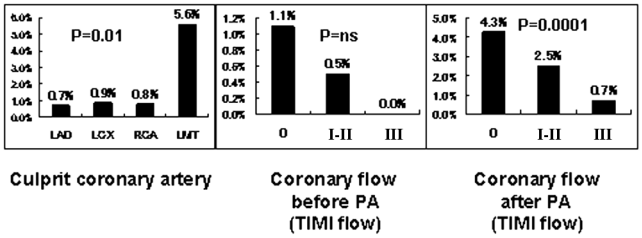
Purpose: Because emergent coronary angiography (CAG) and durable reperfusion strategy with primary coronary angioplasty (PA) for acute myocardial infarction (AMI) was demonstrated to reduce rates of death or nonfatal reinfarction, the indication of angiography for patients with AMI is becoming more frequent than ever. But it is not clear FWR can be predicted from CAG.

Methods: In our prospective database of consecutive 3138 AMI patients seen between May 1985 to May 2002, 3096 patients (98.7%) who underwent CAG was analyzed retrospectively.

Results: FWR occurred in 43(1.3%) patients. 3 patients were excluded from this study because FWR had occurred before arrival. Acute FWR occurred in 28/40 patients (70.0%) and subacute in 12/40 patients (30.0%). Operative repair was performed in 17/40 patients (42.5%), 8 dying after operation. Of the 199 (6.4%) AMI-patients dying in the hospital 25 (13.3%) died from FWR, yielding a 62.5% (25/40) mortality rate. In univariate analysis having PA significantly protected from FWR (3.2% v.s. 0.9%, $p<0.001$). And in patients those having PA (n=2536) FWR occurred in 22 patients (0.9%) and higher rate of FWR was associated with reperfusion unsuccess (the final Thrombolysis In Myocardial Infarction <TIMI> grade flow under 3) and LMT-related infarct in CAG. There was no difference in the incidence of FWR between LAD, LCX and RCA related infarct (see figures).



The incidence of FWR.

Conclusions: Coronary flow after PA was one of the most significant protective factor of FWR. Prompt successful reperfusion by PA reduced FWR complicating AMI and should make possible safe early rehabilitaton and shortening of hospitalization.

P1605 Primary percutaneous transluminal coronary angioplasty: is ST-segment resolution at intracoronary electrocardiogram a prognostic marker for left-ventricular function recovery and 12-month follow-up outcome?

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Background: Intracoronary (IC) ST segment changes are more sensible and specific than surface ECG when evaluating ischemia. The aim of the study was to evaluate if patients without ST elevation at IC ECG registered before performing a primary PTCA have a different outcome than those with ST elevation at same stage.
Methods: Continuous IC ECG recorded from the tip of a guide wire and 12 leads surface ECG were obtained in 96 consecutive patients (p.) undergoing a primary PTCA, performed within 12 hours of symptoms onset, with ST segment elevation at the surface ECG at the beginning of the procedure. Three groups were defined after positioning the tip guide-wire distal to the obstruction site: Group A: 19 p. with no significant ST elevation at IC ECG before and after a successful procedure (TIMI flow grade 3 achievement with less than 30% of residual lesion), Group B: 27 p. with ST segment elevation at IC ECG before angioplasty, and less than 50% reduction at IC ECG after a successful PTCA and Group C (50 p.) with ST segment elevation at IC ECG before angioplasty and more than 50% reduction at IC ECG after successful procedure. End diastolic volume in ml/m^2 (EDV), End Systolic Volume in ml/m^2 (ESV) and Ejection Fraction (EF) were assessed through the area-length method, in 2 ventriculograms performed immediately before (B.) and 24 hours after (A.) 12 month follow up was achieved in 98% of patient population (94/96). Statistical analysis was issued through 2 tailed Student t, ANOVA, chi square, and Fisher exact tests.
Results: Clinical history, age and gender, was similar in all groups (P=NS), no differences were found between Groups A and C in outcoming ventricular function and 1 year mortality (0/19 vs. 3/50). Group A showed a lower mortality rate than Group B (0/19 Vs. 6/27) $p < 0.05$ with a better post PTCA ventricular function, evidenced through a larger number of patients reducing their EDV in Group A (10/13 p.) Vs. 5/27 p. in Group B ($p< 0.001$ RR: 4.15 95% CI 1.78; 9.67) and reducing also their ESV in Group A. (10/13 p.) Vs. 9/27 p in Group B. ($p< 0.05$ RR: 2.31 95% CI 1.25; 4.25).
Conclusions: Patients with ST elevation in the surface ECG and no ST segment elevation in IC ECG before procedure yield a good prognosis group with more patients recovering left ventricular function.

P1606 The OYSTER-AMI study results: cardiac enzyme kinetic, ST-segment changes and left-ventricular function recovery

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Background: Intracoronary infusion of hyperoxemic blood has demonstrated to attenuate reperfusion microvascular injury. Microvascular injury may result in poor recovery of left ventricular (LV) function despite primary percutaneous coronary intervention (PCI).
Aim: To assess cardiac enzyme kinetic, ST-segment evolutionary changes and LV function recovery in primary PCI pts treated with intracoronary hyperoxemic blood infusion and compare them with the results obtained in matched control pts.
Methods: We studied 50 pts treated by primary PCI for ST-elevation anterior AMI. In 26 pts (AO group), hyperoxemic blood (pO2:760-1000 mmHg) was selectively infused with the AO system for 90 min into the LAD via a 4F infusion catheter immediately after coronary recanalization, while the other 24 pts (control group) had normoxemic blood autoperfusion. The two groups were matched in clinical and angiographic characteristics and showed similar pre-procedural LV function (2D-echo). No significant difference was also observed in time to presentation (AO group: 3.4±1.5 hrs; control group: 2.75±1.39 hrs) and maximum ST elevation (AO group: 5.9±3.2 mm; control group: 5.5±3.1 mm). LV function recovery was evaluated by serial 2-D echo (EF and WMSI) at 24 hrs, 7 days and six month in both groups.
Results: LAD recanalization (100% stenting) was successful in all pts. No difference was observed in CK peak levels between AO group (3330±2165 IU/l) and control group (3648±2547 IU/l). However, AO group showed a 5.28±2.9 hrs shorter time to peak CK release (p=0.002) and a shorter CK half-life period (24.9±9 vs. 30.5±5.6 hrs, p=0.002) compared to the control group. Furthermore, AO group had more significant reduction of ST-segment elevation immediately after LAD recanalization (3.6±1.6 mm vs. 2.5±1.8mm, p=0.02). Compared to baseline values, a significant mean relative improvement of LV function (%EF) at 24 hrs, 7 days and 6 months was observed only in AO pts (AO: 5%, 16.7% and 18.3%, respectively) while control pts did not show any significant change (2.4%, 4.5% and 2.5%, respectively).
Conclusion: After successful primary PCI, cardiac enzyme kinetic and ST-segment evolutionary changes in AO treated pts suggest faster and more complete microvascular reperfusion. This may explain the better LV function recovery in AO treated pts compared to controls.

P1607 Early dobutamine echocardiography predicts clinical outcome and improvement in left-ventricular function in patients with acute myocardial infarction treated with primary angioplasty

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Background: Dysfunction of left ventricular contractility after primary coronary angioplasty (pPTCA) for acute myocardial infarction (AMI) may be reversible. Both reversible and irreversible injury may be manifested by regional wall motion abnormalities. Improved wall thickening after dobutamine infusion can identify reversibly injured segments. The accuracy of early dobutamine echocardiography (DE) after successfully treated AMI with pPTCA is still unclear. Patients who respond to early DE may have potentially better chance for left ventricular function improvement and possibly better clinical outcome.
Aim: The objective of the study was to assess whether early DE can predict spontaneous functional recovery in patients treated successfully with pPTCA for AMI and whether responders to DE have better clinical outcome than non-responders.
Methods: DE (5 and 10 ug/kg/min) was performed in 110 consecutive patients (61±10 years, 34 women) 4±1 days after first AMI successfully treated with pPTCA (Thrombolysis in Myocardial Infarction flow grade 3, residual stenosis<30%). Left ventricular ejection fraction (LVEF) and wall motion index (WMI) were the main echocardiographic parameters measured (16 segment model). Reversible myocardial dysfunction was indicated by increase of contractility in at least two segments. All the patients underwent clinical assessment and two-dimentional echocardiography at 3 and 6 months.
Results: In DE responders (74 pts) LVEF increased significantly from 40%±9% at baseline to 49%±10% at 6 months (p<0,001), whereas improvement found in non-responders (36 pts) was insignificant (from 38%±10% at baseline to 39%±9% at 6 months, p=0.6). Recovery of contractility was more frequently observed in hypokinetic then in akinetic segments (p<0.01). Non-responders to DE had higher incidence of death (3/34 (9%) vs 0/76 (0%), p=0.0086), reinfarction (5/34 (14.7%) vs 2/76 (2.6%), p=0.28) and subsequent revascularization (4/34 (11.8%) vs 3/76 (3.9%) p=0.12). The incidence of combined end-point (death, reinfarction and revascularization) was significantly lower in the group of responders to early DE (p=0.03).
Conclusions: These data indicate that early DE can precisely predict spontaneous functional recovery and the extend of irreversibly damaged myocardium in patients with AMI in whom anterograde flow is fully restored. Furthermore positive response do early DE is associated with significantly better clinical outcome and prognosis.

P1608 Early assessment of coronary flow reserve by transthoracic Doppler echocardiography predicts late remodelling in reperfused anterior myocardial infarction

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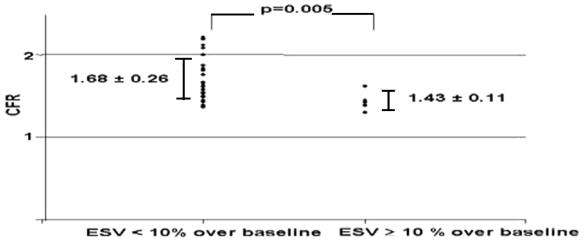
Aim: To assess the effects of coronary flow reserve (CFR) in predicting late left ventricular remodeling in patients with reperfused acute anterior myocardial infarction.
Methods: 31 patients (age 58±13 years, 21 males) admitted with acute anterior myocardial infarction underwent primary angioplasty of the infarct- related vessel. On the first day after infarction, all underwent adenosine (0,140 mcg/kg x 3 m') or Dipyridamole (up to 0.84 mg/kg over 6') stress echo and CFR evaluation of left anterior descending artery by transthoracic Doppler. A CFR <2 was considered abnormal. All patients had resting 2D echo at 1,3,6 months for assessment of left ventricular ejection fraction, wall motion score index and end-systolic volume (ESV).
Results: CFR could be successfully assessed in 31 patients (100%) and separated 2 groups, with either normal (Group 1, CFR> 2.0, n= 5) or abnormal (Group 2, CFR < 2.0, n= 26) response. At study entry, the 2 groups had similar values of ESV (Group 1=76±14 ml vs Group 2= 84±22 ml; p=NS), ejection fraction (Group 1= 42 ±4% vs Group 2= 39±3%; p=ns), and wall motion score index (Group 1= 1.7±0,3 vs Group 2= 2,0±0,2; p=ns). After 6 months, Group 1 patients showed higher ejection fraction (Group 1=53%±3% vs Group 2=44%±7%; p=0.0001), lower wall motion score index (Group 1= 1.3±0,1 vs Group 2=1.6±0,3; p=0.001) and lower ESV(Group 1=55±11ml vs Group 2=76±21 ml; p=0.008). A reduced CFR on day 1 after infarction predicted adverse left ventricular remodeling at 6 months (figure).



Conclusion: Early assessment of CFR by transthoracic Doppler echocardiography is feasible, safe, and useful in identifying patients at high risk of adverse remodeling in spite of successful primary angioplasty.

P1609 Validation of the 12-lead admission electrocardiogram in patients with acute chest pain for diagnosis of myocardial infarction by late contrast enhanced magnetic resonance imaging

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Background: Non ST elevation myocardial infarction (NSTEMI) is a diagnosis that is currently confirmed retrospectively. Current guidelines suggest that up to 6% of NSTEMI patients will have a normal presenting ECG. Contrast enhanced magnetic resonance imaging (ceMR) is a highly sensitive and specific means of detecting infarcted myocardium and is capable of detecting an infarct mass of less than 2g. We hypothesised that among patients admitted to hospital with acute chest pain, the standard 12-lead ECG on presentation is insufficient to identify myocardium subsequently shown to be necrotic by ceMR.
Methods: 52 male and 23 female (mean (range) age=55 (25-83) years) index hospital admissions with chest pain were consecutively recruited. Admission ECGs were analysed by a core lab. Blood sampling for troponin I (TnI) took place after 8-12 hours and peak values for creatine kinase (CK) and CKMB were recorded. MR was performed at a median (range) of 69 (16-120) hrs on a Siemens Sonata 1.5T system using a phased array chest coil. LV dimensions were evaluated by cinematographic (TrueFISP) breath-hold sequence. ceMR was performed 10 minutes after injection of 0.2 mmol/kg gadolinium-DTPA using a breath-hold segmented turboFLASH inversion-recovery sequence. Images were evaluated by planimetry by 2 independent and blinded observers.
Results: Of the 85 patients, 41 had evidence of myocardial infarction (MI) by presence of late enhancement on ceMR. 20/41 (49%) received thrombolysis (infarct mass = 37 (29) g); among these, by ECG core lab, 19 (95%) had confirmed ST elevation, and 1 (5%) had ST depression in keeping with a posterior infarct (mean (SD) TnI=101 (102) pg/ml; CK=1594 (1365) IU/l; CKMB=138 (140) mg/ml). 21/41 (51%) did not receive thrombolysis (infarct mass = 16 (16) g); among these, by ECG core lab, 2 (10%) had ST elevation, 9 (43%) had ST depression, 3 (15%) had T wave inversion and 7 (33%) were classified as normal (TnI=22 (28) pg/ml, p=0.003; CK=588 (779) IU/l, p=0.007; CKMB=50 (77) mg/ml, p=0.02). None of the patients who had no evidence of MI by ceMR had ST-segment elevation on the presenting ECG.
Conclusion: In this study population, 33% of patients who were subsequently diagnosed with MI by ceMR and who did not have ST-segment elevation on the presenting ECG (by definition an NSTEMI), had a completely normal ECG at presentation as assessed by the ECG core lab. ceMR could be useful in the development of more accurate measures of acute ischaemic heart disease.

P1610 Cardiogenic shock in patients with acute coronary syndromes with and without ST-segment elevation: clinical, echocardiographical and angiographical particularities

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Aim of the study: Cardiogenic shock occurs more frequently in patients with acute myocardial infarction (AMI) with ST elevation. The characteristics of patients with non-ST elevation myocardial infarction (NSTEMI) who develop cardiogenic shock are less well identified. Our study assessed the particularities of patients in this setting.
Material and Methods: 626 patients (pts), mean age 65±12 years old, hospitalized between june 1999 - oct 2002 in our Department with a diagnosis of AMI. Fourty-seven pts (7.5%) developed cardiogenic shock (CS). All pts underwent echocardiographical study within 24 hours from hospitalization, and angiographical study during hospitalization. The study pts were divided in: group 1 = 10 pts (21.2%) with NSTEMI, and group 2 = 37 pts (78.8%) with STEMI. We noted during hospitalization the incidence of recurrent ischemic events and of cardiovascular deaths.
Results: Cardiogenic shock developed in 4.6% of pts with NSTEMI as compared with 9.5% of pts with STEMI (OR 0.48, p<0.001), particularly in pts with anterior AMI (80% vs 86.4%, ns). Pts had a similar age (65.3 vs 64.5 years old, ns) and sex distribution (80% vs 75.7% males, ns). Prior MI and angina pectoris were more frequent in the first group (60% vs 21.6% for MI, 60% vs 40.5% for angina, p<0.005). Left ventricular (LV) systolic function was significantly altered in pts with NSTEMI vs STEMI (ejection fraction of 29% vs 31.4%, p=0.04), and as well as LV diastolic function (50% vs 37%, p=0.02), with a predominence of a restrictive pattern of the transmitral flow in pts with NSTEMI. Angiographical findings showed significantly more extensive coronary disease in the first group (3-vessel disease in 40% vs 18.9%, p<0.001). The time to development of CS was significantly longer in pts with NSTEMI (69.4 h vs 42.4 h, p=0.002), and time spent in the ICU was shorter (32.1 h vs 69.9 h, p<0.001). Interestingly, we did not fiind differences in the rate of deaths (40% vs 43.2%, ns) and recurrent ischemia (30% vs 29.7%, ns) between the 2 groups.
Conclusions: Pts with NSTEMI who develop CS have a lower ejection fraction, a more altered diastolic function, more extensive coronary disease than pts with STEMI who develop CS. The incidence of cardiovascular death and ischemic recurrence was not different between the two groups.

P1611 Determinants of N terminal pro-brain natriuretic peptide levels in patients with acute myocardial infarction and no ST-elevation

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Background: Recent studies raised the strong prognostic value of Brain Natriuretic Peptide (BNP) in patients with ST elevation myocardial infarction (MI). No data are available on determinants of BNP levels in patients with non ST segment elevation MI (NSTEMI).
Patients and Methods: RICO is a French regional survey for patients hospitalized with acute MI (increased in troponin level > UNL with either symptoms of ischemia and/or typical ECG changes). From 01 March 2002 to 31 December 2002, all patients with NSTEMI were included in the study. The N-terminal fragment of the BNP prohormone (Nt-proBNP) plasma level was assessed 3±1 days after symptoms onset. Continuous data were tested with linear regression with Nt-proBNP values. Dichotomous variables were tested with regression logistic model to test for predictive value for high (i.e supra median) Nt-proBNP level.
Results: 101 patients with NSTEMI were included in the study, with median age 69 y, 31% female, 17% with previous MI, 25% current smoker, 50% hypertension and 42% with Troponin I peak > X 10 UNL. Median Nt-proBNP level was 136 (40-335) pmole/l. Patients with death or recurrent MI at 30 days had higher Nt-proBNP levels than event-free patients (respectively, median 136 vs 109 pmole/l, $p<0.05$). We found a strong correlation in Nt-pro-BNP level with age ($r=0.349$, $p<0.001$), LVEF ($r=0.353$, $p<0.001$), and serum creatinine level ($r=0.442$, $p<0.001$). Univariate analysis showed that age >65 y, killip >1 on admission, hypertension, LVEF < 50%, troponin I X 10 UNL, female and current smoking were predictor for high Nt-proBNP levels. When matched for age and sexe, multivariate analysis raised hypertension and LVEF > 50% as independent predictors for high Nt-proBNP values in NSTEMI patients.
Conclusion: Our data in unselected population of NSTEMI patients indicate that high levels of circulating Nt-proBNP levels are associated with early cardiovascular events. Moreover, altered LVEF and hypertension are independent predictors for high Nt-proBNP levels in this specific population.

ST-ELEVATION ACUTE MYOCARDIAL INFARCTION: PROGNOSTIC MARKERS II

P1612 Similar cumulative 1-year mortality of ST- and non-ST-elevation myocardial infarction in clinical practice: results of the ACOS registry

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Background: Patients with ST-elevation myocardial infarction (STEMI) have a higher inhospital mortality than patients with non-ST-elevation myocardial infarction (NSTEMI). Little is known about the longterm outcome of patients with NSTEMI after the redefinition of myocardial infarction in 2000 as compared to the longterm-outcome of STEMI.
Methods: Between June 2000 and November 2002 consecutive patients with acute coronary syndromes (ACS) have been enrolled into the ACOS registry in 154 hospitals in Germany. We examined the hospital and longterm outcome of patients with STEMI as compared to patients with NSTEMI in clinical practice.
Results: Out of 15954 consecutive patients with ACS, 7415 patients (46%) presented with STEMI and 6470 patients (41%) with NSTEMI. Patients with NSTEMI were older and more often had concomittant diseases.

Differences STEMI versus NSTEMI

Parameter	STEMI (n=7415)	NSTEMI (n=6470)	p-value
Age (years)	65	69	<0.01
Male Gender	70.4%	65.5%	<0.01
Prior MI	15.4%	26.5%	<0.01
Prior PTCA	6.9%	11.9%	<0.01
Prior CABG	3.6%	9.4%	<0.01
Hospital Mortality	9.5%	5.8%	<0.01
Additional 1-Year-Mortality	5.9%	8.2%	<0.01
Cumulative 1-Year-Mortality	13.2%	11.3%	<0.01

Conclusion: Patients with NSTEMI were older and more often already had undergone coronary interventions than patients with STEMI. Hospital mortality was significantly higher for patients with STEMI as compared to NSTEMI, whereas mortality within one year of follow-up was significantly higher for NSTEMI than for STEMI. The cumulative 1-year-mortality (Kaplan-Meier) for NSTEMI with 11.3% was nearly as high as for STEMI with 13.2%.

P1613 In-hospital mortality following hospital admission for acute myocardial infarction in Switzerland: is it related to in house cath-lab availability?

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Background: Several randomized trials have shown significant differences in favor of primary percutaneous coronary intervention (PCI) over thrombolysis using a composite endpoint including mortality, reinfarction and stroke. This analysis is designed to evaluate whether there is any impact of a cath-lab available in house (including primary PCI) on hospital mortality.
Method: From the AMIS-Plus data-base 7,861 patients admitted in 52 hospitals (January 2000 to October 2002) over Switzerland were extracted.
Results: The characteristics of the population of patients admitted in hospital without cath-lab (Pop 1) and with cath-lab (Pop 2) are shown in this table: Pop 2 was more often treated with reperfusion (thrombolysis + Primary PCI), and with primary PCI. This strategy was associated with a significantly lower mortality, but baseline characteristics such as age differed. A multivariate analysis of mortality predictors will be available at the time of presentation.

table comparing pop 1 et pop 2

	Population 1	Population 2	p value
Number of cases	3860	4001	
Male	69.8%	75.5%	p<0.001
Female	30.2%	24.5%	
Age mean ± sd	67.6 ± 12.7 y	63.4 ± 12.9 y	p<0.001
Killip class I	68.7%	73.8%	
Killip class II	21.4%	17.9%	
Killip class III	7.2%	5.5%	
Killip class IV	2.6%	2.8%	
Delay (median)	4:30 h	4:57 h	p<0.016
Thrombolysis	35.4%	25.3%	p<0.001
PCI primary	5.0%*	27.9%	p<0.001
PCI performed	27.4%*	67.4%	p<0.0001
Hospital stay (median)	10 d	8 d	p<0.001
In-hospital mortality	10.6%	8.9%	p<0.009

* performed at other center

Conclusion: In Swizerland, reperfusion strategies are more often used in hospital with "in house" cath-lab, specifically primary PCI, and this appears to be associated with a survival benefit.

P1614 Left-ventricular geometry in patients with first acute coronary syndrome

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Background: Risk of development congestive heart failure (CHF) in patients with acute coronary syndrome (ACS) is high. Undouptedly, degree of changed left ventricular (LV) geometry in subclinical period of the syndrome acquires great significance in occurring CHF. Aim of the present study was to compare prevalence of patterns of LV geometry in patients with different ACS.
Methods: Demographic, clinical, echocardiographic and coronarographic data was analyzed in 545 patients (76,0 percent males, median age 57,3±9,3 years) with first ACS admitted to cardiological clinic of Kaunas medical university hospital. One hundred twenty eight of them were with unstable angina pectoris (UAP), 179 – with acute myocardial infarction (MI) without Q wave and 238 – with Q wave MI. LV geometry was assessed by relative LV wall thickness and LV mass index. Four patterns of LV geometry were separated: normal geometry, concentric remodelling, concentric and eccentric hypertrophy.
Results: During acute phase of ACS changed LV geometry was obtained in 81,3 percents of patients. While the older age (>65 years), arterial hypertension, Q wave MI, abnormal diastolic function ($p<0,05$) were more frequently found in pts with changed geometry than with normal one, the prevalence of other clinical variables did not differ significantly between the groups. Normal geometry was evaluated only in 22,9 percent of patients with UAP, 21,1 percent with non Q wave MI and 14,3 percent with Q-wave MI, ($p<0,05$). Concentric remodelling and concentric hypertrophy were most frequent findings in patients with ACS (41,5 percent and 31,6 percent respectively), but concentric remodelling was more often in pts with UAP than in pts with Q wave MI (47,3 percent and 37,3 percent, respectively $p<0,05$) and concentric hypertrophy in patients with Q wave MI than in pts with UAP (38,1 percent and 25,7 percent respectively, $p<0,05$). Eccentric hypertrophy was more frequent in patients-with Q wave MI than with UAP (10,4 percent and 4,1 percent respectively) ($p<0,05$).
Conclusion: These date suggest that LV geometry is changed in most patients even with UAP during acute phase of disease, and ACS develops on the background of different degree of LV remodelling. Investigation of LV geometry may be perspective not only in determining risk of heart failure but also in understanding mechanisms of silent ischemia and electric instability of myocardium – mediators of sudden cardiac death in patients with ischemic heart disease.

P1615 Women with a high-risk myocardial infarction have a higher incidence of heart failure as compared to men

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Background: Numerous studies have reported substantial gender-related differences in patients with coronary heart disease. The OPTIMAAL trial included patients with a high-risk acute myocardial infarction (AMI), and randomized them within 10 days to treatment with either losartan or captopril. High-risk AMI was defined as an AMI with additional criteria as follows; new anterior Q-waves, re-infarction with pathological Q waves in the anterior wall, and/or evidence of heart failure, defined as the need of diuretic or intravenous vasodilator treatment, presence of pulmonary rales or radiographic evidence of pulmonary congestion. The aim of this analysis was to look at gender-related differences in signs and symptoms, according to which patients were included to the trial.
Results: A total of 5477 patients, 1575 (28.8%) women and 3902 (71.2%) men were randomized at 329 different centres in seven western European countries. Table 1 presents the main results. It should be noted that many patients fulfilled > 1 inclusion criteria.

Table 1

Inclusion criteria	Women	Men	P value
Any heart failure criteria	1353 (85.9%)	3064 (78.5%)	<0.0001
Diuretic/vasodilator treatment	1135 (72.1%)	2347 (60.1%)	<0.0001
Pulmonary rales	996 (63.2%)	2099(53.8%)	<0.0001
Pulmonary congestion	629 (39.9%)	1283 (32.9%)	<0.0001
New or old anterior Q waves	816 (51.8%)	2380 (61.0%)	<0.0001

Conclusion: Among patient suffering from a high-risk AMI, women present with a higher incidence of heart failure symptoms, despite the fact that men present with a higher incidence of anterior Q wave myocardial infarction.

P1616 Acute myocardial infarction with normal coronary arteries: risk profile and prognosis

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Introduction: Although acute myocardial infarction (AMI) is usually caused by a sudden thrombotic occlusion of a coronary artery at the site of a fissured atherosclerotic plaque, myocardial infarction with normal epicardical coronary arteries have been documented. The possible mechanisms are coronary vasospasm, thrombosis with spontaneous reperfusion, coronary embolism, cocaine abuse, hipercoagulable states, coronary trauma, but in most cases the ethiology is unknown.
To improve the understanding of this clinical entity, we studied patients (pts) admitted with AMI and normal coronary angiography (AMI-NC) and we evaluate its coronary risks factors and signs of prognosis.
Methods: In 60 consecutive pts with AMI-NC we found some possible causes: coronary artery vasospasm (5 pts), prothrombotic state (4 pts) and cocaine use (2 pts). In the remaining 49 pts we didn't detect any obvious aetiology and this group was compared with a group of 45 consecutive pts with AMI and one-vessel disease (stenosis >50%) (AMI-CD).
Results: The pts with AMI-NC were more often females (44.9% vs. 20.0%, $p<0.01$), younger than the group with AMI-CD (55±12 vs. 67±12 years, p=0.02). Male age was similar (49±14 vs. 51±12 years, p=0.51) between groups. Pts with AMI-NC, compared with those with AMI-CD, had no coronary risk factors (CRF) (20.4% vs. 4.4; p=0.02) or had only one CRF (36.7% vs. 22.2%; p=0.03): smoking in 41% and hypertension in 41%. Although they are not established causes, 5 cases of AMI-NC were related to the use of oral contraceptives (23% of women), 4 cases of milking of coronary artery and 2 cases of thrombi without visible atherosclerotic plaque.
In AMI-NC group we found more AMI's without ST segment elevation (57.1% vs. 24.4%; $p<0.01$), less elevation of peak CK/CK-MB (medians: 415/35 vs. 1761/118 U/l; $p<0.01$), less elevation of peak troponin I (median: 13.2 vs. 37.9 ng/ml; $p<0.01$), higher evolution of symptoms (median: 7 vs. 2 hours; $p<0.01$), less direct catheterization (16.3% vs. 60.0%; $p<0.01$).
Pts with AMI-NC had better global systolic left ventricular function (ejection fraction>40%= 91.8% vs. 75.6%; p=0.03), less intercurrences, mechanical or electrical complications (6.1% vs 22.2%; p=0.02) and inferior hospital stay (7.1±4.9 vs. 10.1±5.0 days; $p<0.01$) than pts with AMI-CD.
Conclusion: AMI-NC has a distinct risk profile from AMI-DC, appearing in young women, probably unrelated to classic CRF and with more favourable prognostic markers.

P1617 Arterial hypertension doesnt worse the in-hospital outcome of patients with acute myocardial infarction. A case-control study

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Purpose: it is not well established if arterial hypertension influence the in-hospital complications and outcome of patients with acute myocardial infarction (AMI). The purpose of this study was to investigate clinical patterns, risk factors, and in-hospital complications in HT patients with AMI vs NT ones.
Methods: we analysed the in-hospital clinical outcome (fatal and non fatal complications) of 1582 patients with AMI, 791 hypertensives (HT), 433 males and 358 females, mean age 69.1 ± 9.3 years and 791 normotensives (NT) matched for sex and age, as control group.
Results: No significant difference was found between NT and HT, as concerns as the site of AMI, anterior or inferior. ST segment depression at ECG (48.7 vs 32.1%) and non-Q wave AMI (73.5 vs 37.8%), were more common in HT ($p < 0.01$). HT showed more frequently a previous AMI (32.1 vs 23.5%), diabetes (7.8 vs 5.2%), dislipidemia (33.3 vs 21.8%), renal failure (4.4 vs 1.2%), PAD (2.7 vs 1.1%), CVD (3.9 vs 1.6%) and COLD (8.6 vs 4.4%). HT showed a significantly higher prevalence of post-AMI angina (9.9 vs 7.6%, $p < 0.05$), silent myocardial ischemia (1.4 vs 0.6%, $p < 0.01$), paroxysmal atrial fibrillation (7.1 vs 3.8%, $p < 0.01$) and a significantly lower prevalence of cardiogenic shock (2.9 vs 8.6%, $p < 0.01$), A-V block (3.3 vs 5.1%, $p < 0.05$) and VT or VF (3.2 vs 4.5%, $p < 0.05$). No significant difference was found in LV failure, re-infarction, endo-ventricular thrombosis, pericarditis or concomitant stroke between the groups. Mortality was higher in patients with anterior vs inferior AMI, both NT (16.38% vs 9.65%, p=0.023) or HT (7.17% vs 2.78%, p=0.013). Mortality was also increased in all-NT with AMI (anterior or inferior), in comparison with HT (13.65% vs 5.18%, p=0001), as well as in patients with anterior AMI (NT=16.38% vs HT=7.17%, p=0.0001) or with inferior AMI (NT=9.65% vs HT=2.78%, p=0.0001).
Conclusions: HT patients with AMI, when excluding confounding factors such as sex and age, had a better in-hospital outcome than NT, perhaps due to a less extension of the infarction area and other pathophysiological mechanism such as a greater development of collateral circulation.

P1618 The serum cardiac sarcoplasmic Ca-ATPase immunoassessment: a new diagnostic marker of acute myocardial infarction

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The detection of cardiac proteins in blood after non-reversible ischemic episode is the most specific and sensitive indicator of acute myocardial necrosis. Sarcoendoplasmic reticulum Ca-ATP-ases (SERCAs) are encoded by three different genes and additional alternative splicing in tissue and developmentally regulated manner generates multiple isoformes. SERCA1a and SERCA1b are found in fast-twitch adult and neonatal skeletal muscles, SERCA2a in cardiac and slow-twitch skeletal muscles, and SERCA2b and 3a-e in a variety of non-muscle tissues.
We developed a sensitive capture ELISA to detect SRCA2a levels in serum using specific monoclonal antibodies raised against cardiac Ca-ATPase from canine myocardium. The assay displayed good linearity up to 50 ng/ml of Ca-ATPase protein added into normal plasma.
15 patients with acute myocardial infarction (AMI) were tested by this method in addition to standard determination of serum Troponin-T and CK-MB. No detectible levels of Ca-ATPase were found in 20 control subjects or in 5 patients with known coronary artery disease. In patients with AMI serum Ca-ATPase was elevated within 4 to 6 hours, reached a mean pick level of 2,6 ng/ml (range from 0,8 to 9,0 ng/ml) at 8 to 12 hours. In contrast to Troponin-T, the Ca-ATPase remained elevated only for up to 72 hours. This relatively rapid serum clearance of Ca-ATPase permitted to detect re-infarction in one patient during subsequent blood sample collection-second pick elevation.
Immunoassay of cardiac Ca-ATP-ase is a sensitive and specific diagnostic aid in the detection of irreversible myocardial damage/necrosis.

P1619 Hyperplasia, degranulation and regranulation of mast cells from the intima of human aorta and pulmonary artery in acute myocardial infarction

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Purpose: To study the reactions of intimal mast cells (MC) from human aorta and pulmonary artery in acute myocardial infarction.
Methods: The morphofunctional state of aortic and pulmonary artery intimal MC has been studied in acute cardiovascular insufficiency related to myocardial infarction. The material was collected from 44 men died of acute myocardial infarction at the age of 42-73 years. The cells were examined using intimal film preparations and transverse sections of aorta and pulmonary artery. The density of MC, number of degranulating MC and MC polymorphism were evaluated. Practically healthy people died from different unnatural causes served as a control group. Lymphocytes (CD-3, 4, 45) and monocytes (CD-68) were typified in 10 cases.
Results: Pronounced hyperplasia of MC (44.0 vs. 9.6 MC/mm^2 in the control group), considerable increase in the number of degranulating MC (36.9 vs. 4.0% in the control group) and pronounced polymorphism were detected in the aortic intima of all patients with myocardial infarction. The same although less pronounced changers occurred in the pulmonary artery intima. The increase in the number of intimal MC coincided with increased content of T cells and monocytes. In polymorphous MC the processes of irregular degranulation and regranulation were observed.
Conclusion: Hyperplasia, high level of degranulation and pronounced polymoprhism of intimal MC are typical of acute cardiac insufficiency related to myocardial infarction. These changes in the population of aortic and pulmonary artery MC are regarded as a reaction aimed at stabilizing circulation in myocardial infarction.

ST-ELEVATION ACUTE MYOCARDIAL INFARCTION: PROGNOSTIC MARKERS III

P1620 The prognostic significance of hyponatremia in acute ST-elevation myocardial infarction

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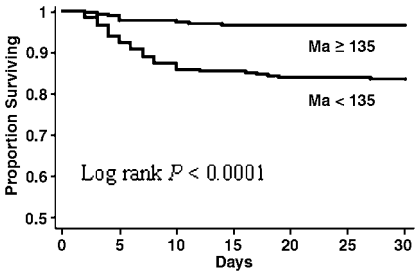
Introduction: Hyponatremia (HNa) is a common electrolyte disorder among hospitalized patients and is associated with adverse prognosis. The prognostic value of HNa in heart failure is well established. However, data on the prevalence and prognostic significance of hyponatremia in the setting of acute myocardial infarction is sparse.
Methods: We studied 699 consecutive patients (pts) (age 60 $\pm$ 12) presenting with acute ST-elevation myocardial infarction (STEMI). Plasma sodium concentrations (PNa) were obtained on admission and at 24-h, 48-h, and 72-h. Multivariate Cox proportional hazard analyses were performed to determine the relation between hyponatremia and 30-day mortality adjusting for age, sex, diabetes, hypertension, smoking, Killip class, peak CK, ejection fraction, anterior infarction, use of diuretics, and reperfusion therapy.
Results: HNa, defined as PNa <135 mmol/L at any time during the first 72-h of hospital stay developed in 273 (39%) pts. PNa decreased to 130 mmol/L or less in 61 (8.7%) of pts (lowest PNa 119 mEq/L). Although pts receiving diuretics developed HNa more commonly compared to pts who were not (55.6% vs 34.8%, P < 0.0001), the majority of pts (71%) who developed hyponatremia were not receiving diuretics. Kaplan-Meyer curves indicated that pts who developed HNa were at increased risk of 30-day mortality (Figure). In a multivariate Cox regression analysis HNa remained independently associated with 30-day mortality (RR 3.5, 95% CI 1.8-6.6, P = 0.002). Both Killip class and ejection fraction showed lower adjusted risk estimates than HNa with regard to 30-day mortality.



Kaplan-Meier survival curve.

Conclusion: Early development of HNa during STEMI is a strong independent predictor of 30-day mortality. PNa may serve as a simple marker to identify pts at high risk.

P1621 Are the Framingham and PROCAM coronary heart disease risk functions applicable to different European populations? The PRIME Study

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Purpose Our aim was to assess whether the Framingham and PROCAM risk functions were applicable to men in Belfast and France.
Methods We performed an external validation study within the PRIME (Prospective Epidemiological Study of Myocardial Infarction) cohort study. This cohort comprised
men recruited by the WHO MONICA centres in Belfast (2399) and France (7359) who were aged 50 to 59 y, free of CHD at baseline (1991 to 1993) and followed over 5 years for CHD events (coronary death, myocardial infarction, angina pectoris). We compared the relative risks of CHD associated with the classic risk factors in PRIME with those in Framingham and PROCAM cohorts. We then compared the number of predicted and observed 5-year CHD events (calibration). Finally, we estimated the ability of the risk functions to separate high risk from low risk subjects (discrimination).
Results The relative risk of CHD calculated for the various factors in the PRIME population were not statistically different from those published in the Framingham and PROCAM risk functions. The number of CHD events predicted by these risk functions however clearly overestimated those observed in Belfast and France. The two risk functions had a similar ability to separate high risk from low risk subjects in Belfast and France (c-statistic range:0.64-0.68).
Conclusion The Framingham and PROCAM risk functions should not be used to estimate the absolute CHD risk of middle-aged men in Belfast and France without any CHD history because of a clear overestimation. Specific population risk functions are needed.

P1622 Treatment of reinfarction is associated with 30-day survival- regional geographic variations in treatment and outcomes following reinfarction in the HERO-2 trial

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Purpose: Reinfarction (reMI) is associated with worse outcomes following fibrinolytic therapy. Readministration of fibrinolytic therapy and/or revascularisation procedures following reMI have been associated with better outcomes.
Methods: In the HERO-2 trial, reMI was adjudicated by a Clinical Endpoints Committee (CEC) according to pre-defined criteria: a) <18 hours (≥30min chest pain and ≥1mV ST elevation in 2 leads), b) >18 hours (CK level >2x upper limit of normal (ULN)or CKMB >ULN and >50% above prior baseline), c) with percutaneous intervention (PCI) (CK or CKMB levels >3x ULN) or d) surgical revascularisation (CABG) (CK or CKMB levels >5x ULN); also in b-d new LBBB or new Q waves. We examined these and associated clinical data sent to the CEC to determine associations between treatment of reMI (fibrinolytic therapy or revascularisation in under 12 hours) and 30-day mortality in patients with confirmed reMI.
Results: Of 17073 patients enrolled, 772 were referred to the CEC, of whom 552 had reMI confirmed. After reMI (compared to patients without reMI), mortality within 30 days of randomisation was increased (24% vs 10%, p<0.001). 30-day mortality was 15% in Western Countries, 29% in South America, 27% in Eastern Europe, 27% in Russia, 20% Asia (p=0.12). Patients in Western Countries (n=112) more frequently received further fibrinolysis or revascularisation compared to patients from non-Western Countries (n=440) (32.1% and 18.8% vs 6.1% and 6.1%, p<0.001). On multivariate analysis, geographic region was significant after adjustment for baseline risk factors, treatment of reMI and time to reMI (p=0.03). Following reMI, mortality was 20% in patients readministered fibrinolytic therapy (Hazard Ration (HR) 0.70 (95%CI 0.39-1.23)), 9% in those who had revascularisation (HR 0.31 (95%CI 0.11-0.83)) and 27% with conservative management (p=0.02). The difference in hazard between revascularisation and further fibrinolytic therapy was not significant (p=0.12). After exclusion of deaths within 12 hours of reMI, and after adjustment for other significant predictors of death following reMI (age, time to reMI and Killip class at entry) revascularisation was still associated with a lower risk of mortality (p=0.02), whereas readministration of fibrinolytic therapy was not.
Conclusion: ReMI, which varied according to geographic region, was associated with a significantly higher mortality within 30 days of randomisation. Revascularisation <12 hours in patients with reMI was associated with lower mortality, although readministration of fibrinolytic therapy was not.

P1623 Validation of the RECPAM in-hospital risk score after acute myocardial infarction myocardial infarction: follow-up of 537 patients

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Aim of the study: In order to introduce in our practice new methods of prognostic stratification of acute myocardial infarction (AMI) patients, we assessed the usefulness of the RECPAM (recursive partitioning and amalgamation) risk stratification algorithm (Fresco et al, Am Heart J 1999) on a population of 820 patients with AMI.
Material and Methods: 537 patients (pts), 386 males (72%), mean age = 61.5 ± 12.7 years old, admitted in our department with AMI between Jan 2000 - Dec 2002. We classified all pts on the basis of RECPAM algorithm, from class 1 (most severe prognosis) to class 6 (best prognosis), and we assessed in-hospital outcome with regard not only to in-hospital mortality (as in the main study), but also to hemodynamic and arrhythmic complications.
Results: Patients were divided in the 6 RECPAM classes, and in-hospital mortality, heart failure, arrhythmias, stroke showed significant differences between the 6 classes (see table).

RECPAM class	1	2	3	4	5	6
No pts (%)	162	48	80	122	43	82
In-hospital mortality (%)	40 (25%)	12 (25%)	4 (5%)	7 (5%)	1 (2.3%)	1 (0.01%)
OR mortality (95% CI)	4.1 (2.4-6.7)	2.19 (0.1-4.8)	1.81 (0.6-4.8)	0.59 (0.2-1.3)	0.23 (0.03-1.7)	0.11 (0.01-0.8)
Reinfarction (%)	28 (30%)	7 (14.5%)	5 (6.2%)	11 (9%)	5 (1.1%)	6 (7.3%)
Ventricular arrhythmias	15 (16.1%)	0 (0%)	5 (5.7%)	8 (6.4%)	3 (6.9%)	5 (5.9%)
Stroke	0	0	0	1	0	0

Conclusions: The RECPAM risk stratification algorithm is a useful tool in assessing short-term (in-hospital) risk with regard not only to mortality, but also to reinfarction and ventricular arrhythmias in pts hospitalized with AMI.

P1624 Different outcomes in patients with ST-elevation myocardial infarction among countries with different gross national income

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Purpose: Recent studies have reported differing outcomes in patients with acute coronary syndromes between developed and developing countries. The purpose of this study was to compare the 30-day mortality rate in ST Elevation Myocardial Infarction (STEMI) among countries with different Gross National Income (GNI).
Methods: A retrospective analysis of the databases of five trials that included 50,310 patients with STEMI from 53 countries in the five continents (COBALT 7,169, GIK-II 2,931, HERO-II 17,089, ASSENT-II 17,005 and ASSENT-III 6,116 patients) was performed. These countries were classified in 3 groups according to the world bank GNI categorization: low (less than U$S 2,900), medium (between U$S 2,900 and 9,000) and high (more than U$S 9,000). Baseline characteristics, in-hospital treatment, in-hospital procedures and 30-day mortality were assessed in each group. The GUSTO risk model and a logistic regression model that takes into account the GNI were used to calculate the expected mortality rate and to compare it with the observed mortality rate.
Results: see table

GNI group		30-day mortality (%)	95% CI
Low	Predicted (GUSTO model)	10,10	9,85-10,35
	Predicted (GNI model)	9,97	9,87-10,07
	Observed	12,20	
Medium	Predicted (GUSTO model)	7,60	7,41-7,80
	Predicted (GNI model)	10,02	9,92-10,13
	Observed	9,60	
High	Predicted (GUSTO model)	7,46	7,33-7,54
	Predicted (GNI model)	6,52	6,44-6,59
	Observed	6,16	

Conclusions: The observed mortality rate was inversely correlated with the GNI. Baseline characteristics of the population partially explain this difference. The logistic regression model including the GNI estimates mortality rate better than the GUSTO risk model. This variable should be considered in predictive models for STEMI.

P1625 Reinfarction as a complication of acute myocardial infarction in the PRIMVAC registry. Clinical profile and determinant factors

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There are few studies about characteristics and determinants of reinfarction in patients with acute myocardial infarction during their stay in coronary units.
Objective: To identify the incidence of reinfarction, its prognosis and the predictors of reinfarction in coronary units in the PRIMVAC registry. **Methods:** All myocardial infarctions admitted in 17 hospitals with coronary units in the Comunidad Valenciana region(Spain) in the period January 1995- December 2000 were included. After determining reinfarction incidence, bivariate analysis (categorical variables: Chi-square test) and multivariate analysis (with logistic regression spreaded out at intervals) were performed. Several clinical and therapeutic variables entered into the analysis. Only significant differences are cited.
Results: The number of patients admitted with myocardial infarction was 12071 (median age 65.5 years, 24.3% female gender). Incidence of reinfarction in PRIMVAC registry was 2.8%(344 cases). Overall mortality among patients with reinfarction was 37.8% vs 12.6% in no reinfarction patients with a higher rate of electrical and mechanichal complications in the first group. Median age was greater in the reinfarction group (69.5 years) than in the no reinfarction group(65.4 years). Reinfarction was more prevalent in women (4.1%) than it was in men (2.5%), more in patients with positive coronary history(4.2%) than in patients without it(2.5%), more in no smokers(3.4%) than in smokers (1.9%) and more in diabetic patients(4.1%) than in no diabetic ones(2.4%). Reinfarction was also more prevalent in patients who underwent to thrombolysis (3.1%) than in patients who did not receive thrombolytic therapy (2.5%). Statistically significant differences were not found between Q-wave and non Q-wave infarction. Neither differences were found with hypertension, hypercholesterolemia and infarction location. Multivariate analysis showed these factors as independent determinants for reinfarction appearance: age (OR: 1.02), female gender (OR: 1.27), positive coronary history (OR: 1.82), and diabetes (OR: 1.37).
Conclusions: Reinfarction implies a very high morbidity and mortality. Some clinical data at admission allow to identify a higher risk profile for developing this complication after myocardial infarction.

P1626 Effect of preinfarction angina pectoris on outcome in patients with acute myocardial infarction treated with primary angioplasty: data from the acute myocardial infarction Florence registry

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Background: Preinfarction angina (PA) is associated with better clinical outcome in patients with acute myocardial infarction (AMI) who receive intravenous thrombolysis. The protective effect of PA has not been yet proved in patients with AMI treated with primary percutaneous coronary intervention (PCI).
Methods: We analyzed the data of AMI Florence Registry which is a prospective observational registry including all the Florence area residents who experienced AMI from March 1, 2000 to February 28, 2001 and were admitted to hospital within 24 hours from symptom onset. Of the 920 patients enrolled, 459 (50%) were treated with primary PCI. Out of these patients, 90 (20%)had PA within 4 weeks before AMI (group 1), and 369 (80%) had not (Group 2).
Results: According to univariate analysis, no difference between the 2 groups was observed regarding age, sex, habit of smoking, diabetes, hypertension, hypercolesterolemia, previous heart failure, Killip class >1 and anterior location of AMI. Peak creatine kinase was similar in the two groups (group 1: 2081 $\pm$ 1601 U/l vs group 2: 2388 $\pm$ 2206 U/l, p=.22). During PCI stent use was similar in the two groups (group 1: 94.4% vs group 2: 97%, p=.23), while glycoprotein IIb/IIIa inhibitors were used more frequently in group 1 (70% vs 58.3%, p=.041). However, TIMI grade 3 flow was restored in the same proportion of patients (group 1: 94.4% vs group 2: 93.8%, p=.31). At discharge a similar rate of left ventricular (LV) systolic dysfunction (LV ejection fraction $<$50%) was found in the two groups (group 1: 40% vs group 2: 38.2%). At univariate analysis a lower in-hospital and 1-year mortality was observed in group 1, although the difference was not significant (in hospital: 3.3% vs 7.6%, p=.15, and 1 year: 7.8% vs 13.8%, p=.12). Cox regression analysis did not confirm a significant protective effect of PA for in-hospital (HR 0.58, 95% CI 0.15 to 2.25) and 1-year mortality (HR 0.74, 95% CI 0.33 to 1.65).
Conclusions: Our data suggest that PA does not have a protective effect on the outcome of patients with AMI treated with primary PCI.

P1627 Does infarct size measured by creatine kinase-MB predict clinical outcomes after fibrinolysis and primary percutaneous coronary intervention?

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Background: Myocardial infarct size has been shown to correlate with clinical outcomes but little is known about the relationship among modes of reperfusion. The CARDINAL trial is the largest contemporary dataset of serial CKMB assessments in patients with acute ST elevation myocardial infarction treated with reperfusion therapy.
Methods: The Complement and ReDuction of INfarct size after Angioplasty or Lytics (CARDINAL) program included 1734 patients with acute ST-segment elevation myocardial infarction treated with fibrinolysis (n= 920) or primary percutaneous coronary intervention (n= 814) to evaluate the safety and efficacy of pexelizumab, a novel complement inhibitor. The primary endpoint was myocardial infarct size assessed by CKMB area under the curve (AUC) through 72. For these analyses patients who died before 72 hours were excluded (n= 69) and linear interpolation used for missing values.
Results: CKMB AUC was calculated for 1637 (94%) patients (n=857, fibrinolysis; n=780, PCI). Age was similarly distributed across categories of CKMB AUC. Median (25th, 75th) infarct sizes for fibrinolysis and PCI were (4831 (2080, 8104) and 4527 (2216, 7450), respectively). Mortality and non-fatal congestive heart failure(CHF) or shock at 90 days and median (25th, 75th) QRS score at 6 days by quintiles of CKMB AUC are shown.

Quintiles of CKMB AUC

	Mortality		CHF/Shock		QRS Score	
	PCI	Fibrinolysis	PCI	Fibrinolysis	PCI	Fibrinolysis
Q1	2/143 (1.4%)	6/175 (3.4%)	2/143 (1.4%)	14/175 (8.0%)	3 (1,5)	3 (1,6)
Q2	2/182 (1.1%)	6/150 (4.0%)	2/182 (1.1%)	5/150 (3.3%)	5 (3,7)	4 (2,7)
Q3	2/165 (1.2%)	6/165 (3.6%)	7/165 (4.2%)	9/165 (5.5%)	5 (4,8)	6 (4,8)
Q4	4/159 (2.5%)	8/176 (4.6%)	11/159 (6.9%)	15/176 (8.5%)	8 (5,9)	7 (4,9)
Q5	5/131 (3.8%)	17/191 (8.9%)	25/131 (19.1%)	32/191 (16.8%)	8 (6,11)	8 (5,10)

Conclusions: Death and non-fatal heart failure were more common among patients with largest infarct sizes. However, the lack of a gradient of risk across the lower 60% of infarct size, particularly with primary PCI, suggests a threshold exists for determining early outcomes.

P1628 Prognostic significance of stress hyperglycemia in non-diabetic patients with acute myocardial infarction: a prospective study

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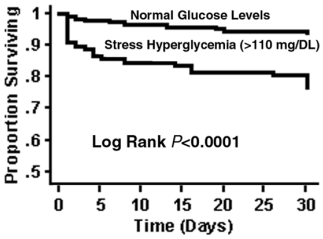
Background: Several studies have suggested that high blood glucose levels may increase the risk of death after acute myocardial infarction (AMI). However, these studies were small, retrospective, and have not adjusted for other important determinants of prognosis.
Methods: We prospectively enrolled 398 consecutive patients (age 61 $\pm$ 13) with AMI. Stress hyperglycemia was defined as fasting glucose $>$ 110 mg/dL on the first morning after admission, based on the American Diabetes Association definition of impaired fasting glucose. Patients with known diabetes were excluded. Left ventricular ejection fraction was determined by echocardiographic examination on day 2 or 3.
Results: Stress hyperglycemia was present in 136 (34%)of patients. At 30-days 40 (10.0%) patients died. Kaplan-Meier survival curves indicated that patients with stress hyperglycemia were at increased risk of 30-day mortality (Figure). Adjusted 30-day mortality was evaluated using Cox proportional-hazards model with the following covariates: age, gender, hypertension, smoking, prior myocardial infarction, Killip class, HR $>$ 100/min on admission, SBP $<$ 100 mm Hg on admission, ST-elevation infarction, presence of anterior infarction, peak CK, ejection fraction, and use of reperfusion therapy. In a Cox's multivariate analysis, stress hyperglycemia was powerful independent predictor of 30-day mortality (Relative Risk = 4.2, 95% CI 1.6-11.4, p = 0.005).



Survival curve according to FG.

Conclusion: Stress hyperglycemia in patients with acute myocardial infarction is a strong predictor of 30-days mortality independent of infarct size and other traditional predictors of outcome.

P1629 Prognostic impact of sulfamide therapy in diabetic patients with ST-elevation acute myocardial infarction in the real world: results from the French USIC 2000 registry

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The possible deleterious prognostic impact of sulfonylurea therapy in diabetic patients with acute myocardial infarction (AMI) is debated. Our aim was to assess the outcome of diabetic pts with ST elevation AMI, according to the use of sulfonylureas prior to hospital admission. The nation-wide French USIC 2000 study is a registry including all pts admitted to ICUs for AMI $<$ 48 hours from symptom onset in November 2000. More than 80% of the ICUs in France participated in the study. Of the 2,320 pts recruited, 485 were diabetics, among whom 364 had ST elevation MI. Of those, 161 were on sulfamide therapy at the time of onset of their infarct (Gr1), and 203 were not (Gr2). Group1 pts tended to be older 70 $\pm$ 9 vs 68 $\pm$ 13 years (p=0.06). Most other baseline characteristics, however, were comparable (Gr 1 vs Gr 2): women (35% vs 40%), BMI $>$ 30 (26% vs 23%), hypertension (68% vs 60%), previous MI (20% vs 20%), previous heart failure (6% vs 5%), previous stroke (9% vs 9%), peripheral vascular disease (11% vs 16%), anterior location of MI (45% vs 46%). All cardiovascular medications used prior to hospital admission (aspirin, beta-blockers, calcium antagonists, ACE inhibitors, angiotensin receptor antagonists, nitrates, and diuretics) were found in similar percentages in the 2 groups. Likewise, Killip class on admission was similar in the 2 groups. Systemic arterial pressure on admission was more often $>$ 160 mm Hg in Gr 1 (29% vs 17%, p=0.006), and pulse pressure was more often $\geq$ 60 mm Hg (62% vs 46%, p=0.002). Reperfusion therapy with either PTCA or thrombolysis was used in 43% and 45%, respectively.

Five-day mortality was 5.0% (Gr 1) vs 12.8% (Gr 2), p=0.01. Using stepwise logistic regression analysis, use of sulfamide therapy remained an independent predictor of improved 5-day survival (OR for 5-day mortality: 0.39; 95% CI: 0.16-0.97, p $<$ 0.05), while the other significant predictors were younger age, lower Killip class, and higher pulse pressure on admission. Similar results were observed regarding one-month mortality, as well as in patients treated with direct PCI or thrombolysis.

Conclusion: in this large "real world" registry, there was no evidence of increased risk in diabetic patients receiving sulfonylureas who sustained a STEMI, compared with those not treated with sulfonylureas. This conclusion is reinforced by the results of the multivariate analysis.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

P1630 Distal embolization during primary angioplasty: prevalence and histopathological features

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Background: Distal embolization during primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction may affect myocardial reperfusion.The prevalence, entity, and qualitative features of this phenomenon are yet to be elucidated.

Methods: Sixteen consecutive patients were treated by primary PCI performed with the non-occlusive distal protection device FilterWire Ex. The embolic fragments retrieved from the device filter were processed for morphometric and histopathological analysis. Morphometric analysis was performed through the use of a micrometric grid. Serial histological sections (5μm intervals) were stained with hematoxylin-eosin and, Weigert stain or Alcian blue. Macrophages were detected using the antibody direct to the macrophage colony stimulating factor.

Results: Particles were recovered in 16 out of 16 devices. The number of particles $>$20μm ranged from 5 to 118 per filter (mean 38). Particles with the major axis $>$500μm were 6$\pm$5 per filter with a mean major axis of 1405$\pm$690μm. Number and size of particles recovered in 6 patients pre-treated with IIb/IIIa inhibitors were not significantly different from those recovered in the remaining 10 patients (number of particles: 39$\pm$37 vs 37$\pm$41, P=NS; particles $>$500μm: 5$\pm$4 vs 7$\pm$6, P=NS; major axis: 1933$\pm$714 vs 1088$\pm$460μm, P=NS). Histologically, the 53% of particles were composed by platelets, red cells, and a wide network of fibrin, which led to classification as fresh thrombus. Cellularity was widely variable, often including polimorphonuclear cells. Macrophages and necrotic cores in the context of the fibrin network, suggesting the presence of ongoing thrombus organization, or plaque remnants, were present in 40% of particles. In 10% of particles fibroblasts were observed indicating an organized thrombus. Alcian blue-positive mucopolysaccharidic extra-cellular matrix, indicating the presence of plaque remnants within the embolized debris, was observed in 8% of particles. Foam cells, smooth muscle cells, cholesterol clefts, and calcifications were not observed.

Conclusion: Multiple, distal embolization always occurs during primary PCI, regardless of the use of IIb/IIIa inhibitors. A significant fraction of emboli during primary PCI is represented by plaque-containing debris and partially organized clots, which are likely to be unresponsive to pharmacologic therapy.

P1631 Transfer for primary angioplasty in real practice. Short-term results and predictors of mortality

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The efficacy of primary angioplasty (PA) in the treatment of acute myocardial infarction is well established. The main limitation of this treatment is its accessibility and delay in hospitals without catheterization facilities. Most of the information about transfer for PA is obtained from randomized trials, and data about feasibility, results and predictors of mortality in an unselected population are limited.

Methods: Prospective observational study by intention-to-treat analysis of in-hospital results and predictors of mortality in consecutive patients with AMI treated systematically with PA in a hospital located 10 kilometers of the reference catheterization laboratory. Results: Between June 2000 and December 2001, 138 patients were included (86% of patients admitted with AMI and reperfusion treatment criteria). Coronariography was performed in 135 patients (98%) and 114 (83%) underwent coronary angioplasty. Mean age 66$\pm$13 years; 28 (20%) females; anterior localization 58(42%). Median (25°-75° percentiles) of delay since the beginning of symptoms to PA, since patient admission to PA onset, transfer to catheterization laboratory and diagnosis to culprit vessel aperture was 167 (125-259), 65 (54-101), 20 (15-20) and 70 (53-83) minutes respectively. At admission 13% suffered cardiogenic shock. PA procedure was successful in 86% of cases. Stents were deployed in 86% of the lesions and IIb/IIIa inhibitors were administered to 61% of the patients. In-hospital mortality was 14.5% (78% and 5% in patients with and without shock). In a multivariate analysis including sex, age, diabetes, anterior location, PA procedure result, shock on admission, and delay until treatment, only shock on admission and unsuccessful PA procedure were independent predictors of in-hospital mortality.

Conclusions: PA as the election reperfusion treatment of AMI in a hospital 10 Km away of catheterization laboratory is associated to higher mortality (14.5%) previously reported in randomized trials. Shock on admission and failed PA are the major in-hospital predictors of mortality.

P1632 Benefits of primary stenting plus abciximab in diabetic patients suffering from myocardial infarction. Results of the STOPAMI 1 and 2 trials

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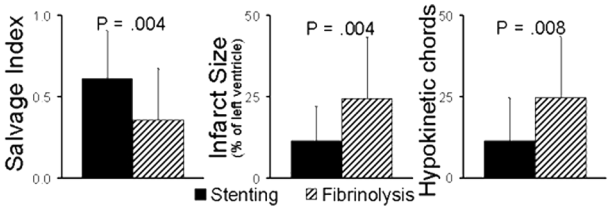
Diabetes mellitus is an independent risk factor for mortality in patients suffering from an acute myocardial infarction (AMI). In the STOPAMI 1 and 2 trials, we demonstrated an improved myocardial salvage after stenting as compared to fibrinolysis for patients with AMI. In this pre-specified subgroup analysis, the impact of reperfusion therapy on myocardial salvage in diabetic patients was investigated.

Methods: In the STOPAMI (Stent vs Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction) 1 and 2 trials, 58 diabetic patients were randomized to receive stenting plus abciximab (28 pts) or fibrinolysis (30 pts; alteplase alone 13 pts, alteplase with adjunctive abciximab 17 pts). Technetium-99m sestamibi scintigraphy was performed on admission and after 7-14 days to calculate the salvage index as the proportion of the initial perfusion defect salvaged with reperfusion therapy. Left ventricular (LV) angiography was done after 7-14 days to quantify the extent of LV wall hypokinesis.

Results: The Figure presents the salvage index, infarct size and number of hypokinetic chords. At 18-month follow-up, 3 (11%) of the stent and 5 (17%) of the fibrinolysis patients died (P=.51).



Scintigraphic and angiographic results.

Conclusion: In diabetic patients with AMI, coronary stenting plus abciximab leads to a greater degree of myocardial salvage, smaller infarct size and a reduced extent of LV hypokinesis as compared to fibrinolysis. The favorable results for stenting may be translated in clinical benefits, which needs to be confirmed by larger trials.

P1633 Prevalence and prognostic value of arrhythmic propensity after primary angioplasty for ST-segment elevation myocardial infarction

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Purpose: Arrhythmic propensity (ArrP) on ambulatory ECG monitoring (AEM) is associated with increased mortality, when performed early after ST segment elevation myocardial infarction (STEMI) treated with fibrinolysis. The prevalence and prognostic implications of ArrP after STEMI treated vith primary angioplasty (PA) however remain unclear. In the present study, we compared the prevalence and prognostic value of ArrP detected by AEM after discharge from STEMI in patients randomised to either fibrinolysis or PA.

Methods: AEM was performed for 24 hours at discharge from hospital, and analysed for ArrP, defined as $>$ 20 ventricular premature beats/hour (VPB/h) or episodes of non-sustained ventricular tachycardia (nsVT) in 1013 patients early after STEMI randomised to either fibrinolysis (n = 502) or PA (n = 511) as part of the DANAMI-2 study. Primary endpoint was all cause mortality during follow-up (1-5 years; median 2.1 years).

Results: The prevalence of ArrP was not significantly different in the 2 treatment groups (fibrinolysis: 16.5% vs. PA: 15.9%; p = 0.77). In fibrinolysed patients ArrP was associated with increased mortality both among patients whose ventricular ejection fraction (EF) was $\geq$ 40% (12.1% vs. 2.7%; p $<$ 0,001; RR = 5.3; CI = 1.9 - 14.2) and those with EF $<$ 40% (33.3% vs. 12.2%; p = 0.015; RR = 2.7; CI 1.2 - 6.2). In the PA group the detection of ArrP was associated with a trend toward an increased mortality among patients with EF $\geq$ 40% (2.7% vs. 7.0%; p = 0.059; RR = 3.0; CI 0.9 - 9.5) but not among patients with EF $<$ 40% (9.5% vs. 12.8%; p = 0.68).

Conclusions: We conclude that the selection of an invasive treatment for STEMI has no influence on the subsequent prevalence of ArrP as compared to fibrinolysis. After fibrinolysis ArrP is very useful in identifying high risk patients both with EF $\geq$ 40% and EF $<$ 40% respectively. However, in patients treated with PA, the prognostic value of ArrP is less certain, especially among patients with EF $<$ 40%.

P1634 Percutaneous coronary intervention in recent myocardial infarction: similar outcome and worse remodelling in comparison to medical treatment

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Background: Old randomized clinical trials did not demonstrate benefit of routine balloon angioplasty in recent myocardial infarction patients (RMI). If that concept is valid in the era of stent and GP IIb/IIIa antagonists it is unclear.

Aims: To compare the efficacy of medical treatment and percutaneous coronary intervention (PCI) in RMI patients.

Methods: Historical prospective cohort trial of 129 asymptomatic RMI pts. with single vessel disease selected between 5200 pts catheterized (1996-1999). 77 pts (55$\pm$11 years old, male 81%) PCI treated compared to medically treated patients (MT): 52 pts (58$\pm$13 years old, male 79%). Baseline clinical, angiographic and echocardiographic characteristics were analysed. Follow up period: one year. Clinical end points: Death, recurrent myocardial infarction, unstable angina and repeated PCI rate. Echocardiographic end point: Difference in end diastolic diameter (EDD) and end systolic diameter (ESD) between initial and follow-up echocardiogram.

Results: No differences in baseline clinical, angiographic and echocardiographic characteristics were observed. Anterior MI (52% vs 45%), LAD as culprit vessel (49% vs 48%), complete occlusion (36% vs 29%), collateral circulation (35% and 26%) and severe LV dysfunction (10% vs 6%) were respectively observed in MT and PCI groups. In PCI, stent was applied in 56% and Abciximab used in 22% of cases.

One year rate of death (2% vs.3%), recurrent MI (2% vs 1%), unstable angina (13% vs. 7%), PCI (6% vs.4%) were similar for MT and PCI respectively. In the echocardiographic follow up (718 $\pm$ 520 days) significant enlargement of the EDD (5 $\pm$6 mm vs 1$\pm$5 mm, p $<$0.013) and ESD (5$\pm$7 mm vs 1$\pm$7mm, p$<$0.03) was observed in the PCI group.

Conclusions: 1) Percutaneous coronary intervention in asymptomatic patients with recent myocardial infarction does not appear to offer clinical benefit in comparison to medical treatment. 2) Increasing ventricular remodeling was observed in patients treated with PCI. The meaning of this finding should be studied prospectively in a large sample of patients.

P1635 Prognostic significance of transient myocardial ischaemia after primary angioplasty for ST-elevation myocardial infarction

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Purpose: Transient myocardial ischemia (TMI) detected by ambulatory ECG monitoring (AEM) after ST Elevation Myocardial Infarction (STEMI) is associated with an increased risk of subsequent cardiovascular events. Previous studies however have not investigated patients treated with primary angioplasty (PA).

The aim of this study was to compare the prevalence and prognostic value of TMI detected by AEM after discharge from STEMI in patients treated with either fibrinolysis or PA.

Methods: 954 patients with electrocardiographic evidence of STEMI were randomised to immediate treatment with either accelerated alteplase (n = 476) or PA (n = 478). On the day of discharge AEM was performed for 24 hours and analysed for ST segment deviations. Primary endpoints for this study were death or nonfatal reinfarction within 1 year of index infarction, and death during long term follow-up (1-5 years; median 2.1 years).

Results: The overall prevalence of TMI on AEM was 27.5%. There was no significant difference between the 2 treatment groups (fibrinolysis: 29.8% vs. PA: 25.1%; p = 0,10).

In the fibrinolysed group, patients with ST segment deviations showed a significantly increased incidence of the combined endpoint of death or nonfatal reinfarction (11.1% vs. 5.4%; p = 0.036; RR = 2.1; CI 1.04 - 4.10) and a trend towards an increased rate of nonfatal reinfarctions (6.4% vs. 2.7%; p = 0.07; RR = 2.36; CI 0.90 - 6.14), within the first year after index infarction. Mortality rates among fibrinolysed patients with ST segment deviations were significantly increased during long term follow-up (p $<$ 0,001). However, in the PA group there was no significant relationship between ST segment deviations and subsequent cardiovascular events or death.

Conclusions: Our results confirm previous findings, showing a positive relationship between detection of TMI early after STEMI, and the risk of subsequent cardiovascular events in patients treated with fibrinolysis.

Despite the prevalence of ST segment deviations observed in patients treated with PA being equal to patients receiving fibrinolytic therapy, it did not have similar prognostic implications.

P1636 Prehospital triage for primary angioplasty and aborted ST-elevation myocardial infarction

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Background: Previous reports have shown a three times higher occurrence of aborted ST elevation myocardial infarction in patients treated by prehospital thrombolysis in comparison to in-hospital treatment. Prehospital infarct triage with primary angioplasty has reduced symptom-to-balloon times considerably. Therefore we studied the incidence of abortion of myocardial infarction with this strategy.
Methods: A total of 545 patients were thrombolysed for acute myocardial infarction in the cities of Rotterdam and Nijmegen, The Netherlands, and were compared with 236 patients treated with angioplasty after prehospital triage in Zwolle, The Netherlands. All patients were treated with nitroglycerin s.l and aspirin. Patients with prehospital triage for angioplasty were treated with heparin before transport. Time to reperfusion is defined as symptom to balloon time in primary angioplasty or symptom to thrombolysis time plus 90 minutes in prehospital thrombolysis. Abortion of acute myocardial infarction is defined by resolution of characteristic symptoms and ECG-changes, combined with a rise of cardiac enzymes less than 2 times normal value.
Results: (Table) Basic characteristics of patientsts (age, sex, anterior infarction, diabetes, Killip at presentation) were not significantly different in both groups. Abortion of myocardial infarction and 30-day mortality is comparable in both groups. Time to treatment was an independent variable for the incidence of abortion of myocardial infarction in both groups, using a stepwise regression analysis.

	Prehospital thrombolysis (n=545)	Primary angioplasty (n=236)	p
Time to reperfusion, median, minutes	180	170	0.6
Aborted MI (%)	87 (16.0)	26 (11.0)	0.07
Haemorrh stroke (%)	10 (1.8)	0	0.12
30-day mortality	38 (7.0)	10 (4.2)	0.2

Conclusion: Prehospital triage for primary angioplasty results in a similar reperfusion time as prehospital thrombolysis. The incidence of aborted myocardial infarction is the same, but primary angioplasty seems to be safer.

P1637 Impact of time to reperfusion on microvascular damage after primary coronary angioplasty for acute myocardial infarction

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Backgrounds: Previous studies have reported that time to reperfusion may be less important with primary coronary angioplasty for acute myocardial infarction (AMI). The aim of this study was to evaluate the impact of time to reperfusion on microvascular damage after primary coronary angioplasty for AMI.
Methods: We studied 87 patients with a first anterior wall AMI, without cardiogenic shock, who underwent primary coronary angioplasty within 12 h of onset. Coronary flow velocity parameters were assessed immediately after reperfusion using a Doppler guidewire. We assessed the presence of systolic flow reversal (SFR), systolic velocity integral (SVI) and diastolic deceleration time (DDT) as markers of microvascular damage.
Results: Reperfusion was achieved within 2 h in 11 patients (13%; early reperfusion group). SFR was not found in the early reperfusion group. SVI was the highest and DDT was the longest. In addition, peak CPK was the lowest and left ventricular ejection fraction was the highest. There were no differences in other clinical characteristics by time to reperfusion.

CFV parameters and clinical results

	<2 h (n=11, 13%)	2 tp <4 h (n=45, 52%)	4 to <6 h (n=17, 19%)	≥6 h (n=14, 16%)	P value
SFR, %	0	31	41	57	0.02
SVI, cm	4.2±2.1	1.6±2.1	0.7±2.2	0.7±2.6	0.006
DDT, sec	1076±289	530±319	538±365	597±422	0.001
Peak CPK, IU/l	2008±1103	5076±2423	5275±3041	4613±1954	0.002
LVEF at 1M %	66±8	53±11	52±15	54±14	0.03

Conclusions: Time to reperfusion, within 2 h, is important for preventing microvascular damage, which results in reduced infarct size. However, after 2 h, microvascular damage after primary coronary angioplasty is not dependent on time to reperfusion in patients with anterior AMI.

P1638 The degree of restored myocardial perfusion in acute infarction influences immediate and long-term results after primary coronary angioplasty

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Introduction: Primary coronary angioplasty (PCI) permits an opening of the infarct related artery (IRA) in acute myocardial infarction (AMI). However, in one in four patients the restoration of epicardial coronary blood flow does not ensure adequate perfusion of myocardial tissue.
Methods: The aim of this study was to evaluate the relation between IRA epicardial blood flow grade and tissue perfusion grade and clinical course in one-year follow-up of 434 patients (pts) (age 58.5±11.2 years) with AMI treated by primary angioplasty (PCI). Coronary blood flow (TIMI grade) and myocardial perfusion (TIMI Myocardial Perfusion Grade, TMPG) were evaluated before and after PCI. A composite clinical success after a one-year observation was defined as freedom from death, reinfarction, urgent revascularisation and repeated cardiovascular hospitalisation. After a one-year follow-up all pts were classified according to NYHA scale.
Results: Before PCI TIMI–3 was observed in 3.2% of pts, TIMI-2 in 6,2% of pts and TIMI-0/1 in 90,6% of pts. Before PCI TMPG–3 was observed in 2.1% of pts, TMPG-2 in 3,2% of pts and TIMI-0/1 in 94,7% of pts. After PCI TIMI-3 was achieved in 86.2% of pts, TIMI-2 in 10.8% of pts. and TIMI 0/1 in 3% of pts. After PCI TMPG-3 was achieved in 30.4% of pts, TMPG-2 in 41% of pts. and TMPG 0/1 in 28,6% of pts. At the end of follow-up 5.6% of pts with TMPG-3 was in NYHA 1/2 grade and 1.4% was in NYHA 3/4 grade, 6.7% of pts with TMPG-2 was in NYHA 1/2 grade and 1.7% was in NYHA 3/4 grade, 44.8% of pts with TMPG-0/1 was in NYHA 1/2 grade and 14.9% was in NYHA 3/4 grade. The composite clinical success for pts. with final TMPG-3 was 77.8%, with TMPG-2 70.3%, and with TMPG-0/1 40.1% ($p<0.01$ vs. TMPG-3 or -2).

TMPG after primary PCI vs. mortality

TMPG after PCI	In-hospital	1 month	6 month	12-month
3	0%	0%	0%	1.4%*
2	1.7%	2.7%	3.7%	3.7%**
1	12.1%	13.6%	15.1%	15,1%
All pts	4.1%	5.1%	6.0%	6.5%

*p<0,001 vs. TMPG-0/1, **p<0,01 vs. TMPG-0/1, for abbreviations see the content of the abstract.

Conclusion: High tissue myocardial perfusion grade achieved after primary angioplasty in AMI is associated with low mortality and better clinical result in a long-term observation.

P1639 A myth of large volume centre

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Purpose: Percutaneous coronary intervention(PCI) is the most effective procedure to improve mortality rate in patients with acute myocardial infarction (AMI). Many specialists believe that the mortality rate in AMI patients with direct PCI is lower at high-volume hospital. There is a great difference of direct PCI rate between Japan and the United States (U.S.A.). To clarify the difference of direct PCI rate and the causal factors,we compare databases from both countries.
Methods: We analyzed data from Japanese and American AMI databases. Japanese databases and surveys are CAMPAIGN study (Oct. 2000, n = 2007, Hospitals; H = 22, PCI rate = 75%), JSIC (Japanese Society of Interventional Cardiology) PTCA database (1996-1999, n = 1914, H = 38), community survey by Nonoki (Oct. 2000 one month, n = 541, H = 591, PCI rate = 51%) and JSIC survey (Feb. 2001, n = 1786, H = 261, PCI rate = 80%). American databases and published reports are CCP (Cooperative Cardiovascular Project 1995), NRMI 3 (the National Registry of Myocardial Infarction 3 1999), Medicare Claim Files, meta-analysis by Heidenreich (1975-1995), NRMI 3 (H = 1432, PCI rate = 15%, Rogers WJ, JACC 2000;36:2056), American Best Hospital (1997,PCI rate = 15%, Chen J, NEJM 1999;340:286), MEDPAR. (1996) and the study by McGrath PD (JAMA 2000;284:3139).
Results: As in table 1, more AMI patients receive direct PCI in Japan, compared to patients in U.S.A. The mortality rate is a liitle bit lower in Japan. The percentage of low-volume hospitals (PCI cases per year<200) is 86% in Japan, but only 26% in U.S.A.In the Japanese low volume hospitals, the rate of direct PCI is higher (30-51%) and most AMI patients (75-100%) were treated by direct PCI.

Table1. Outcome of all patients with AMI

	Japan	U.S.A.
Prevalence of direct PCI	50-80%	15-24%
Thrombolysis	5%	21%
Mortality rate		
In-hospital (crude)	10%	12%
30-days (crude)	10%	17%
Hospital stay (median)	23days	7days

Conclusion: Both the Japanese and American AMI databases suggest that the outcome of AMI patients by direct PCI would be better, if more low-volume hospitals become available for direct PCI.

CORONARY CIRCULATION: EXPERIMENTAL STUDIES

P1640 Myocardial infarction aggravates chronic renal function loss in a rat model of cardiorenal interaction

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Purpose Clinical studies show that the level of kidney function plays a role in the long term cardiovascular morbidity and mortality in the general population (Framingham) and in cardiovascular compromised patients (HOPE-study). However, no data are available whether cardiac function determines the outcome of progressive renal function loss. We therefore studied the development of proteinuria in rats with and without unilateral nephrectomy (UnX), with and without an additional myocardial infarction (MI).
Methods At t=0, UnX was performed, followed by MI at t=1 wk by ligation of the left anterior descending coronary artery. Groups: UnX (n=15), MI (n=9), UnX + MI (n=18), and 2K-CON (two-kidney controls; n=15). Proteinuria and systolic blood pressure (SBP) were evaluated using metabolic cages and the tail-cuff method, respectively.
Results At t=16 wks, cardiac function was measured using a microtip pressure transducer. Data are given as mean ± SEM. At t=16 wks, proteinuria in the UnX group averaged 14.0 ± 2.9 mg/24h, 13.2 ± 2.9 mg/24h in the MI, and 16.7 ± 3.1 mg/24h in the 2K-CON group. In contrast, proteinuria in the UnX + MI group gradually increased to a level of 54.1 ± 9.3 mg/24h at that time point, which was significantly higher ($P < 0.05$) compared with the other groups. SBP at week 16 averaged 119 ± 3 mmHg in UnX, 117 ± 4 mmHg in MI and 114 ± 6 mmHg in 2K-CON. SBP in UnX + MI was highest, averaging 130 ± 6 mmHg. Left ventricular pressure (LVP) was lower in both MI groups (+UnX: 112.2 ± 2.3 mmHg; -UnX: 108.8 ± 4.3 mmHg) compared to no-MI groups (2K-CON: 120.7 ± 2.9 mmHg; UnX: 126.9 ± 6.0 mmHg). Heart weight was increased in both MI groups (+UnX: 1.46 ± 0.03 g; -UnX: 1.51 ± 0.04 g) compared to no-MI groups (2K-CON: 1.23 ± 0.03 g; UnX: 1.21 ± 0.04 g).
Conclusions We conclude that MI has no detectable effect on the healthy kidney. However, MI aggravates the mild state of chronic renal function loss (as induced by UnX) measured as an accelerated increase in proteinuria. Since kidney function may in turn influence long term cardiovascular morbidity and mortality (not studied in this model), these findings stress the importance of unraveling cardiac-renal interaction to allow future improved protection for both heart and kidneys.

P1641 Regulation of G protein coupled receptors reserve during treatment with cyclosporine A

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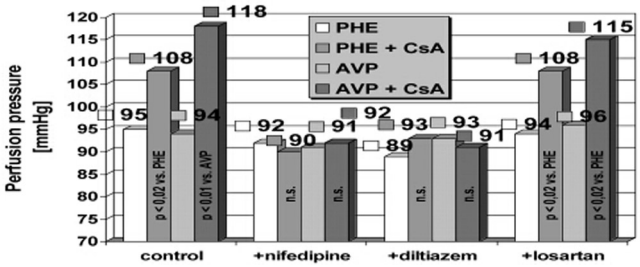
Background Treatment with cyclosporine A (CsA) is associated with reduced endothelium-dependent vasodilatation and altered vascular smooth muscle reactivity, resulting in arterial hypertension in about 30% of treated. The molecular mechanism of CsA action on vascular smooth muscle cells (SMC) are not completely understood, thus treatment of CsA-induced hypertension is mostly empiric.
Methods Experiments were performed on male Wistar rats tail artery. Cumulative response curves (CRCS) to phenylephrine (PHE) and vasopressine (AVP), KA values and calcium movements between cellular compartments were calculated using the commonly approved pharmacometric methods.
Results In the presence of CsA (1 nM - 30 min) the AVP and PHE CRCS was shifted to the left without change in maximal responses. The calculated KA values for AVP (1,37 (±0.36)x10-8) and PHE (3,38 (±0,45)x10-7) in the absence and in presence of CsA did not differ significantly. Thus, CsA did not change the affinity of receptors to agonists. The KA/ED50 value for AVP and PHE significantly increased in the presence of CsA. Analysis of calcium movements in the SMC suggest increase of the influx from extracellular space in the CsA pretreated tissue during contraction induced by AVP and PHE. Increase of calcium influx was absent in BAY K8644 (agonist of calcium channel type L) induced contraction. Effect of CsA was significantly inhibited by calcium antagonists (see figure).



Conclusion Our results strongly suggest that effect of CsA after 1/2 hour incubation is predominantly result of increasing of signal transduction between receptor and calcium channel. CsA may increase activity of G protein or protein kinase C, thus best treatment of CsA-induced hypertension seems to be treatment with calcium antagonists.

P1642 Multichannel magnetocardiographic mapping of small animals in an unshielded laboratory

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Contactless multichannel magnetocardiographic mapping (MMCG) is increasingly used in humans for non-invasive study of ventricular repolarization (VR) in patients with coronary artery disease, cardiomyopathy, and for three-dimensional (3D) localization and imaging of cardiac arrhythmogenic substrates. From clinical practice with MMCG, the need has raised for experimental investigations aimed to investigate and interpret the electrogenetic mechanisms underlying abnormal patterns. Furthermore, MMCG could be used to non-invasively study specific problems in animal models, especially in genetically altered mice with cardiomyopathy. So far no study had been reported on MMCG of small animals. This study was aimed to test the feasibility of unshielded MMCG of small intact animals.

Method: A 36-channel DC-SQUID MMCG system designed for clinical application in unshielded laboratories (sensitivity: 20 fT/Hz$\frac{1}{2}$) was used for simultaneous MMCG from a 36-point grid, covering the area of 20 cm x 20 cm. Alternatively MMCG was performed sequentially with a 9-channel system (CardioMag Imaging Inc., USA). The latter system was also used to record a 9-point mini-map. 10 animals of different breeds (rabbits, rats and hamsters; body weight between 200 and 2000 grams) were studied, to define the minimum size still compatible with adequate MMCG imaging of cardiac magnetic fields and to define the limit of the method for contactless electrophysiologic source localization. Equivalent current dipole (ECD), Effective Magnetic Dipole (EMD) and distributed currents (DC) models were used in the inverse calculations for 3D localization of cardiac sources.

Results: In rabbits and rats, reproducible imaging of both atrial and ventricular magnetic fields providing localization of cardiac sources, was possible after averaging 120 seconds of MMCG. Different breed-related patterns of VR were found in rats, which allowed breed differentiation of apparently identical rats on the basis of MMCG. Cardiac magnetic fields of hamsters were much weaker, thus a magnetocardiographic signal-to-noise ratio adequate for reproducible source localization was achievable only with ventricular signals.

Conclusions: Contactless MMCG in small animals is feasible, even in an unshielded laboratory, with both 36 and 9-channels systems designed for clinical recordings. In smaller animals (rats and hamsters), a 9-channel system can be sufficient to detect the whole cardiac magnetic field distribution, with a single recording. The minimum animal weight to detect and study both atrial and ventricular magnetic fields was about 400 grams.

P1643 Adenosine diphosphate receptor antagonist Ticlopidine treatment reduces in-stent neointimal hyperplasia in porcine coronary artery

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Purpose: The objective of the present study was to investigate the effect of Ticlopidine treatment as an additive therapy to aspirin on the development of neointimal hyperplasia after intracoronary stent implantation in porcine coronary arteries.

Methods: Twenty-two coronary Genius stents (Eurocor, Germany) were implanted under general anaesthesia in 12 pigs either in the left anterior or in the left circumflex coronary artery. The pigs were divided into two groups: 7 animals (Group 1) with 13 stents received aspirin (100 mg/day per os) alone and 5 pigs with 9 stents aspirin (100 mg/day per os) and Ticlopidine (2x250 mg loading dose, then 250 mg/day per os), 1 day before the stent implantation and during the entire follow-up. One month after the first procedure, coronary angiography was repeated and intravascular ultrasound (IVUS) was performed to assess macroscopically the development of neointimal hyperplasia. All IVUS images were recorded on a videotape and analysed by using 3D reconstruction (EchoPlaque2, Indec Systems). Neointimal, outer plaque (tissue between stent and vessel wall) and vessel volumes, the mean intimal area and maximal intimal thickness were calculated automatically.

Results: The size and length of the implanted stents were similar in both groups: mean stent diameter 3.2±0.3 mm in Group 1 and 3.3±0.4 mm in Group 2; mean stent length 15±0 mm in Group 1 and 14.3±3.7 mm in Group 2. One pig of the Group 1 died due to subacute stent thrombosis and acute myocardial infarct 3 weeks after the stent implantation. No cardiac events occurred in Group 2. At 1 month follow-up, IVUS revealed significant smaller mean intimal area (1.91±0.95 vs 2.87±0.78 mm^2, p=0.01) and intimal volume (29.9±21.1 vs. 43.9±16.0 mm^3, p=0.05), and a trend towards smaller maximal intimal thickness (0.29±0.14 vs 0.38±0.1 mm, p=0.06) in pigs of Group 2 compared to Group 1 animals. No differences were found between Group 2 and Group 1 as regards outer plaque volume (43.0±15.8 vs. 40.6±10.6 mm^3, p=0.35) and vessel volume (151±50 vs 179±44 mm^3, p=0.10).

Conclusion: Adenosin diphosphate receptor antagonist therapy additive to aspirin decreases not only the rate of subacute complications after coronary stent implantation, but reduces the development of neointimal hyperplasia, probably by interrupting the link between the initial coagulation cascade and local inflammation.

P1644 Increased microvascular permeability in diet-induced hypercholesterolemic rabbits: a magnetic resonance imaging-based longitudinal study

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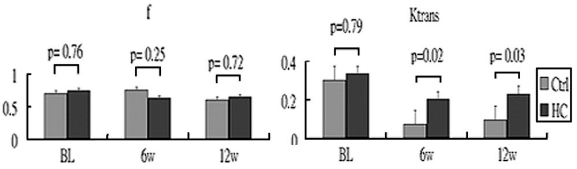
Hypercholesterolemia is associated with atherosclerosis in systemic arteries. Its impacts on myocardial microcirculation are less well known. We designed a MRI-based longitudinal study to test the hypothesis that diet-induced hypercholesterolemia can result in increased myocardial microvascular permeability. 15 New Zealand white rabbits were assigned into control (Ctrl, N = 7) and hypercholesterolemic (HC, N = 8) groups at the age of 8 weeks. Rabbits in HC group were fed with 0.5% cholesterol-enriched diet. Each rabbit from both groups received examination at the age of 8, 14 and 20 weeks. With a 1.5T Siemens Sonata scanner, myocardial first-pass dynamic imaging by TrueFISP saturation sequence was acquired after a bolus of Gd-DTPA (dosage: 0.02 mmol/kg, injection rate: 0.5 ml/sec). Indices of regional blood flow (f) and microvascular permeability (Ktrans) were quantified from the signal-time curves using standard pharmacokinetic models. Serum lipid level were also recorded during the study. At the age of 20 weeks, all hearts were removed and processed for pathological study. As a result, serum level of cholesterol, triglyceride and Ktrans significantly increased ($p<0.05$) after feeding rabbits with cholesterol-enriched diet for 6 and 12 weeks. No statistical difference in f can be found between control and HC group at any time point (Figure 1). With confocal microscopy, hearts from HC rabbits showed altered arrangement of CD146-positive microvessels and increased VEGF expression.



We concluded that hypercholesterolemia is associated with local VEGF expression and altered arrangement of microvessels, and therefore contributes to increased microvascular permeability without perfusion insufficiency in myocardium.

P1645 The coronary ubiquitin proteasome system is functionally active in the early stage of atherogenesis

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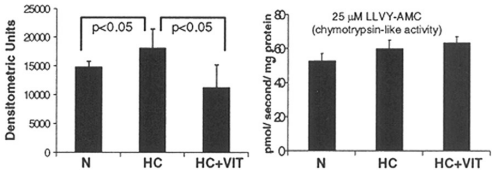
Background: The ubiquitin proteasome system (UPS) is involved in the removal of damaged proteins and the activation of transcription factors like nuclear factor kappa B. Recent reports, however, questioned the functional activity of the UPS under conditions of increased oxidative stress, including the early stage of atherosclerosis.
Methods and Results: For a study period of 12 weeks, female domestic pigs were placed on a normal chow diet (N) or on a hypercholesterolemic diet without (HC) or with daily vitamin C (1000 mg) and E (100 IU/kg) supplementation (HC+VIT) (n=5 per group). Compared with N, plasma concentration of total cholesterol was higher in both HC and HC+VIT (84 $\pm$ 4 vs. 413 $\pm$ 213 and 450 $\pm$ 104 mg/dL, respectively, $p<0.05$ for N vs. HC and HC+VIT). Serum LDL-malondialdehyde concentration was higher in HC than in N and HC+VIT (8.7 $\pm$ 0.5 vs. 7.2 $\pm$ 0.9 and 6.3 $\pm$ 0.6 nmol/mg protein, $p<0.05$). Tissue activities of radical scavenger enzymes were lower in HC than in N and HC+VIT (catalase: 12.5 $\pm$ 2.5 vs. 20.5 $\pm$ 2.9 and 21.0 $\pm$ 2.2 IU/mg protein, $p<0.05$; MnSOD: 2.0 $\pm$ 0.2 vs. 2.5 $\pm$ 0.1 and 2.4 $\pm$ 0.1 IU/mg protein, $p<0.05$). As demonstrated by immunoblotting, the level of ubiquitination in the coronary arterial wall 42.3% and 49% higher in HC than in N and HC+VIT, which was not attributable to an impairment in 20S proteasome proteolytic activity (figure). As seen by double-immunostaining, ubiquitin conjugates accumulated predominantly in the cytoplasm of media smooth muscle cells.



Conclusions: These results demonstrate that the UPS is functionally active in experimental early atherogenesis in association with an increase in oxidative stress. This study supports a role for UPS in the pathophysiology of atherosclerosis.

P1646 Improved haemodynamics with a novel chest compression device

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Introduction: The purpose of this clinical study was to determine if a novel chest compression device (AutoPulse?, Revivant Corp.) would exhibit increased circulation when compared to manual chest compression during cardiopulmonary resuscitation (CPR).
Methods: A total of 31 sequential patients with in-hospital sudden cardiac arrest were screened and 16 successfully enrolled (68 $\pm$ 6 years, female). All patients had received prior treatment for cardiac disease and most had other co-morbid illness. Patients were included following 10 minutes of failed ACLS protocol. Fluid-filled catheters were advanced into the thoracic aorta and the right atrium. Placement was confirmed by pressure waveforms and chest radiograph. The coronary perfusion pressure (CPP) was measured as the difference between the aortic and right atrial pressure during the chest compression's decompressed state. Following 10 minutes of failed ACLS and catheter placement, patients received alternating manual and AutoPulse? chest compressions for 90 seconds each. Chest compressions were administered without ventilation pause at 100 beats/min manual and 60 beats/min AutoPulse?. All patients received endotracheal intubation and ventilated by bag-valve at 12 breaths/minute between compressions.Epinephrine (1 mg IV bolus) was given at the request of the attending physician at 4 to 5 minute intervals.
Results: AutoPulse chest compressions increased peak aortic pressure from 122 $\pm$ 11 mm Hg to 150 $\pm$ 8 mm Hg (mean $\pm$ SEM, $p < 0.05$) as well as peak right atrial pressure from 85 $\pm$ 9 mm Hg to 126 $\pm$ 8 mm Hg ($p<0.002$). Furthermore, AutoPulse chest compressions increased CPP from 15 $\pm$ 3 mm Hg to 20 $\pm$ 3 mm Hg ($p<0.02$). For the average patient, this increase in CPP with the AutoPulse was 62%. Manual chest compressions were of consistent high quality (47 $\pm$ 3 kg), and in all cases meeting or exceeding AHA guidelines for depth of compression.
Conclusion: Previous research has shown that increased CPP was correlated to increased coronary blood flow and increased survival from sudden cardiac arrest. The AutoPulse demonstrated increased circulation over manual chest compressions during CPR as measured by CPP and indicated increased coronary and systemic blood flow.

P1647 Platelet function is associated with the amount of neointimal hyperplasia after stent implantation in porcine coronary arteries

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Purpose: The purpose of this study was investigate the correlation between platelet function and neointimal hyperplasia after stent implantation in porcine coronary arteries.
Methods: 34 stents (diameter of 3.1$\pm$0.2 mm and length of 14.8$\pm$1.7 mm) (EuroCOR GmbH, Bonn, Germany) were implanted (8 atm pressure, 30 seconds inflation time) in 26 pigs either into the left anterior or circumflex coronary artery under general anaesthesia and after administration of 200 IU of heparin per kg bodyweight. For prevention of acute and subacute stent thrombosis, the pigs received 250 mg aspirine and 250 mg ticlopidine daily (500 mg ticlopidine as a loading dose 1 day before the intervention). After 4 week follow-up, diagnostic coronary angiography was repeated and intravascular ultrasound (IVUS) was performed. IVUS results were evaluated off-line using a computer-assisted 3D-analysis system (EchoPlaque 2, Indec Systems). Arterial blood samples were drawn before and 1 hour after the intervention, and the counts of white blood cells and platelets were measured. According to literature data, the function of platelets was derived from platelet size (mean platelet volume, MPV; platelet large cell ratio, P-LCR; platelet distribution width, PDW). Larger platelets were regarded more reactive than smaller ones.
Results: At follow-up, maximal neointimal thickness and neointimal volume as assessed by IVUS were 0.2$\pm$0.1 mm and 19.8 $\pm$ 14.1 mm^3, respectively. White blood cell count was not associated with the amount of neointima (pre intervention 16,800$\pm$5,100, post 17,600$\pm$4,500 cells/ml, p=non significant, n.s.; normal range 7,000-20,000 cells/ml). Platelet count pre intervention was 459,000$\pm$122,000, post intervention 409,000$\pm$133,000 cells/ml (p=n.s.; normal range: 325,000-715,000 cells/ml). Higher MPV, P-LCR and PDW measured before intervention were significantly correlated with a larger amount of neointima as expressed by maximal neointimal thickness (MPV: r=0.43, $p<0.05$; P-LCR: r=0.56, $p<0.01$; PDW: r=0.46, $p<0.01$) and mean neointimal area (MPV: r=0.36, $p<0.05$; P-LCR: r=0.51, $p<0.01$; PDW: r=0.44, $p<0.05$).
Conclusion: Higher activity of circulating platelets is significantly associated with an increased amount of neointimal hyperplasia in the porcine model of coronary in-stent-restenosis.

P1648 Flow-dependent vasodilatation in the normo- and hypertensive rats under conditions of nitric oxide synthase inhibition

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Objective: To investigate a possible role of nitric oxide (NO) in the maintenance of arterial distensibility, conductivity, and intravascular pressure stability in normotensive Wistar-Kyoto (WKY) compared to spontaneously hypertensive rats (SHR).
Methods: Blood perfusion of hindquarter vascular bed, prior to and 15 min after a subsequent administration of nitric oxide synthase inhibitor L-NAME (10 mg/kg, iv), was performed on anesthetized and mechanically ventilated WKY (n=10) and SHR (n=11) male rats. The perfusion schedule was set at a step-wise flow rate mode, from 1,5 to 12 ml/min, to achieve perfusion pressure (PP) values 30 to 250 mm Hg.
Results: Thereafter, the following parameters were mathematically derived from "flow-pressure" dependencies: hydraulic resistance (HR), vascular distensibility (VD), and index of intravascular pressure stability (IPS) which is inversely related to the difference between maximal and minimal PP. The "flow-pressure" dependencies were plotted both before and after L-NAME injection. The blockade of NO synthesis increased systemic blood pressure both in WKY and SHR on 31 and 36%, respectively. It was associated with the increase in HR of the hindquarter vessels and concomitant decrease in IPS. After L-NAME administration, VD became significantly less in WKY (-0,16 $\pm$ 0,05 vs. 0,52 $\pm$ 0,06, $p<0.01$) while in SHR it became higher (0,68 $\pm$ 0,15 vs. 0,2 $\pm$ 0,07, $p<0.05$).
Conclusions: The results obtained support the key role of NO in the maintenance of conductivity and intravascular pressure stability both in WKY and SHR. The major determinant of VD in this model, flow-dependent vasodilatation in normotensive (WKY) rats involves NO release as a primary mechanism in contrast to SHR in which VD seems to be regulated by another factors.

CONTRAST ECHOCARDIOGRAPHY IN ACUTE MYOCARDIAL INFARCTION

P1649 Assessment of myocardial reperfusion by intravenous myocardial contrast echocardiography in patients with acute anterior myocardial infarction compared with ^{99m}Tc-sestamibi single-photon emission computed tomography

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Microvasculature damage after myocardial infarction has wide-ranging implications, as there are both non-invasive and invasive parameters facilitating flow assessment at tissue level.
The study aimed to assess the efficacy of intravenous contrast echocardiography (MCE) in detecting myocardial perfusion defects in patients (pts) with acute myocardial infarction compared with 99m Tc MIBI SPECT study.
Methods: 19 pts (13 M; 6 F, mean age 55.4±10.2) underwent primary percutaneous coronary (PCI) for acute anterior myocardial infarction. TIMI grade flow, myocardial blush grade (MBG), corrected TIMI frame count (cTFC), wall motion score index (WMSI) and segmental perfusion were estimated in real time before and immediately after PCI, using low MI (0.3) after 0.3 ml bolus injections of intravenous Optison. MCE was repeated on the third day after PCI. All patients underwent a rest 99mTc MIBI SPECT study (SPECT) on the third day after PCI.
Results: A MCE perfusion defect size after PCI greater than 50% of the MCE perfusion defect size before PCI was used to define myocardial non-reperfusion. Based on MCE, 12 pts had reperfusion, and 7 had non-reperfusion. Pts from the non-reperfusion group showed a higher creatine kinase peak (p= 0.03), higher kinase-MB (p=0.03) and higher level of troponine (p= 0.006), longer time from the onset of pain to reperfusion (p= 0.04), and worse baseline regional contractile function (p=0.001). All angiographic parameters were worse in this group before as well as after PCI: TIMI before 0.8± 0.9 v. 1.6± 0.5, TIMI after 2.3± 1.0 v 3± 0, MBG before 0.8± 1.3 v 2.1± 0.4, MBG after 1.2 ±1.4 v 2.6± 0.5, cTFC before 86.85± 51.51 v 30.85± 8.9, cTFC after 42.8± 40.1 v 15.3± 3.9. MCE on the third day revealed further improvement of myocardial perfusion in 8 pts.
The agreement between MCE and SPECT for detecting perfusion abnormality was 88% (ê 0.78).
Conclusions: MCE allowed for the identification of myocardial perfusion abnormalities in patients with acute myocardial infarction. Serial MCE facilitated identification of pts with early and late improvement of myocardial perfusion. MCE correlated very well with SPECT images in assessing perfusion defect.

P1650 Real time myocardial perfusion study in acute myocardial infarction and its relation with revascularized coronary territory

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Myocardial contrast echocardiography (MCE) can be performed in real-time (RT-MCE) during the acute phase of myocardial infarction (AMI), but its real clinical value remains unknown. The aim of our study was to assess RT-MCE pattern of the left ventricle (LV) during early days post AMI (3rd day). We studied a sample population of 48 patents (pts) with AMI clinical, ECG and laboratorial diagnosis, mean age 61.8±12 years (43-79 years), 66.6% (32/48) male gender. For the RT-MCE study, we applied a destructive technique and the MCE agent we used was SonoVue (Rovi AS-Bracco, Italy) $\frac{1}{2}$ vial bolus followed by an intravenous infusion of 8 microl/ml during 3 min. In the 2D echocardiographic studies for myocardial perfusion we used electronic multifrequency 2,5-3,5 MHz probes, grey scale imaging, with RT-MCE destructive 2D-CCI technique for continuous imaging acquisition in real-time, with a time delay of 70 msec. In each case through we evaluated regional LV wall motion abnormalities (normal-0; hypoquinesia-1; aquinesia-3; dysquinesia-3; aneurysm-4) and calculated the correspondent contractility index (LVCI). To assess the LV myocardial perfusion pattern we evaluated RT-MCE of the segmental LV myocardial wall thickness (normal-0; patchy-1; late filling 2; absent-3) and calculated the correspondent perfusion index (LVPI).
Results: We analysed a total number of 768 LV myocardial wall segments, including 2,8% (22/768) considered as inadequate for analysis. From these pts, 56% (24/48) were submitted to percutaneous coronary angioplasty, with successful intervention on 41,9% (161/384) of the LV myocardial wall segments. LV segments with wall motion type 2 registered a perfusion pattern type 2 in 27% (16/60) and type 3 in 37% (22/60). The LV myocardial wall segments located in the revascularized coronary territory (n=161) registered a tissue perfusion type 0 in 26% (42/161; p=0.04), type 1 in 33% (54/161), type 2 in 16.7% (27/161) and type 3 in 23.6% (38/161; p=0.02), with a significant statistical difference when compared with the non revascularized territory (n=223; 58.1% of the LV myocardial wall segments).
Conclusions: The RT-MCE has the capability to identify different LV myocardial perfusion patterns during the acute phase of myocardial infarction, and to assess the importance of the relationship between myocardial perfusion, regional contractility, wall motion and coronary revascularization.

P1651 Vasodilator myocardial contrast echocardiography accurately predicts flow limiting coronary artery stenosis following thrombolysis in acute myocardial infarction

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Introduction: Despite successful thrombolysis, complete patency of the infarct related artery (IRA) is not always achieved in patients after acute myocardial infarction (AMI). The detection of flow-limiting coronary stenosis as demonstrated by a reduced coronary flow reserve (CFR) both in the IRA territory showing significant viable myocardium, and in the non-IRA remote territory may help to identify patients who may benefit from mechanical revascularisation. We aimed to evaluate the ability of myocardial contrast echocardiography (MCE) with vasodilator stress to demonstrate reduced CFR in the IRA and remote territories to detect flow-limiting stenosis in this patient cohort.
Methods: Consecutive patients with AMI underwent low power MCE using Sonovue® infusion 7-10 days after thrombolysis. A semi-quantitative scoring system was used to assess contrast intensity: 2-homogeneous opacification; 1-reduced or heterogeneous opacification; 0-minimal or absent opacification. Dipyridamole (0.56mg/kg) administered over 4 minutes was used to assess CFR. Any reduction in contrast intensity in the stress images compared to rest was considered to represent reduced CFR. For the IRA territory, only patients with significant myocardial viability (homogeneous contrast opacification in >60% of the myocardium) were assessed for CFR. All patients underwent coronary angiography prior to hospital discharge. A coronary stenosis ≥70% in the major epicardial artery was considered flow limiting.
Results: Of the 62 patients in the study, 48 demonstrated significant myocardial viability in the IRA territory of which 42 showed flow-limiting IRA stenosis. Of these, MCE detected reduced CFR in 37 (88%). The sensitivities of MCE for the detection of flow-limiting stenosis in the anterior and posterior circulations were similar (85% and 94% respectively). MCE correctly detected preserved CFR in the six patients without flow-limiting stenosis. Furthermore, MCE correctly predicted remote flow-limiting stenosis in 18 (70%) out of the 26 patients. The sensitivities for the detection of flow-limiting stenosis in the anterior vs posterior circulation were 100% and 58% respectively. MCE correctly predicted preserved CFR in 35 (97%) out of 36 patients without remote flow-limiting stenosis.
Conclusion: Vasodilator stress MCE accurately predicts flow-limiting stenosis both in the IRA and remote territories after AMI. This information is important for identifying patients who may benefit from mechanical revascularisation.

P1652 Can myocardial contrast echocardiography predict left-ventricular remodelling following acute myocardial infarction?

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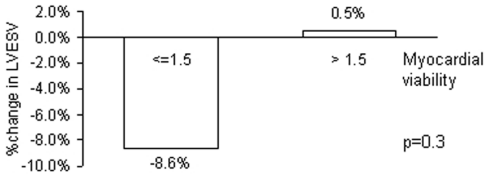
Background: Detection of myocardial viability (MV) following acute myocardial infarction (AMI) has been shown to have important therapeutic and prognostic implications. It is known that the presence of MV after AMI prevents left ventricular (LV) remodelling. We hypothesised that MCE can detect MV which will influence the degree of LV remodelling as assessed by cardiovascular magnetic resonance imaging (CMR).
Methods: 25 patients who had suffered AMI underwent MCE using intravenous injections of Optison® to assess MV. Segments were deemed viable if they demonstrated homogenous contrast opacification (score=1), and not viable if they demonstrated heterogenous or no opacification (score=2 or 3). A Viability index(VI) was calculated by adding the contrast scores in the infarct related territory and dividing by the total number of segments in that territory. A VI of 1.5 or less was taken to show good MV; more than 1.5 indicated poor viability. CMR was performed to assess LV volumes at baseline and at 6 months. LV remodelling was defined as an increase of 10% or more in LV end-diastolic and end-systolic volume.
Results: Of the 25 patients, 6 showed evidence of remodelling and had a mean VI of 2.1(median 2.2); the remaining 19 patients had a mean VI of 1.8 (median 1.8). Of the 6 patients who demonstrated LV remodelling, 5 patients (83%) showed a lack of myocardial viability; on the other hand, of the 19 patients with no LV remodelling, only 11 patients (58%) showed lack of MV. A similar pattern was seen when LVEDV was considered. There was a trend towards a decrease in LVESV over time in those patients with a viability index of 1.5 or less (figure).



Percentage change in LVESV as compared to myocardial viability.

Conclusion: MCE can detect MV following AMI, the presence of which limits the extent of LV remodelling.

P1653 Early versus late left-ventricular remodelling in reperfused acute myocardial infarction: relative role of infarct size, left-ventricular volumes and microvascular perfusion

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Background: Different patterns of post-infarction left ventricular remodeling (LVR) have been identified. However, main determinants of early or progressive versus late LV dilation are still under discussion. We hypothesized that microvascular integrity, regardless of initial LV volumes and infarct size, may play a crucial role in different patterns of LV dilation after acute myocardial infarction (AMI).
Method: In 52 consecutive patients with first successfully reperfused AMI, myocardial contrast echocardiography (MCE) was performed on day 1 after reperfusion using real-time imaging (Philips Sonos 5500 or CnTI Esaote). Continuous infusion of SonoVue® (Bracco) with a prototype (Bracco Imaging) rotating infusion pump at 120-180 ml/h infusion rate was used. The endocardial length of residual contrast defect after reperfusion in apical 4- 5- and 2- chamber views (CD%) was calculated. Left ventricular ejection fraction (EF%), end diastolic and end systolic volumes (EDV,ESV) and wall motion score index (WMSI) on admission (T1), at pre-discharge (T2) and at 6-months follow-up (T3) were calculated. Early remodeling was defined as T2 and late as T3 20% increase in EDV.
Results: LVR occurs in 22/52 patients (early in 33% and late in 66%). No statistical differences were observed between LVR group and no-LVR group as for mean age (55±10 vs 58±8 yrs), time to reperfusion (5±3 vs 3±2 hrs), T1-EDV (98±21 vs 97±23 ml), T1-ESV (55±13 vs 50±12 ml) and T1-EF (43±3% vs 47±5%), whereas incidence of anterior MI (90% vs 60%, $p<0.0001$), T1-WMSI (1.8±0.1 vs 1.4±0.3, $p<0.001$) and CD% (22±15 vs 8±7%, $p<0.001$) were significantly greater in LVR group. However, whereas CD% was significantly higher in early LVR as compared to late LVR (33±10 vs 15±8%, $p<0.001$), T1-WMSI and T2-WMSI were not statistically different (1.8±0.1 vs 1.7±0.1, ns and 1.8±0.5 vs 1.6±0.2, ns, respectively)
Conclusions: This study confirms that in patients with reperfused AMI, anterior infarct location, larger infarct size and extensive microvascular damage are the main determinants of LV remodeling. However, the status of microvascular perfusion play a key role in late LV remodeling irrespective of pre-discharge infarct size and LV volumes. Thus, the MCE assessment of post-reperfusion extent of microcirculatory damage may have important implications in patient management.

P1654 Effects of early pravastatin therapy on microvascular integrity in patients with acute myocardial infarction underwent primary stenting. A myocardial contrast echocardiography study

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Background: In adition to their lipid-lowering properties, recent studies of statins therapy in unstable coronary syndromes demonstrate an improvement in endothelial function, improved perfusion to ischemic myocardium, reduction of inflammation, inhibition of platelet aggregation and anticoagulant effects. The present study was addressed to evaluate the effects of pravastatin on myocardial perfusion in patients with acute myocardial infarction (AMI).
Methods: Fifty-eight patients (male n=42, mean age 66.3 ± 10.8 years) treated with primary stenting achieving TIMI 3 flow in the infarct related artery were included. Thirty patients (51.7%) were randomized to receive pravastatin 40 mg. daily irrespective of lipid values. The pravastatin therapy was started early before stenting. Myocardial contrast echocardiography (MCE) was performed 6 ± 1 days after AMI with intravenous Optison. MCE was assessed using intermittent harmonic imaging, 4 and 2-chamber views (six segments each) and off-line digital image processing. According to their MCE flow pattern, patients were divided in 2 groups: reflow group (all segments showed normal perfusion) and no-reflow group (≥1 segments showed patchy enhancement or no visible contrast effect).
Results: In the intervention group 11 patients (36.6%) showed adequate myocardial perfusion (reflow pattern) while 19 (63.3%) did not. In the control group (no pravastatin therapy) only 3 patients (11.1%) showed the reflow pattern while 25 (88.9%) did not, p = 0.02.
Conclusions: In successfully reperfused AMI, early pravastatin therapy seems to be associated with limited microvascular damage. In this clinical setting, the pleiotropic properties of pravastatin probably play an important role to avoid the no-reflow phenomenom.

P1655 Assessment of myocardial viability by intravenous myocardial contrast echocardiography early after reperfusion in patients with acute myocardial infarction

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Study Objective: to assess whether intravenous myocardial contrast echocardiography (MCE) would be useful in detecting stunned but viable myocardium in patients with reperfused acute myocardial infarction (AMI) and residual wall motion abnormalities within the distribution of the infarct related artery.
Patients and Methods: One hundred patients (85 male, mean age 55 years) with first AMI successfully treated with primary coronary angioplasty (71 patients) and rescue coronary angioplasty (29 patients), underwent MCE echocardiography at baseline, before discharge, and echocardiography 1 year later. Intravenous MCE was performed with venous Levovist administration and intermittent Harmonic Power Doppler (HPD). In each pt the contrast score index (CSI) for the infarct related area was calculated according to the standard protocol. Myocardial viability was defined as the presence of contrast effect (normal or patchy) by MCE.
Results: A total of 465 akinetic segments were identified within the distribution of the infarct related artery. A total of 5% (n = 25) of segments were not adequately visualized during MCE. Thus, 440 akinetic myocardial segments were available for complete analysis. Out of 440 akinetic segments, 201 (46%) improved at least one functional grade at 1 year follow-up. The combined end point of either normal or patchy perfusion predicted segmental recovery of function with sensitivity 97%, specificity 55%, positive predictive value 65%, negative predictive value 96%, overall accuracy 74%. According to CSI patients were divided in two groups: CSI > 0.5 (n=78; mean CSI 0.8±0.18) and CSI < 0.5 (n=22; mean CSI 0.2±0.13). Patients with CSI > 0.5 showed at 1 year follow-up a significant increase in ejection fraction (46±6% vs 53±5%, $p<0.001$) and a significant functional recovery (regional wall motion index 1.62±0.25 vs 1.27±0.23, $p<0.001$) while no change were observed in end diastolic volume. On the other hand, patients with CSI < 0.5 showed at 1 year follow-up a significant increase in end diastolic volume (104±23 ml vs 124±36 ml, $p<0.01$) and no significant variation in EF% and regional wall motion index.
Conclusions: MCE may identify stunned myocardium and accurately predict late recovery of LV function in pts with AMI.

P1656 Identification of myocardial viability early after myocardial infarction: a comparison between intravenous myocardial contrast echocardiography and dobutamine echocardiography

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Aim of study was to determine the value of intravenous myocardial contrast echocardiography (MCE) and dobutamine echocardiography (DE), alone or in combination, in predicting functional recovery in patients with acute myocardial infarction (AMI) and residual wall motion abnormalities within the distribution of the infarct related artery. Seventy-one patients with first AMI successfully treated with primary coronary angioplasty (47 pts) and rescue coronary angioplasty (24 pts), underwent MCE and DE before discharge, and echocardiography 6 months later. Intravenous MCE was performed with venous Levovist administration and intermittent Harmonic Power Doppler (HPD). Myocardial viability was defined as the presence of contrast effect (normal or patchy) by MCE and contractile reserve by DE. A total of 312 akinetic segments were identified within the distribution of the infarct related artery. Out of 312 akinetic segments, 115 (37%) improved at least one functional grade at 6 months follow-up. Perfusion by MCE predicted recovery of segmental function with an excellent sensitivity (96%) but with a low specificity (60%); DE had a similar excellent sensitivity (88%) but an higher specificity (80%). Both MCE and DE had an excellent negative predictive value for functional recovery (96% and 92%, respectively). Combination of DE and MCE. Concordance between DE and MCE for the presence or absence of viability was 81% (252/312 segments): 135 segments met viability criteria while 117 segments were considered not viable. At follow-up, 100 of 135 regions meeting viability criteria by the combination of these techniques, improved at follow-up (positive predictive value 74%). On the contrary, 117 segments were considered not viable by both techniques, and of these, only 4/117 improved (negative predictive value 97%). The sensitivity and specificity of the MCE-DE combination were 96% and 76%, respectively. In 60/312 segments (19%) the two techniques did not agree: 54 regions showed perfusion yet no viability by DE criteria; only 10 of these 54 segments improved at follow-up. MCE and DE are useful techniques in identifying myocardial viability in AMI. DE and MCE exhibited good sensitivities but poorer specificities in the group of patients studied. The combination of both techniques proved better then either one alone in predicting potential functional recovery. The absence of regional myocardial perfusion as assessed by MCE is a strong negative predictor of functional recovery.

P1657 Myocardial contrast echocardiography reliably predicts collateral blood flow after acute myocardial infarction

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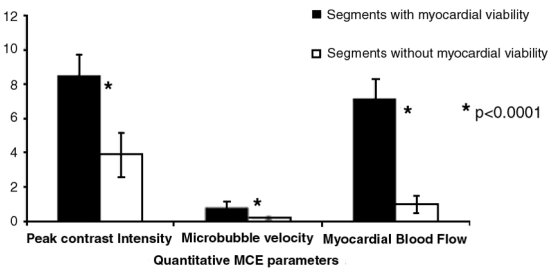
Background: Adequate collateral blood flow can sustain myocardial viability despite persistent occlusion of the infarct related artery (IRA) in acute myocardial infarction (AMI). Experimental studies have shown that during intravenous (IV) myocardial contrast echocardiography (MCE), the presence of microbubbles in the myocardium subtended by the occluded IRA implies myocardial blood flow through coronary collaterals. However, studies addressing the value of IV MCE to detect collateral blood flow after AMI in humans are limited.
Methods: Seventy consecutive patients with AMI underwent low-power IV MCE using Sonovue® infusion 7-10 days after thrombolysis. Myocardial perfusion detected by MCE was analysed (qualitatively and quantitatively) in the akinetic segments in patients with occluded IRA on angiography. Myocardial viability was assessed with low dose dobutamine 12 weeks after mechanical revascularisation.
Results: Twenty patients (29%) showed occluded IRA. There were 102 (32%) akinetic segments, of which 37 (36%) showed myocardial viability. Homogenous contrast opacification was observed in 31(83%) of the 37 segments with myocardial viability and was reduced/absent in 53 (82%) of the 65 segments without viability. Quantitative peak contrast intensity, myocardial blood velocity and the myocardial blood flow were significantly higher ($p<0.0001$) in the segments with preserved myocardial viability when compared to those without viability (figure).



Conclusion: MCE may be used as a reliable bedside technique for the accurate evaluation of collateral blood flow in presence of an occluded IRA after AMI. The detection of adequate collateral blood flow by MCE may be important in the prediction of myocardial viability, the presence of which has major therapeutic implications.

P1658 Assessment of myocardial perfusion by real-time contrast echocardiography in patients with previous myocardial infarction. Comparison with ^{99m}Tc-sestamibi single-photon emission computed tomography imaging

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The aim of this study was to compare myocardial perfusion by real-time myocardial contrast echocardiography (MCE) with 99mTc-sestamibi single photon emission computed tomography (SPECT) during rest in patients with previous myocardial infarction.
Methods: 100 patients (78 men, age 63 ± 12 years) with previous MI (more that 5 days but less than one year previously) underwent MCE and 99mTc-sestamibi SPECT. With both methods, myocardial perfusion was graded semi-quantitatively as 1=normal, 2=patchy and 3=absent. MCE images were obtained in apical two- and four-chamber view, and a 12-segment model of the left ventricle was used for the analysis.
Results: For final comparison, 1122 segments were used. Overall agreement between MCE and SPECT was 86% (k 0,68) for normal versus abnormal perfusion. For the detection of SPECT perfusion abnormality by MCE, the sensitivity was 74% and the specificity was 91%. Agreement between the 2 methods for each of the 3 coronary territories was 85% (k 0,65) for the left anterior descending artery, 82% (k 0,63) for the right coronary artery and 84% (k 0,67) for the left circumflex artery.
Conclusion: Real-time MCE can reliably detect myocardial perfusion, however the sensitivity of this method for detecting SPECT abnormalities is moderate.

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY

P1659 The usefulness of intraoperative transoesophageal echocardiogram in 482 open heart operations: a 3-years experience from a tertiary centre

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Background: Intraoperative transesophageal echocardiogram (IOTEE) is an emerging tool for cardiac and non-cardiac surgery. The aim of the study was to explore the contribution of IOTEE in open heart operations in a tertiary center.
Methods: Within 3 years (2000-2002), IOTEE was performed in 482 patients with acquired heart disease. There were 244 men (50.6%) and 238 women (49.4%). The mean age was 64.3±13.8 years (range 20-88). In 357 patients (74.1%) the patients were studied both pre- and postoperatively, whereas in 57 patients (11.8%) there was only a preoperative study, and in 68 (14.1%) - only a postoperative study. In 60 patients (12.4%) the surgery was a re-do one. Coronary artery bypass grafting (CABG) was performed in 182 patients (37.8%), and was the only procedure in 56 (11.6%). Valve replacement was performed in 253 operations (52.5%). Valve repair was conducted in 121 cases. The influence of preoperative and immediate postoperative echocardiographic study on the operative plan and postoperative management were evaluated.
Results: The preoperative study affected the operative plan in 167 operations (34.6%). The most frequent contribution was regarding the need and mode of mitral valve surgery-65 (13.5%), tricuspid valve surgery-26 (5.4%), extent of damage in infective endocarditis - 27 (5.6%), and extent of aortic dissection and aortic valve involvement - 17 (3.5%).
Overall, a second pump run was requested in 21 operations (4.4%). The Most frequent indications for a second pump run were: unsuccessful valve repair - 7 (5 mitral, 2 tricuspid); perivalvular leak-6 (4-aortic, 2-mitral); malfunctioning leaflet-4 (all mitral). Additional useful data included the follow-up of biventricular function and volume and air in cardiac cavities, which were dealt with pharmacological therapy, volume expansion and prolonged venting.
Conclusions: IOTEE has a major effect on operative plan and intraoperative evaluation of the surgical results in a variety of patients undergoing heart surgery, and should be widely implemented.

P1660 Over-reliance on transoesophageal echocardiography in the diagnosis of endocarditis

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Purpose: Duke's major criteria for infective endocarditis (IE) includes echocardigraphic confirmation of vegetations or abscess, which can lead to a tendency for indiscriminate use of echocardiography as a screening tool. As transesophageal echocardiography (TEE) has higher sensitivity for detection of vegetations than transthoracic echocardiography (90% vs 50%) it is often the initial study performed in many centres. We hypothesized that TEE is overutilized in patients with low clinical probability of IE.
Methods: Between August 31, 2001 and August 30, 2002, TEE was performed in 104 consecutive patients in our centre with the indication "Rule out IE". Clinical variables were collected from the medical chart and patients were classified into low, medium, or high probability of having IE based on the Von Reyn criteria.
Results: Among the 104 TEEs performed, only 11 (10.5%) were positive for vegetations. Ninety six (92%) patients had a low clinical probability of IE. The table below shows the incidence of clinical variables in our subjects. In a logistic regression analysis, only persistently positive blood cultures ($p<0.001$) and a new regurgitant murmur ($p<0.001$) were found to be independent predictors of a positive TEE. TEE results led to a change in management in only 20 (19%) patients.

Clinical Correlates With Positive TEE

Clinical variable	N (%)	P-value for Positive TEE
New Regurgitant Murmur	13 (12.5)	<0.001
Positive Blood Cultures	68 (65.3)	NS
Persistently Positive Blood Cultures	20 (19.2)	<0.001
Fever	68 (65.3)	NS
Peripheral Manifestations	6 (5.7)	NS
History of Rheumatic Disease	6 (5.7)	NS

Conclusion: TEE is performed in a high percentage of patients with low clinical likelihood of IE, and the results often do not lead to a change in management. This may reflect clinicians'over-reliance on TEE as a screening tool rather than a confirmatory test. Selective use of TEE would have led to a net cost savings of $30 960 in our institution. More stringent guidelines for performing TEE in patients with low clinical probability of IE need to be developed.

P1661 Transoesophageal echocardiography for detection of cardiac source of embolism: different benefit according to age groups

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Background: Transesophageal echocardiography (TEE) is a very useful diagnostic tool to identify cardiac source of systemic embolism. Is the diagnostic capacity and the identified anomalies detected the same for different age groups?
Objectives: We sought to evaluate the diagnostic capacity and the findings detected by TEE in the search for a cardiac source of systemic embolism according to age.
Population and Methods: Retrospective analysis of 726 consecutive patients submitted to TEE from 1994 to 2003 to exclude cardiac embolic source. Patients were divided in 3 groups: Group 1: $<$ 60 years (n=463, 45 $\pm$ 10 years, 53% males); Group 2: 60-75 years (n=212, 66 $\pm$ 4 years, 48% males); Group 3: $\geq$ 75 years (n=51, 78 $\pm$ 3 years, 31% males). We evaluate the type of embolic phenomenon, the presence of spontaneous contrast (SC) or thrombi in left atrial appendage and/or left atrium, atrial septum defect (ASD), atrial septum aneurism (ASA), patent foramen oval (PFO), prominent plaques in the thoracic aorta, mitral disease, valvular endocarditis and intra-cardiac tumours.
Results: There were strokes in 75, 74 e 72% of patients (p=NS), transient ischemic attacks in 20, 18 e 12% (p=NS) and peripheral embolism in 5, 8 e 16% of patients ($p<0.05$), respectively. The findings detected are reported in the table (*$p<0,05$)

n (%)	Group 1	Group 2	Group 3
ASD	4 (0.9)	3 (1)	0
PFO	31 (7)	14 (7)	3 (6)
ASA	27 (6)	15 (7)	1 (2)
Thrombi	24 (5)	29 (14)	4 (8)
SC*	29 (6)	45 (21)	14 (27)
Aortic plaques*	33 (7)	47 (22)	23 (45)
Positive source*	145 (31)	119 (56)	34 (67)
$\geq$ 2 embolic sources*	3 (0.6)	14 (7)	9 (18)

Conclusions: There was a better diagnostic capacity in elderly patients, where there was frequently an association between several potentially embolic changes. Spontaneous contrast and aortic plaques were the predominant findings in patients above 60 years of age.

P1662 Prospective assessment of a managment strategy based on transoesophageal echocardiograhy in suspected pacemaker lead infection

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The aim of this prospective study was to assess the clinical value of a management strategy in patients with suspected pacemaker transvenous lead infection (PTLI) principally based on the results of multiplane trans-esophageal echocardiography (TEE).
Methods and Results: Seventy-seven consecutive patients were included. Based on Duke's modified criteria, PTLI was considered as definite in 54 patients (70%) and possible in 23 patients (30%). Nineteen patients with a diagnosis of possible infection, as defined by bacteremia without abnormal TEE images and without evidence of pacemaker pocket infection, were treated by antibiotics alone. In all other patients, the whole pacing material was explanted. During a mean follow-up time of 3.1 $\pm$ 2.5 years, 21 patients (27%) died, mostly from cardiovascular causes. Only one patient died from infection and there was only one case of delayed infection recurrence in an other localisation. No significant differences in outcome were observed between explanted and non-explanted patients.
Conclusions: The results observed confirm that early explantation of the whole pacing material has to be done in patients with bacteremia and abnormal images at TEE. But conversely conservation of the pacing system can be proposed to patients with bacteremia but without abnormal images at TEE provided prolonged antibiotic treatment is given.

P1663 Transoesophageal echocardiography and angio-RMN evaluation of pulmonary veins in patients underwent ostial radiofrequency catheter ablation of atrial fibrillation

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Non pharmacological treatment of atrial fibrillation (AF) by ostial radiofrequency catheter ablation (RFCA) of pulmonary veins (PV) is a promising tecnique that can provide a permanent cure in selected patients (pts).
Purpose: The aim of this study was to assess anatomical and functional status of PV in pts underwent ostial RFCA by TEE and Angio-RMN.
Methods and Results: 14 consecutive pts undergone ostial RFCA. Anatomical variants of PV was founded in 7 pts (50%) by Angio-RMN: common ostium in 3 pts, partial interconnection of veins in 2 pts and very small ostium of lower veins in 2 pts. RFCA was carried out in 6 pts by disconnection and mapping of all PV with circular and multipolar catheter (LASSO)and in 8 pts by electro-anatomical encircling of PV. All pts were studied by TEE 1 week before and 1 months after RFCA. It was examined caliber of 50 PV and was assessed peak velocity flow of 42 PV. TEE failed to look veins over when a common ostium was present at Angio-RMN. Upper PV were seen in all cases while lower left PV only in 42% and lower right PV in 71%of cases.(See table)

	Pre - ablation	Post - ablation	p
UL - PV (mm)	15.9 $\pm$ 3.3	11.1 $\pm$ 2.3	0.001
LL - PV (mm)	11.9 $\pm$ 2.7	10.4 $\pm$ 1.2	NS
UR - PV (mm)	14.9 $\pm$ 2.7	11.6 $\pm$ 3.9	0.02
LR - PV (mm)	12.4 $\pm$ 1.2	11.0 $\pm$ 2.1	NS
Vmax - UL (cm/s)	64.4 $\pm$ 9.0	110.1$\pm$ 57.8	0.05
Vmax - UR(cm/s)	62 $\pm$ 19.2	103.9 $\pm$ 46.2	0.03
Vmax - LR(cm/s)	57.6 $\pm$ 10.7	78.1 $\pm$ 33.6	NS
	Post - LASSO	Post - encircling	
Vmax - UL(cm/s)	135.2 $\pm$ 54.4	76.1 $\pm$ 24.7	0.02

UL:upper left,LL:lower left,UR:upper right,LR:lower right

Conclusion: TEE follow-up of PV ablation is feasible with a previous Angio-RMN analysis of anatomical variants of PV. It was often difficult to examine and sample the flow of lower PV. Ostial RFCA seems to produce a significant reduction of upper PV caliber with an increase of peak velocity flow. This seems to be more evident in pts underwent RFCA by disconnection and mapping with LASSO catheter than those underwent electro-anatomical encircling.

P1664 Determinants of early normalization of post-cardioversion mechanical dysfunction of left atrial appendage in patients with non-valvular atrial fibrillation

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Background: post-cardioversion mechanical dysfunction of left atrial appendage (LAA) in patients with atrial fibrillation (AF) is a well known phenomenon. However, determinants and factors influencing this process are not accurately defined.
Aim: to evaluate the clinical and echocardiographic predictors of normalization of LAA contractile function 1 week after successful cardioversion (CV) in patients with non-valvular AF.
Patients and Method: clinical, transthoracic and transesophageal echocardiographic (TEE) data - measured in AF - of 48 patients (30 men; mean age: 65.2 $\pm$ 9.3 years) with successful CV and maintenance of sinus rhythm for at least 1 week were analyzed. TEE guided pulsed Doppler evaluation of LAA emptying velocities were performed immediately before and 1 week after successful CV of non-valvular AF. Based on previous studies effective LAA contraction in sinus rhythm was considered normal if telediastolic LAA anterograde peak flow exceeded 40 cm/sec.
Results: LAA anterograd peak flow was $>$ 40 cm/sec one week after successful CV in 32 (66.7%) patients. The pre-CV LAA flow was higher in patients showing normalization of LAA contractile function 1 week after conversion to sinus rhythm than in those with post-CV LAA dysfunction at 1 week control TEE (39.5$\pm$17.6 vs. 26.2$\pm$10.8 cm/sec, $p<0.001$). By univariate analysis an AF duration $<$ 19 days, a pre-CV LAA anterograde flow $>$ 32 cm/sec and a left atrial parasternal diameter $<$ 47 mm were predictors of early (1 week after CV) normalization of LAA contractile function. On multivariate logistic regression analysis the pre-CV LAA anterograde flow $>$ 32 cm/sec ($p < 0.001$, Chi-square: 7.3, OR = 19.3, CI 95%=2.3-163.8) was the only independent predictor of normalization of LAA mechanical function 1 week after successful CV.
Conclusion: LAA anterograde flow velocity pattern determined by TEE before CV has an independent value in predicting early recovery of LAA mechanical function after successful CV of non-valvular atrial fibrillation

P1665 Determinants of left atrial appendage flow, in patients with sinus rhythm

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Introduction: Left atrial appendage flow has been studied because of its relatioship with intraatrial thrombi in patiens with atrial arrythmias. Changes appeared when cardioversion to synus rhythm are reason for controversy. The determinants of this flow are subject of study.
Objectives: We sought to analyse factors that influence in the left atrial appendage (LAA) flow velocity, concretely those related to left ventricle diastolic function.
Patients and methods: We prospectively analysed, the transesophageal echocardiograms (TEE) of 23 consecutive patients made to rule out an embolic source. All of them had the following measures: LAA flow velocity, mitral inflow velocity, and pulmonary veins flow velocity. Fourteen patients were men, mean age 43$\pm$14 years. Of the total, 10 patients had normal TEE, 11 had patent foramen ovale. Three showed mild left ventricle hypertrophy, and only one had mild left ventricle systolic dysfunction. There were no cases with intraatrial thrombi. Diastolic function was clasiffied in order to the analysis of mitral and pulmonary vein flows, according to the established criteria, as normal or impaired relaxation pattern (fourteen and nine patients respectively). Systolic fraction was calculated as the ratio between systolic time velocity integral/systolic time velocity integral + diastolic time velocity integral, all in pulmonary veins.
Results: Normal mitral inflow pattern group had a LAA flow velocity 0.70$\pm$0.25, and impaired relaxation pattern group had 0.73$\pm$0.24. There were no significant differences between both groups. In normal inflow pattern group we found no correlation between LAA flow velocity and diastolic parameters. Conversely, we found a strong correlation between LAA flow and systolic fraction (Pearson's 0.814, $p<0.05$). Patients with a "worse" diastolic function (lower systolic fraction) had lower LAA flow velocities.
Conclusions: In patients with sinus rhythm and mild diastolic dysfunction, LAA flow velocity correlates well with the degree of that dysfunction.

P1666 Value of transoesophageal dobutamine stress echocardiography in patient qualification towards ischaemic mitral insufficiency cardiosurgical treatment

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The aim of this study was to evaluate the optimal surgical treatment of patients (pts) with severe (+++/++++) post-myocardial infarction mitral regurgitation (MR), based upon transesophageal dobutaine stress echocardiography (TEE-DASE) results. The study group comprised 150 pts (103 men, 55 women; aged 64 $\pm$ 11) with a history of MI following echocardiography and coronary angiography (2-8 weeks post-MI). In this group small and mild MR was observed in 60 pts (38%), severe in 16 pts (10%). Detailed analysis was performed in 16 pts with severe MR. All this pts had multiple vessel coronary disease, significant contractility disturbances (EF$<$40%) and were qualified to coroanry artery bypass graft (CABG). All patients, prior to surgery underwent TEE examination for evaluation of mitral valve aparatus and TEE-DASE examinations for the evaluation of muscle viability and MR. TEE-DASE was performed using Philips Sonos 5500 and 2500 with Omniplane I and II probes. Dobutamine was infused in 5-3-3-3 minutes stages between 10 - 40 mcg/kg/min. Atropine was added when required to achieve 85% maximum heart rate. Each test was recorded on magneto-optic disc and S-VHS tapes for later assessment by 2 independent experienced cardiologists.
Results:

Table 1. Influence of TEE-DASE on MR

Group	Influence
Group 1	6 pts significant MR decrease was noted (at least 2+)
Group 2	10 pts without influence on MR or MR decreased insignifacntly (maximum 1+)

Patients were qualified towards CABG if MR deterioration during TEE-DASE (Group 1), while those without DASE influence on MR (Group 2) underwent CABG and mitral plasty or valve replacement. Further patient analysis, according to administered treatment

Table 2. Degree of MR following treatment

	Group 1: After CABG	Group 2: After CABG+ mitral plasty
Small MR	3 pts	6 pts
Mild MR	1 pts	2 pts
Severe MR	0 pts	0 pts

Conclusions: 1. TEE-DASE enables to select patients with significant MR, in whom CABG improves mitral valve functioning. 2. TEE-DASE enables patient selection, in whom CABG should be performed with mitral plasty or valve replacement.

P1667 Evaluation of left-ventricular function with modified TEI index in patients with essential hypertension

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Purposes: It is pointed out modified TEI index (MTI) might be more effective in the evaluation of global cardiac functions compared to systolic and diastolic measurements alone. Present study was planned to determine applicability of modified TEI index in hypertension and its relation with left ventricular mass index. **Methods:** We studied 68 patients (33 men, 35 women, mean age 55$\pm$7 years) with normal coronary angiography. Twenty-two patients (12 men, 10 women, mean age was 55$\pm$6) with hypertension and normal left vetricular mass index (LVMI) according to Devereux formula were studied in group I (G1), and twenty-six patients (12 men, 14 women, mean age 57$\pm$7 years) with hypertension and increase LVMI in group II (G2). Twenty patients (10 men, 10 women, mean age 53$\pm$7) with normal blood pressure was evaluated as control group. Mitral annulus pulse wave tissue Doppler technique was used for all measurements. Modified TEI index was calculated as diastolic time interval which was measured from end of Am wave to origin of Em wave (a') minus systolic Sm wave duration (b') divided by b (ie a'-b'/b'). **Results:** Modified TEI index measured by tissue Doppler technique is found significantly higher in both groups than normal group (CG: 0.33$\pm$0.05, G I: 0.51$\pm$0.17, G II: 0.68$\pm$0.16, $p<0.0001$). Group II modified TEI index value is also higher than group I (G I: 0.51$\pm$0.17, G II: 0.68$\pm$0.16, $p<0.0001$). **Conclusions:** Modified TEI index which is a marker of left ventricular systolic and diastolic functions were impaired in hypertensive patients before hypertrophy had developed. However impairment was at the highest level in hypertrophied. We concluded that 1) MTI in hypertensive patients is safe, feasible, and sensitive index for evaluation of global ventricular functions, 2) Evaluation of hypertensive patients with MTI periodically may guide interventions directed towards saving systolic and diastolic functions, 3) MTI has gained importance as supplementary to standart Doppler or in case of limitations of standart Doppler technique.

P1668 Diagnosis of isolated ventricular non-compaction by second harmonic echocardiography and magnetic resonance imaging

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Isolated ventricular non compaction (IVNC) is a rare congenital cardiomyopathy due to the persistence of primary spongy myocardium during early development of the heart. Various imaging technique have been used in the diagnosis of IVNC. Peculiar echocardiographic findings for diagnosis of IVNC were described by standard transthoracic echocardiography (TE). The aim of our study was to evaluate the accuracy of second harmonic echocardiography (HE) in detecting the spongy myocardium in comparison to magnetic resonance imaging (MR).

Material and Methods: In this report we describe 7 adult patients initially diagnosed as affected by hypertrophic cardiomyopathy (2 cases), dilated cardiomyopathy (4 cases), cardiac tumor (1 case) in which the presence of IVNC was suspected with standard TE. Diagnostic criteria during HE were considered: 1. presence of multiple, prominent trabeculations of one or more ventricular segments, 2. deep intertrabecular spaces communicating, at color Doppler, with the ventricular cavity, 3. non compacted endocardium/compacted epicardium thickness ratio $>$ 2. MR gradient echo was performed to demonstrate thickened ventricular segments and areas of the myocardium characterized by deep intertrabecular recesses.

Results: In the present series of cases MR was very sensitive to assess the persistence of spongy myocardium in 6/7 patients in the left ventricle and in 3/7 patients the biventricular involvement. HE clearly identified the regions of spongy myocardium in the corresponding 6 patients but in only 1 HE identified the biventricular malformation. One patient with MR and HE negative studies had an exaggerated apical trabeculation of right ventricle. HE focused on the differential diagnosis with more frequently diagnosed conditions. In addition HE demonstrated impaired systolic function of the non compacted ventricle.

Conclusions: HE can be considered the first choice in the diagnosis of IVNC. MR has a potential in patients with poor quality HE imaging and in the evaluation of right ventricle.

THREE-DIMENSIONAL ECHOCARDIOGRAPHY: NEW DEVELOPMENTS

P1669 Automated quantification of left-ventricular volumes and function: a novel clinical tool?

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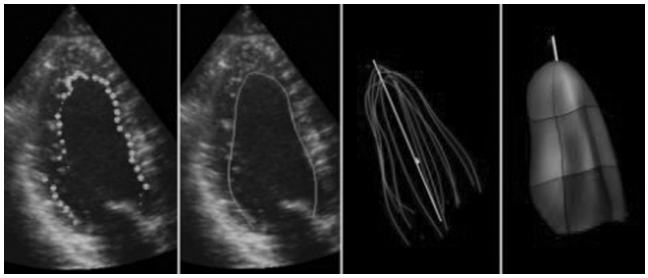
Three-dimensional echocardiographic (3DE) reconstruction with manual tracing of endocardial border allows accurate quantification of left ventricular end-systolic and end-diastolic volumes (ESV, EDV) and ejection fraction (EF). Automated border detection algorithms have been developed to reduce offline analysis time.

Aim: to investigate agreement between novel automated endocardial border detection method (3Dabd) and standard 2DE and 3DE quantification of ESV, EDV and EF.

Methods: 24 patients (mean age 54$\pm$13years) underwent 2DE assessment of LV function (Sequoia, Acuson) and 3DE data acquisition (freehand scanning; Tomtec 4D LV Analysis 1.1). ESV, EDV and EF were calculated from the 2D dataset by single plane and biplane modified Simpson's rule (spSr and bpSr) and from the 3D dataset (6 apical planes) by 3Dabd software (figure) and manual border tracing technique (3Dmt).

Results: Mean time required for 3Dabd and 3Dmt offline analysis was 9min and 28min respectively. Mean ESV, EDV and EF calculated by 3Dmt were 97$\pm$92ml, 151$\pm$92ml and 46$\pm$19% respectively. EDV calculated by 3Dabd was slightly, but statistically significantly underestimated (mean 143$\pm$96ml) when compared to 3Dmt (p=0,008), which led to trend towards underestimation of EF in 3Dabd (44$\pm$20%)(p=0,06). No significant differences were found between 3Dabd, spSr and bpSr results (p=NS). ESV, EDV and EF evaluated by spSr and bpSr did not differ significantly from values obtained with 3Dmt (p=NS).



Conclusions: Automated endocardial border detection algorithms offer significant shortening of offline analysis time with results close to validated manual 3DE and 2DE analysis. Current software tends to underestimate EDV and EF and needs refinements to reach the accuracy of 3Dmt and to further reduce analysis time.

P1670 3-/4-dimensional parametric imaging allows quick visualisation of regional dysfunction and reverberation artefacts

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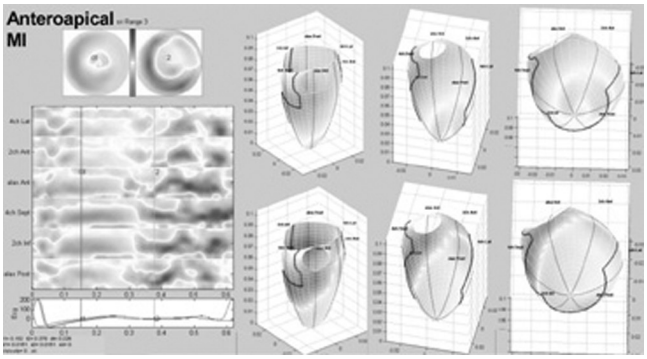
Aims and Methods: 3-D reconstruction can be applied to parametric (functional) as well as anatomical imaging. In this study, tissue Doppler data from three standard apical planes are reprocessed to a 3/4-D data set. Velocity data can be postprocessed to motion, strain rate or strain and displayed in colour imaging, as M-mode arrays, Bull's eye and a 3D surface figure that can be scrolled and rotated. Numerical data and waveforms can be extracted. Feasibility was tested in 6 normal subjects and 6 patients with AMI.

Results: Infarcts were visualised in all patients by mid systolic strain rate, end systolic strain and post systolic shortening. Reverberation artefacts were visible in 3 normals, and 2 patients. They were easily identified by colour. Neither mid syst. SR nor end syst. strain, only peak SR could identify the infarctions, due to artefacts.

Difference min-max	mid syst. SR	Peak syst. SR	End syst strain
Controls	-1.2	-0.21	-22%
Patients	-1.36	-1.68	-30%
P:	NS	0.04	NS

Conclusion: 3D reconstruction is feasible, and aids in identifying pathology and artefacts.



The figure shows an anteroapical infarct in strain rate. M-mode array of all six walls of one heart cycle, bull's eye and 3D display of mid systole and early diastole shows apical a- and dyskinesia and a larger area of post systolic shortening. The 3D surface figure shows the ability to rotate.

P1671 Freehand and rotational transthoracic 3-dimensional echocardiography enable exact quantification of atrial septal defect size prior to amplatzer occluder implantation

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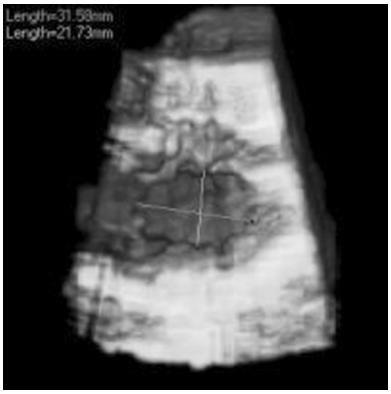
We aimed to compare the feasibility and accuracy of freehand (FH) vs rotational (RO) transthoracic 3-dimensional echocardiography (3D) for the planimetry of secundum atrial septal defect (ASD) before interventional closure with Amplatzer device.

Method: We studied 32 children and young adults (23 female, 3-32 years - mean age 12±7) prior to Amplatzer implantation (accomplished in 27 pts) using transthoracic 3D and TEE. 3D-RO was performed at 3° intervals (TomTec Echoscan 3.0 - 18 pts) 3D-FH by sweep scan, 40-50 slices (EasyScan, 14 pts). Long and short diameter of defect were measured TEE and 3D. Measurements were compared to stretched balloon diameter and final Amplatzer waist diameter.

Results: Quality of 3D was good in 22 pts and satisfactory in 10. FH enabled more focused acquisition with superior data density and study time (28- >16 min, $p<0.001$). ASD tissue rims could be measured in all cases. Mean stretched/Amplatzer diameter was 21±5/22±6mm and was severely underestimated by TEE and much less by 3D: 13±4 vs 18±5 mm ($p<0.001$), mean difference of 2,6±3,8mm by 3D ($p<0.001$) and 7.3±3.6mm by TEE. The results of 3D had good correlation (better for FH than RO, r=0,89 and 0,80) and close agreement in Bland-Altman analysis to stretch and device size diameter (r=0,80 and 0,83 resp.) with underestimation of true Amplatzer size larger for FH than RO (difference 4.6 vs 1.1mm).



Freehand scan of ASD.

Conclusions: Transthoracic 3-D echocardiography is a robust technique, allowing, as opposed to TEE, accurate measurements of ASD diameter and more reliable prediction of necessary Amplatzer size in young patients. Freehand scanning is faster but similarly accurate as rotational scanning thus allowing for accelerated workflow without quality sacrifice.

P1672 Quantification of synchrony of wall motion by correlation analysis

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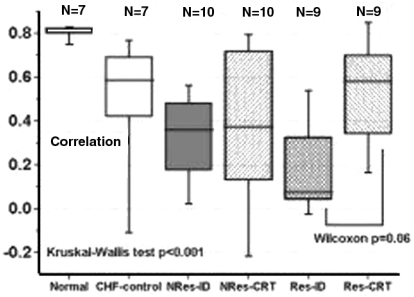
Background: The study assesses three-dimensional correlation as measure of asynchrony of wall motion. The measure should be different in patients without heart disease (Normals) and in patients with contraction abnormalities. It should be reflect effects of cardiac resynchronisation therapy (CRT).

Methods: 13-24 left ventricular volumes/beat were acquired by transoesophageal three-dimensional echocardiography (HP-Sonos 5500, TOMTEC). Endocardial contours were manually traced (ECHOVIEW 4.1) and surfaces were generated from contours (MATLAB 6.1). Asynchrony was quantified by the mean correlation of septal with lateral and anterior with posterior wall excursions at the mid ventricular level. Correlations were compared between Normals (no asynchrony) and patients with CHF without bundle branch block (CHF-control) (minor asynchrony) and with bundle branch block (CRT group) (major asynchrony). A change of correlation related to pacing is expected in responders (Res), who were classified retrospectively by an increase of >1ml/kg/min of maximum oxygen uptake after 12 months on CRT, as opposed to low-responders (NRes). Thus we distinguish Res and NRes at intrinsic depolarization (Res-ID and NRes-ID) and in optimized pacing mode (Res-CRT and NRes-CRT).

Results: The boxplot below demonstrates a high correlation for Normals significantly separated from all other groups(Kruskal-Wallis), a correlation decreasing with increasing asynchrony (CHF-control to CRT groups), and a borderline significant CRT-related increase in the small responder group(Wilcoxon).



Comparison of correlation in subgroups.

Conclusions: Mean correlation of three-dimensional regional wall motion provides a specific measure of asynchrony of left ventricular contraction, which is sensitive to improvement by CRT.

P1673 Measurement of left-ventricular volumes and ejection fraction in patients with ischaemic left-ventricular dysfunction: correlation of magnetic resonance imaging with thallium single-photon emission computed tomography and freehand three-dimensional echocardiography

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Background: The high reproducibility of cardiac MRI makes this test attractive for serial follow-up of LV volumes and EF. As MRI is not freely available at many sites, we sought whether 3D echocardiography or thallium SPECT could best correlate with MRI results in 59 pts with abnormal regional wall motion.

Methods: Three separate echo techniques were employed; biplane Simpson's, freehand 3D echo using electromagnetic localization and automated contour-detection (TomTec, Germany), and a 3D model derived by interpolation between 3 apical views (GE-Vingmed, Norway), in pts undergoing cardiac MRI and gated thallium SPECT. Cardiac MRI was performed using standard cine-gradient images, and LV volumes were calculated from short axis slices using Argus (Siemens). Gated Tl SPECT was performed after rest injection, using the Germano software (QGS, GE Medical Systems).

Results: EF with MRI (47±15%) was similar to 3D echo but significantly different from 2D echo and SPECT. Both end-systolic volume (ESV; 94±57) and end-diastolic volume (EDV; 168±56) by MRI exceeded those with all other methods (Table). Mean differences between the different echo approaches and MRI were similar. The mean difference of 3D echo from 2D for EDV, ESV and EF (-1,7 and -5%) was less than for the 3D model (-47,-25,-5%).

Volumes and EF with echo and SPECT

	2D echo	3D echo	3D model	SPECT
EDV (ml)	124±44	125±45	157±40	116±56
p (vs MRI)	p<0.001	p<0.001	p<0.001	p=0.15
Mean diff from MRI	-46	-50	-53	-68
ESV (ml)	63±34	71±38	84±26	69±50
p (vs MRI)	p<0.001	p<0.001	p<0.001	p<0.01
EF (%)	50±9	45±10	46±9	45±12
p (vs MRI)	p=0.02	p=0.18	p=0.06	p=0.02
Mean diff from MRI	-2	4	19	9

Conclusions: Assessment of EF appears most similar to MRI using 3DE, but all techniques under-estimate MRI volumes.

P1674 Clinical application of three-dimensional echocardiographic reconstruction: a 4-year single centre experience

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Three-dimensional echocardiography (3DE) is a novel and rapidly evolving echocardiographic technique. Theoretically, 3DE should be helpful in difficult cases when 2-dimensional echocardiography (2DE) cannot deliver required information due to complex spatial relationships in diseased heart or inability to obtain a desired cross-sectional view. Accurate quantification is another potential benefit of 3DE.

Methods: In this study we present our 4-year experience in 3DE applied to selected clinical population. Retrospective analysis of our database provided data of 238 3DE studies performed with TomTec Echoscan 3.1 using rotational device from transthoracic or transesophageal window.

Results: A total of 542 3DE acquisitions were performed. The main indications for 3DE were:

– congenital anomalies (64)
– assessment of left ventricular function (53)
– valvular heart disease (49)
– assessment of thoracic aorta (36)
– cardiac masses (24)

Quality of resulting 3D image was graded as 0 - bad (5%), 1 - satisfactory (20%), 2 - good (35%), 3 - demo (40%). The best acquisition in one patient was graded demo in 119 cases (50%), good in 93 cases (39%) satisfactory in 21 cases (9%) and bad in 5 cases (2%). Average quality of reconstruction was 2.1±0.8. Comparing to 2DE, additional morphologic or quantitative information was obtained in 48% of patients, including:

– 61% cases of congenital anomalies
– 42% cases of left ventricular function assessment
– 41% cases of valvular heart disease
– 31% cases of descending aorta assessment
– 63% cases of cardiac masses

Conclusion: 3DE can be incorporated in routine diagnostic pathway with high feasibility rate. 3DE is a valuable tool in clinically indicated cases providing additional qualitative or quantitative information in 48% of cases.

P1675 Freehand three-dimensional echo, a widely available tool for assessment of abnormal left ventricles: a comparison to one-dimensional echo, two-dimensional echo and cardiac magnetic resonance imaging

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Background: The recently published MADIT II study has made it obligatory to have a practical, widely available, accurate and reliable method for assessing left ventricular ejection fraction (LVEF). Freehand 3D echo (TomTec) is a novel commercially available method that permits EF determination with unrestricted echocardiographic windows, but has not been validated in abnormal LVs.

Objective: To validate freehand 3D echo EDV, ESV and EF using Cardiac Magnetic Resonance Imaging (CMR) and to compare the results to 1D and 2D methods.

Methods: 10 patients (age=59 ± 19 yrs, 1 female, BSA 2.04 ± 0.24 m^2) with abnormal LVs (mean LVEF=35%) were imaged by 3D echo using a "flock-of-birds" electromagnetic locating device to provide 3D spatial registration of 10-12 gated apical images. Endocardial borders were obtained by manual correction of an automatic boundary detection algorithm and LV volumes calculated from pyramidal volume elements. 3D imaging time was approximately 5 mins and data analysis took about 20 mins per study. LV volumes for 2D echo were calculated by the biplane method of disks and for 1D echo using the Teicholz equation. Patients underwent CMR using a 1.5 T Siemens Sonata Scanner. Following multiplane localizers, contiguous, short axis, ECG gated, breath-hold, segmented k space, TrueFISP cine images of the LV were acquired, with a 146 x 256 matrix, 8 mm slice thickness and 31 x 38 cm FOV. EDV, ESV and EF by 1D, 2D & 3D echo were compared with CMR values by linear regression and Bland-Altman analyses.

Results: See table.

Comparison of 1D, 2D and 3D echo to CMR

	1D-EDV	2D-EDV	3D-EDV	1D-ESV	2D-ESV	3D-ESV	1D-EF	2D-EF	3D-EF
r	0.90	0.85	0.98	0.98	0.91	0.99	0.89	0.87	0.97
SEE	35	37	16	12	19	8	8	7	3
p	0.0004	0.0017	<0.0001	<0.0001	0.0003	<0.0001	0.0005	0.001	<0.0001
Bias (ml)	-36	-66	-0.5	-32	-45	-0.9	5	0.3	-0.8
LL (ml)	-101	-142	-36	-65	-114	-23	-13	-16	-8
UL (ml)	28	10	26	1	23	21	23	16	6

LL: Lower limits, UL: Upper limits.

Conclusions: 1) Commercially available freehand 3D echo is practical, highly reliable and accurate for LVEDV, LVESV and LVEF in abnormal LV, as compared with CMR. 2) 3D echo volumes and EFs agree more closely with CMR than 1D or 2D echo, showing lower SEE and narrower limits of agreement.

P1676 A new three-dimensional echocardiographic system using digital radio frequency data – visualization and quantitative analysis of aortic valve dynamics with high resolution

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Background - Common 3D-systems have only limited spatial and temporal resolution, since the 3D-reconstruction is based on the slow analogue video signal (frame rate 25Hz). Thin structures like cardiac valves are thus not imaged exactly, rapid movement patterns cannot be precisely recorded. The objective of the present project was to achieve digital image transmission from the ultrasound unit to the 3D-workstation to improve image resolution.

Methods and Results: A commercially available 3D-echocardiographic system (Toshiba Power Vision 6000, 5 MHz multiplane TEE probe) with an integrated raw data-interface enables transmission of digital radio frequency (RF) data (up to 40 MB/sec) to the 3D-workstation. A 3D data set may contain up to 3 GB, so that the entire high-resolution ultrasound information of the 2D-image is available. Frame rates of up to 168 Hz result in temporal resolution six times that of standard 3D systems. The applicability of the system and the image quality under clinical conditions were tested in 10 patients. The structure of the aortic valve and the dynamic changes during the cardiac cycle were depicted by volume-rendering. The changes in the valve orifice areas were measured in frame-by-frame planimetry.

The mean acquisition time was 6.5±0.5 min (5.8 to 7.5 min). The mean number of frames recorded per cardiac cycle was 122±16. The improved structural resolution enabled a detailed imaging of the morphology of the aortic cusps. The rapid systolic movement patterns of the aortic valve were recorded with up to 51 systolic frames. The high number of frames enabled creation of precise area-time diagrams. Thus, the individual phases of aortic valve movement (rapid opening/slow valve closing/rapid valve closing) could be analyzed quantitatively.

Conclusion - A 3D-system based on digital RF data enables high-resolution, three-dimensional imaging of cardiac movement patterns. This offers new perspectives for qualitative and quantitative analyses, especially of cardiac valves.

P1677 Virtual left-ventricular resynchronisation: the ejection fraction that never was

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Background: Recent attention for asynchronous left ventricular (LV) contraction in left bundle branch block generates a need for synchrony assessment. A system is described for quantification of electromechanical LV contraction synchrony using three-dimensional echocardiography (3DE) and semi-automatic endocardial contour detection.

Methods: Eighteen consecutive patients (age 64±15 yrs, 8 female/10 male, ejection fraction (EF) 38±17%, QRS duration 134±40 ms) underwent transoesophageal, rotational 3DE using an HP SONOS 5500™ with built-in 3D acquisition software. Using offline TomTec 4DLV analysis™ software with semi-automatic contour detection, 3D endocardial surfaces were reconstructed throughout the cardiac cycle and LV volumes were calculated. End-diastolic (EDV) and endsystolic volume (ESV) were defined as maximum and minimum volume, respectively. In asynchrony, parts of the LV reach maximal contraction at different points in time, i.e. during different echocardiographic frames. Theoretical ESV (TESV) was calculated by electronically cutting maximally contracted parts of the LV from different frames and pasting them together to form one virtual, "synchronous" LV. Theoretical EDV was calculated similarly. This yields an increased, theoretical EF (TEF), which is the hypothetical EF that would occur at maximal synchrony, but under the assumption of unchanged haemodynamic circumstances. EF deficit, defined as TEF minus EF, is a measure of the impact of asynchrony on LV function.

Results: see table.

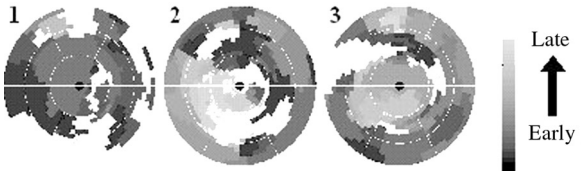
Variable	Value (average ± SD)	Intra-observervariation (mean ± 2SD)
EDV (ml)	146 ± 53	0,1 ± 13,9
ESV (ml)	97 ± 57	0,6 ± 12,8
TEDV (ml)	158 ± 57	0,9 ± 15,5
TESV (ml)	90 ± 53	0,7 ± 11,9
EF deficit (%)	9 ± 3	0,2 ± 2,8

Conclusion: EF deficit is a measure of LV asynchrony. TEF may serve as a target for resynchronisation therapy.

P1678 Polar map visualisation of left-ventricular electromechanical synchrony

J. A. van der Heide, H.J. Spruijt, H.F.J. Mannaerts, C.M.C. Van Campen, C.C. De Cock, O. Kamp, C.A. Visser. *VU University Medical Center, Cardiology, Amsterdam, Netherlands*

Background: Recent attention for asynchronous left ventricular (LV) contraction in left bundle branch block (LBBB) generates the need for synchrony assessment. A system is described for quantitation of electromechanical LV contraction synchrony by three-dimensional echocardiography (3DE) and semi-automatic endocardial contour detection.
Methods: Eighteen consecutive patients (age 64±15 yrs, 8 female/10 male, ejection fraction 38±17%, QRS duration 134±40 ms) underwent transoesophageal, rotational 3DE using an HP SONOS 5500™ with built-in 3D acquisition software. Using offline TomTec 4DLV analysis™ software with semi-automatic contour detection, 3D endocardial surfaces were reconstructed based on 744 endocardial surface points. For each point, distance to the end-diastolic LV center of gravity was calculated throughout the cardiac cycle. Timing was defined as time between electrocardiographic R-wave and moment of minimal distance; dispersion, a measure of asynchrony, was defined as standard deviation of timing. This yields two variables for every LV, one for (average) timing, and one for dispersion. Polar maps were generated to visualise synchrony by homo- or heterogeneity of their colors. Measurements were repeated to assess reproducibility.
Results: See figures of polar map examples. 1; normal: mostly homogeneous, 2; LBBB: delay in inferoseptum as indicated by lighter color in that region, 3; Same patient, biventricular pacing: decreased delay. Bland-Altmann intra-observer variability: timing: -4±130 ms; dispersion: 21±50 ms (mean±2SD, segmental level).



Conclusions: The combination of 3DE with semi-automatic contour detection enables accurate quantitation of LV electromechanical contraction synchrony that can be readily assessed using polar maps.

REGULATION OF ENDOTHELIAL FUNCTION: FROM BENCH TO CLINICS

P1679 Reduced nitric oxide bioavailability and platelet activation in young spontaneously hypertensive rats

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Background: In several cardiovascular diseases such as diabetes, hypertension and heart failure, platelet activation has been described. However, the mechanisms resulting in platelet activation have not been systematically investigated. Phosphorylation of the vasodilator-stimulated phosphoprotein (VASP) in the vascular wall and in platelets is a sensitive monitor of in vivo nitric oxide (NO) bioavailability.
Methods and Results: Whole blood samples were taken from 10 week old Wistar-Kyoto rats (WKY) and spontaneously hypertensive rats (SHR). In vivo surface-expression of P-selectin and platelet-binding of fibrinogen, both reliable markers of platelet activation, were assessed by flow cytometry. Platelet VASP phosphorylation at its Serine 239 and Serine 157 residues was assessed using specific antibodies. Endothelial vasomotor function was assessed in an organ bath.
In SHR we observed a significantly reduced acetylcholine-induced NO-mediated maximum relaxation (% of preconstriction: WKY 85.6±2.4; SHR 67.6±2.7, $p<0.001$) and reduced basal NO formation assessed as additional contraction induced by an NO synthase inhibitor in slightly preconstricted aortic rings (% of maximum constriction: WKY 71.1±4.1; SHR 57.8±2.4, $p<0.05$). Platelet basal VASP-phosphorylation as a monitor of NO bioavailability was significantly reduced at both phosphorylation sites in SHR (Ser 239: WKY: 15.2±0.6 mfu [mean fluorescence units]; SHR: 11.7±0.5 mfu; Ser 157: WKY: 53.0±3.0 mfu; SHR: 35.0±3.5 mfu) and inversely correlated with platelet activation: surface-expression of P-selectin and membrane-bound fibrinogen were significantly enhanced in SHR compared with WKY (P-selectin: WKY: 23.2±3.4 mfu; SHR 58.3±7.9 mfu, $p< 0.05$; platelet-bound fibrinogen: WKY: 8.6±0.5 mfu; SHR: 13.5±1.1 mfu, $p<0.001$). Preincubation with the NO donor sodium nitroprusside (SNP, 1 μM, 15 min) significantly increased platelet VASP-phosphorylation (Ser157: 41.7±0.1 mfu) and normalized the enhanced surface expression of P-selectin in SHR (SHR+SNP: 15.1±1.5 mfu).
Conclusion: Using VASP phosphorylation as a sensitive monitor of in vivo NO bioavailability, these data provide evidence that reduced NO bioavailability substantially contributes to increased platelet activation in young SHR.

P1680 Mycophenolate acid inhibits endothelial NAD(P)H oxidase activity and superoxide formation by a rac1 dependent mechanism

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Background: Recent studies show that an occurrence of coronary endothelial dysfunction predicts the manifestation of cardiac allograft vasculopathy (CAV) and cardiac death in patients after heart transplantation who receive immunosuppressive therapy. Since an increased superoxide formation by activation of endothelial NAD(P)H oxidase induces endothelial dysfunction, the present study was designed to examine the effect of different immunosuppressive compounds on NAD(P)H oxidase activity in cultured human umbilical vein endothelial cells.
Results: The calcineurin inhibitors cyclosporine A and tacrolimus (0.1 μM each, 24 hours of incubation) significantly increased endothelial superoxide production as measured with cytochrome c and 2,7-dihydrodichlorofluoresceine fluorescence assay ($p<0.01$ each). This was inhibited by the specific NAD(P)H oxidase blocker gp91ds-tat. In contrast, the inosine monophosphate dehydrogenase inhibitor mycophenolate acid (MPA, 1-10 μM) reduced endothelial superoxide formation by blockade of the constitutively active NAD(P)H oxidase, as it attenuated the respiratory burst induced by neutrophil NADPH oxidase. The effect of MPA seems to be mediated by depletion of cellular GTP content leading to inhibition of the small GTPase rac1: After 24 hours of incubation with MPA the amount of membrane-bound rac1 which was significantly reduced which went along with a significant attenuation of rac1 activation as indicated by the rac1 specific activity assay. Accordingly, restoration of cellular GTP content with guanosine (1 μM) abolished the inhibitory effect of MPA on endothelial superoxide formation.
Conclusion: Since endothelial dysfunction precedes the development of accelerated CAV after heart transplantation, immunosuppressive regimes which include the functional antioxidant MPA rather than calcineurin inhibitors that generate superoxide might be taken into consideration for prevention of CAV.

P1681 Crataegus spezial extract WS 1442 induces an endothelial-dependent, NO-mediated vasorelaxation in rat aorta and human arteria mammaria

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It has been shown previously that Crataegus extracts are able to induce an endothelium-dependent vasorelaxation (Chen et al. 1998). Therefore, we investigated the influence of WS 1442, a special extract of Crataegus leaves and flowers, on relaxation of isolated rings of rat aortae as well as of human arteriae mammariae obtained from patients undergoing aortocoronary bypass operation. Experiments were performed in the presence and absence (mechanical disruption) of endothelium. Fractions of WS 1442 (fraction A: lipophil, containing flavonoids, yield 12.5%, fraction B: hydrophil, containing flavonoids, yield 69.9%, fraction C: flavonoid-free, enriched in oligomeric procyanides, OPC, yield 21.3%) were investgated as well.
WS1442 induced a concentration-dependent vasodilation in rat aorta and human arteria mammaria precontracted by phenylephrine (concentration needed to induce a halfmaximal relaxation (IC50): rat: 6.39±0.61 μg/ml (n=7), human: 19.3±1.8 μg/ml (n=6)). The maximal vasorelaxation induced after application of WS 1442 (100 μg) was for rat 25.0±5.7% of the papaverine (0.1 mM)-induced vasodilation (%Pap), and for human 20.8±5.8%Pap. If the experiments were performed in the presence of L-nitromethyarginine (10 μM) or after mechanical disruption of the endothelium, no vasorelaxation was observed. The vasorelaxant properties of WS 1442 were mediated only by the OPC-containing fraction C, but not by fraction A or fraction B. In the presence of iberiotoxin (Ib, 100 nM), i.e. after blocking the Ca^{2+}-dependent K^+- channels, the vasorelaxation induced by fraction C was significantly reduced in rat aorta (IC50, con: 6.37±0.48 μg/ml, +Ib: 25.1±0.72 μg/ml). Glibenclamid, an inhibitor of the ATP-dependent K^+-channels did not influence fraction C-induced vasorelaxation.
Conclusions: WS 1442, a special extract of crataegus leaves with flowers, induces an endothelium-dependent, NO-mediated vasorelaxation, which may at least partly be mediated by an opening of Ca^{2+}-dependent K^+-channels.

P1682 Extracellular superoxide dismutase is a major determinant of nitric oxide bio-availability

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The vascular NO bio-availability is limited by superoxide anions (SA), generated in the vessel wall. Three different superoxide dismutase isoforms (SODs) contribute to the detoxification of SA. One of these enzymes, the extracellular SOD (ecSOD) is secreted into the extracellular space, where it binds to the glycocalix. As the role of ecSOD in the control of vascular homeostasis is largely unknown, we set-out to determine the involvement of this enzyme in the maintenance of blood pressure under normal conditions and in reno-vascular hypertension induced by the two-kidney one-clip model in mice. Furthermore we studied the effect of the genetic deletion of ecSOD on endothelium-dependent relaxation ex vivo. Blood pressure was identical in sham-operated ecSOD +/+ and ecSOD -/- mice. Following clip application, blood pressure rose to significantly higher values in ecSOD -/- than in ecSOD +/+ mice. Treatment with human recombinant ecSOD selectively decreased blood pressure in clipped ecSOD -/- mice, whereas ecSOD had no effect in ecSOD +/+ mice, even from the clipped group. Compared to sham-operated ecSOD +/+, ecSOD -/- mice exhibited attenuated endothelium-dependent relaxation. Relaxations in vessels from clipped animals were attenuated, and this effect was more pronounced in ecSOD -/- than ecSOD +/+ mice. Vascular SA, as measured by lucigenin chemiluminescence, was markedly higher in ecSOD -/- compared to ecSOD +/+ mice and further increased by renal artery clipping. Tiron, an antioxidant, normalized relaxations in vessels from sham-operated and clipped ecSOD -/- mice, as well as in clipped ecSOD +/+ mice. In contrast, in vivo application of ecSOD selectively increased endothelium-dependent relaxation in vessel from ecSOD -/- mice. These data demonstrate that ecSOD plays an important role in controlling vascular NO bio-availability, blood pressure and endothelium-dependent relaxation. Although reno-vascular hypertension is associated with a marked increase in vascular SA production, the present observations also suggest that an imbalance of ecSOD activity to oxidative stress does not contribute to reno-vascular hypertension in wild-type animals.

P1683 Myocardial bridging is characterized by endothelial dysfunction

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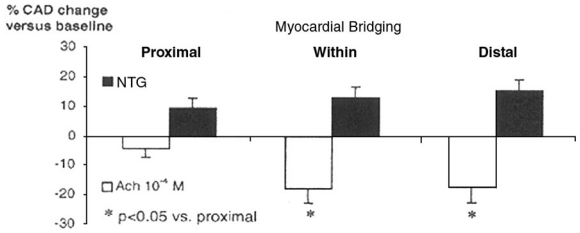
Background: Shear stress has been identified as an important factor for endothelial function. Myocardial bridging (MB) is a congenital condition of shear stress alteration. However, whether MB is also associated with an alteration of endothelial function, particularly an impairment in endothelium-dependent vasorelaxation has been hardly assessed, and was, therefore, the objective of the current study.
Method: Consecutive series of 35 patients with MB in the mid segment of the LAD and no coronary artery stenoses, as diagnosed by angiography. Endothelium-dependent vasorelaxation was examined by selective infusion of acetylcholine (Ach, 10-6 mol/L to 10-4 mol/L), endothelium-independent vasorelaxation by nitroglycerin (NTG) and adenosine. Coronary artery diameter (CAD), coronary flow reserve (CFR), and coronary blood flow (CBF) were assessed by quantitative coronary angiography and intracoronary Doppler analysis.
Results: Endothelium-dependent vasorelaxation of the coronary microcirculation was unimpaired as demonstrated by an increase in CBF of 58 ± 20% following Ach, as well as by a normal coronary flow reserve to adenosine (3.28 ± 0.18). However, as demonstrated by CAD changes after injection of Ach or NTG, endothelium-dependent but not endothelium-independent was impaired within and distal to the MB site (see Figure).
Conclusion: In patients with MB but without overt coronary artery disease, endothelial dysfunction seems to be a characteristic finding at the site of the myocardial bridging. This functional alteration might be a consequence of bridging-associated shear stress alteration and might add to the severity of lumen compression and thus to myocardial ischemia and the clinical presentation of this abnormality.



CAD changes to NTG and Ach.

P1684 The influence of isoprostane F2alpha-III on reflow after myocardial infarction

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Objectives: Isoprostane F2a-III (iP) is a vasoconstrictor formed by lipid oxidation during myocardial ischemia/reperfusion. We investigated whether contributes to the low/no reflow phenomenon following acute myocardial infarction (AMI) in the human and murine heart (MH).
Methods: (1) 20 patients undergoing primary percutaneous coronary intervention (PCI) for AMI had iP measured by high performance liquid and gas chromatography-mass spectrometry after PCI. iP concentrations were correlated to four modalities of microvascular reperfusion assessment. (2) In isolated MH we established: (a) the concentration-coronary flow (CF) relationship for iP; (b) the concentration of iP antagonist SQ29548 required to reverse iP-mediated coronary constriction; (c) the effect of SQ29548 on CF post-AMI.
Results: In patients, mean peak iP concentration was significantly higher during AMI than in controls respectively (1.8±1.3 x 10-9M vs. 1.6±0.6 x 10-10M, $p<0.001$). A positive correlation existed between mean iP concentration and ST-segment resolution at 90-minutes ($R=0.62$, $p<0.05$). In MH: (a) coronary vasoconstriction only occurred at, or above, iP concentrations >1.0 x 10-6M (reduction in CF by iP as percentage of basal flow: 1 x10-7M:101±20%, 1 x 10-6M:43±12%, 1.0 x 10-5M:31±10%, 1.0 x 10-4M:24±12%, $p<0.001$); (b) SQ29548 1.0 x 10-6M completely reversed the effects of iP 1.0 x 10-5M; (c) the presence of SQ29548 1 x 10-6M during reperfusion following 30 minutes of global ischemia had no effect on CF or infarct volume.
Conclusion: The vasoconstrictor iP is released during the reperfusion phase of AMI but concentrations are 1000-fold less than those that diminish CF. This suggests that iP is not associated with the low/no reflow phenomenon in humans during AMI.

P1685 Continuous therapy with nitroglycerin impairs flow-mediated vasodilatation but does not cause nitrate tolerance in conductance arteries

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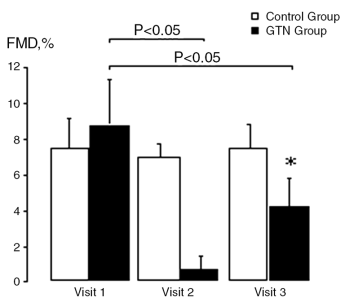
Background: Continuous therapy with nitroglycerin (GTN) causes impaired endothelial vasomotor function and nitrate tolerance in resistance arteries. We set out to investigate whether endothelial vasomotor dysfunction and nitrate tolerance are present in conduit arteries and whether they follow the same time frame.
Methods and results: Sixteen healthy young male volunteers were randomized to continuous treatment with transdermal GTN (0.6 mg/hr/24hrs for 6 days) or no therapy. Endothelium-dependent (flow-mediated) dilatation (FMD) and endothelium-independent (GTN-mediated) dilatation (GMD) were evaluated in three separate occasions: before randomization (visit 1), after six days of transdermal GTN treatment (visit 2), and three hours after withdrawal of transdermal GTN (visit 3). FMD and GMD were assessed using high frequency vascular ultrasound imaging of the brachial artery. On visit 1, there were no significant differences between treatment groups. On visit 2, in the GTN group, brachial artery diameter was significantly larger as compared to visit 1 (0.47±0.1 vs 0.38±0.03 cm, $P<0.05$). At this time point, both FMD and GMD were blunted in the GTN group ($P<0.05$ for both). On visit 3, three hours after patch removal, baseline brachial artery diameter and GMD returned to pretreatment values, while FMD remained significantly blunted as compared to visit 1 (see figure. visit 1: 8.7±6.1%; visit 3: 4.1±4.2%, $P<0.05$). There were no changes over time in the control group.



FMD is impaired after GTN treatment.

Discussion:
Our data show that sustained continuous treatment with transdermal GTN, while causing a significant impairment in endothelium-dependent vasodilatation, does not induce nitrate tolerance in conduit arteries.

P1686 Clinical outcome of patients with prinzmetal variant angina

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Background: Most epidemiological studies concerning patients with Prinzmetal variant angina (brief episodes of rest angina associated with ST segment elevation on the ECG) were performed more than 25 years ago. The impressive progress in the prevention, diagnosis and treatment of patients with ischemic heart disease in the most recent years may have significantly changed the short and long term outcome of such patients.
Methods: In this study we report follow up data of 176 patients with a diagnosis of variant angina (59.7±11.6 years; 29 women, 147 men) admitted to our Instiute from January 1991 to June 2002. Typical ST segment elevation occurred in anterior leads in 59% of patients, in inferior leads in 35%, and in both anterior and inferior leads in 6% of patients. Coronary angiography was performed in 136 patients (77.2%) and showed normal epicardial coronary arteries in 68 patients (50%), and 1-vessel, 2-vessel and 3-vessel coronary artery disease in 50 (36.7%), 10 (7.3%) and 8 (6%) patients, respectively.
Results: At a median follow-up time of 45 months (range: 6-318 months) 64 major cardiac events (cardiac death, myocardial infarction, life-threatening arrhythmias) were recorded in 58 patients (32.9%). Specifically, 3 patients had cardiac death (1.7%), 4 patients (2.3%) were resuscitated from cardiac arrest caused by ischemia-induced ventricular tachycardia/fibrillation or asystole, and in further 29 patients (16.5%) with syncopal or pre-syncopal episodes, tachy- or brady-arrhythmias were documented during ischemic attacks. A myocardial infarction occurred in 28 patients (15.9%). The risk of cardiac events was not correlated to age, gender or presence of significant coronary artery disease. In contrast, ST segment elevation involving both anterior and inferior ECG leads (suggesting multifocal coronary spasm) was associated with a higher risk of events (80% vs 28% of patients with anterior and 40% of patients with inferior ST segment elevation, p=0.004). Most events occurred within 1 month from symptom onset, suggesting that a timely diagnosis and treatment can prevent occurrence of clinical events.
Conclusion: Our data show a low cardiac mortality in appropriately diagnosed and treated patients with variant angina. However, the occurrence of life-threatening cardiac events (arrhythmias, myocardial infarction) is quite high, in particular in those with evidence of multifocal coronary vasospasm, pointing out the need for a timely diagnosis and appropriate drug treatment in these patients.

P1687 Myocardial infarcts in the obese differ significantly from infarcts in the non-obese patient: management and prognosis implications

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Background: Obesity (Body mass index > 30) and overweight (BMI = 25 - 30)status are a major health problem in the United States. We have previously demonstrated reduced risk of in-hospital death with AMI in obese patients. Long-term outcome with regard to obesity following AMI remains unclear.
Methods: We retrospectively reviwed 941 myocardial infarct patients admitted to the Mayo clinic CCU from Jan 1988 to December 2001 and analyzed the impact of obesity on outcome.
Results: Obese patients (n = 313) were younger (mean age ± SD, 60 ± 12 years) compared to 66 ± 11 years for normal weight patients (n= 250) ($P < 0.01$). 72% were male compared to 52% in the non-obese. Infarct location, infarct type (ST or non ST elevation MI), Killip class and ejection fraction were similar. Incidence of hyperlipidemia, hypertension and smoking were similar but diabetes was twice as common in the obese 23% versus 12% ($p < 0.01$). Extent of angiographic coronary artery disease (one, two, three vessel disease, left main or LAD disease was similar in all groups. Actuarial survival at one, five and ten years was similar in all groups(p=0.2) despite a higher incidence of cardiac death in the overweight (57%) and obese groups (61%), $p<0.01$ compared to normal weight patients (30%)over the same time period. The risk of re-infarction was significantly higher in the overweight (RR 2.42, 95% CI 1.25, 4.69 $p < 0.01$)and in obese patients (RR 1.80, 95% CI 0.87, 3.72 p= 0.12) compared to normal weight patients.
Conclusion: In summary obese patients who infarct do so at a younger age - typically 6 years earlier than non-obese patients, are twice as likely to be diabetic but otherwise are remarkably similar to non-obese patients in risk factors and extent of disease. While late survival is similar to older non-obese patients who infarct, they have a higher risk of re-infarction and cardiac death. Obesity mirrors older chronological age with regard to late survival.

P1688 The role of the multidrug resistance related protein 1 on the glutathione redox system under shear stress

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Purpose: Oscillatory shear stress (OSS) is thought to predispose to the development of atherosclerotic lesions by stimulating the production of reactive oxygen species by the endothelium. In contrast, laminar shear stress (LSS) induces protective radical scavenging enzymes such as eNOS and the Cu/Zn SOD. Glutathione is a major source of intracellular reducing equivalents. In the present study we investigated the effects of OSS/LSS on the intra and extracellular glutathione levels and studied the role of the multidrug resistance related protein 1 (MRP1) as a glutathione transporter under conditions of OSS and LSS.
Methods: We exposed human aortic endothelial cells (HAECs) to OSS of ± 15 dynes/cm^2 and LSS of 15 dynes/cm^2 for 4 and 12 hours. The intra and extracellular glutathione levels were measured by HPLC.
Results: Under conditions of OSS we found a significant decrease in intracellular reduced glutathione (GSH) combined with an increase in extracellular GSH and oxidized glutathione (GSSG). LSS significantly increased the intracellular GSH. The increase of extracellular GSH/GSSG in response to OSS could be inhibited by the use of MK571 (5μM) a specific inhibitor of MRP1, a protein we found to be expressed at high levels in HAECs by RT-PCR and Western analysis. Downregulation of MRP1 by transfecting HAECs with specific siRNA also inhibited GSH/GSSG export.
Conclusion: These data suggest that OSS and LSS modulate endothelial cell GSH levels in divergent fashions, and demonstrate a role of MRP1 as a modulator of endothelial cell redox state.

P1689 Comparison of the effects of pentaerythritol tetranitrate and nitroglycerin on endothelium-dependent vasorelaxation in humans

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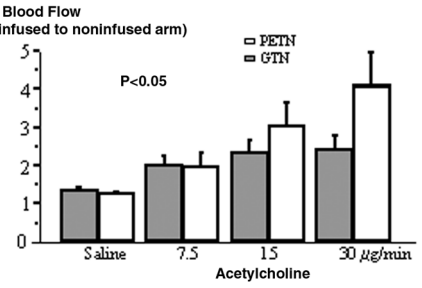
Background: We previously demonstrated that sustained therapy with nitroglycerin (GTN) impairs responses to endothelium-dependent vasodilators and vasoconstrictors. The effect of other organic nitrates on these parameters of endothelial function has not been studied. In order to do this, we investigated whether treatment with pentaerythritol tetranitrate (PETN), as compared to GTN, is associated with impaired endothelium-dependent vasodilation.
Methods and results: We randomized 28 healthy young volunteers to continuous transdermal GTN (0.6 mg/hr/24hr) or long-acting PETN (80 mg po tid) for 6 days. The responses to intraarterially infused acetylcholine (7.5, 15, 30 μg/min) were studied with strain gauge plethysmography. GTN treatment induced a profound impairment in endothelium-dependent vasodilation (max increase in forearm blood flow 91±35%). As compared to GTN, PETN treatment was associated with significantly greater responses to acetylcholine (max increase in forearm blood flow 203±53%, $P<0.05$).



Discussion: As compared to GTN, treatment with PETN appears to have a lesser impact on endothelial dysfunction. This, and our previous observation that PETN does not induce nitrate tolerance after continuous treatment, suggest that the use of this organic nitrate in clinical practice should be reconsidered.

ENDOTHELIAL DYSFUNCTION AND OXIDATIVE STRESS

P1690 Impaired endothelium-dependent brachial arterial reactivity in patients with familial combined hyperlipidaemia

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Background: Familial combined hyperlipidemia (FCHLP) is associated with a markedly increased risk of premature coronary artery disease. The present study was designed to evaluate whether preclinical atherosclerotic functional abnormalities are detectable in the systemic arteries of FCHLP patients.
Methods: Sixty subjects were recruited for the study: 30 individuals with FCHLP (mean age, 48 ± 9 years), defined by fasting total plasma cholesterol and/or triglyceride concentrations > 250 mg/dL and by the occurrence of multiple lipoprotein phenotypes within a family, and 30 age- and sex-matched healthy controls. All subjects underwent high resolution B-mode ultrasound examination and the brachial arterial reactivity, a marker of endothelial function, was measured by using a semiautomated computerized program. Lipid profile, insulin, C-reactive protein, resting blood pressure, body mass index, and smoking status were also determined.
Results: Compared with controls, FCHLP subjects had significantly higher body mass index, diastolic blood pressure, fasting total cholesterol, triglycerides, apoB and insulin concentrations. There was no difference in baseline vessel diameter between the two groups (3.4 ± 0.5 mm for FCHLP vs 3.6 ± 0.6 mm for controls, p = 0.17). In response to flow increase, the arteries of the control subjects dilated 8.9 ± 4.9% (range 2.3 to 20.8%), whereas in the FCHLP subjects, brachial arterial reactivity was significantly impaired (5.5 ± 2.5%, range 0 to 10.1%, p = 0.002). In multivariate analysis, diastolic blood pressure values were independent determinants of attenuated brachial artery response to reactive hyperemia.
Conclusions: The present findings suggest that vascular reactivity is impaired in the systemic arteries of FCHLP patients.

P1691 Relation between coronary response to ergonovine and lipid profile in patients with non-significant coronary artery stenosis

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Background: High lipid values are significant risk factors for development and progression of coronary atherosclerosis, but the relation between coronary vasospasm and vasoconstriction as provoked by ergonovine (Erg) and lipid profile has not been completely defined.
Objectives: The aim of our study was to evaluate the relation between response of coronary arteries to Erg provocation and lipid profile in consecutive patients with chest pain syndrome and non-significant coronary artery stenosis. Methods: In cath lab, ergonovine test at doses of 0.05, 0.10 and 0.20mg of ergonovine maleate given i.v. at 3 min intervals, was performed in 100 consecutive patients (45 male, 55 female, mean age 52±8 years) with chest pain syndrome at the end of diagnostic catheterization disclosing non-significant coronary artery stenosis (<50% diameter stenosis). All patients were off therapy at the time of testing. Coronary spasm was defined as total or near total obstruction of the coronary artery. By quantitative coronary arteriography we have evaluated changes of minimal luminal diameter (MLD) during Erg provocation. In all patients we have measured total cholesterol, LDL- and HDL-cholesterol, and triglycerides.
Results: Coronary vasospasm was found in 5 patients (5%), whereas in the whole group of patients MLD decreased from resting 1.90±0.49mm to 1.67±0.53mm at maximal Erg ($p<0.05$). Mean lipid values were 6.5±1.0, 4.9±1.0, 1.5±0.3, and 1.3±0.6mmol/L for cholesterol, LDL-, HDL-cholesterol and triglycerides, respectively. There was significant negative correlation between resting MLD and LDL-cholesterol (P=0.03). However, there was significant positive correlation between MLD decrease provoked by Erg and total cholesterol (p=0.006), as well as LDL-cholesterol (p=0.004), but not for HDL-cholesterol and triglycerides (p=ns).
Conclusions: In consecutive patients with nonsignificant coronary artery stenosis evaluated by ergonovine provocation, there was not only significant negative correlation between MLD and LDL-cholesterol, but also positive correlation between coronary vasoconstriction to ergonovine provocation and both total cholesterol and LDL-cholesterol.

P1692 Aortic compliance correlated with left-ventricular function in patients with coronary heart disease

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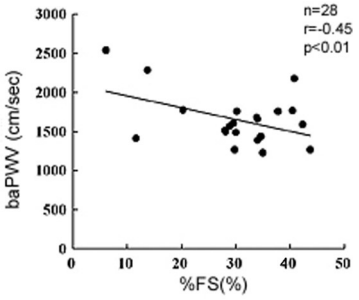
Background: Despite pulse wave velocity (PWV) is an index of atherosclerosis and a reliable marker of cardiovascular event, the relationship between PWV and cardiac function has not been fully evaluated. Recently, PWV has been reported to be simply and invasively measured as brachial-ankle PWV (baPWV). In this study, we evaluated the relationship between severity of coronary artery disease (CAD), leftventricular function and aortic compliance which was determined based on baPWV.
Methods and Results: We evaluated 60 patients (42men and 18women, 57+11y.o.) with CAD (Group-I, n=28, 63+10y.o.) and without CAD (Group-N, n=32, 55+13y.o.) determined by coronary angiography. There was no difference in age and mean blood pressure between the two groups. The baPWV was greater in Group-I compared with Group-N (1793+350 vs 1469+292cm/sec, $p<0.01$). In addition, in Group-I, patients with multivessel disease had greater baPWV than those with single vessel disease (1794+449 vs 1603+255cm/sec, $p<0.05$). In Group-I, baPWV was significantly correlated with %fractional shortening measured by UCG ($r=-0.45$, $p<0.01$)(Figure).



Conclusions: The baPWV, which can be simply measured, is associated with leftventricular function and there is a graded relationship between baPWV and severity of CAD.

P1693 Nebivolol restores endothelium-dependent vasodilatation and inhibits atherosclerosis in apolipoprotein E-deficient mice

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Nebivolol is a beta 1-selective adrenergic receptor agonist with a direct vasorelaxant effect that involves activation of the L-arginine - nitric oxide (NO) pathway.
Objective: The present study was designed to investigate whether treatment with nebivolol, by restoring of NO availability, may exert vascular protective effect in atherosclerosis-prone mouse model.
Methods: 50 apoE-deficient male mice were fed for 30 weeks with Western type diet (42% milk fat, 0.15% cholesterol) in the presence and in the absence of nebivolol (10 mg/kg/day) or atenolol (100 mg/kg/day). After this period animals were sacrificed and the entire aorta from the heart to the iliac bifurcation was removed, dissected and stained with Oil-red-O to visualize the atherosclerotic plaques. Plaque area was detected and expressed as a percentage of the total vascular area. Aortic rings were also used for isometric tension recordings.
Results: Systolic blood pressure measured by tail-cuff method during the last week of treatment was not affected by both drugs. NO-mediated, endothelium dependent relaxation to acetylcholine was markedly impaired in untreated group (6.3±15.5% relaxation to 10-4M acetylcholine). In some mice from this group paradoxical vasoconstriction to acetylcholine was observed. Chronic treatment with nebivolol increased relaxations to 44.2±8.5% ($p<0.05$ vs untreated), no one mouse had paradoxical vasoconstriction. In contrast, atenolol did not prevent the blunting effect of chronic hyperlipidemia on acetylcholine-induced response (25.6±15.5% relaxation, ns vs untreated). Within 30 weeks all animals developed severe atherosclerosis covering one-third of the aortic surface area. Treatment with nebivolol as well as with atenolol reduced the area of the aortic tree occupied with atheromatous lesions by 20±4% and 28±8%, respectively ($p<0.05$ vs control for both beta-blockers).
Conclusion: Our findings showed that relationship between such phenomena as vascular reactivity and subsequent plaque formation is much more complicated then it is traditionally assumed. Despite only nebivolol was able to prevent endothelial dysfunction, both nebivolol and atenolol could reduce atherosclerosis in apoE-deficient mice.

P1694 Endothelial dysfunction and intramural plaques in angiographically normal coronary arteries of patients with diabetes mellitus type 2 and coronary artery disease

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Background: It was the aim of this study to assess in patients with diabetes mellitus type 2 and coronary artery disease whether angiographically normal coronary arteries show endothelial dysfunction and intramural plaques in intracoronary ultrasound.
Methods: Patients with diabetes mellitus type 2 had to be on oral antidiabetics or insulin therapy. Furthermore, coronary angiograms had to reveal at least one coronary artery without detectable stenoses and at least one vessel with a stenosis of > 50% luminal narrowing. After informed consent was obtained intracoronary ultrasound and assessment of endothelial function was performed by infusion of acetycholine, adenosin and nitroglycerin.
Results: We enrolled 17 consecutive patients who fulfilled the inclusion criteria. Patients' age was 62±5 years. Their HbA1c was 7.75 ±1.32%, C-reactive protein 1.78 ±2.79 mg/d, and LDL 2.44 ±0.72 mmol/l. All patients showed paradoxical and thus pathological coronary vasoconstriction in response to infusion of vasodilators such as acetylcholine. Furthermore, in all angiographically normal vessels in which we also performed intracoronary ultrasound diffuse intramural plaques were detected all along the vessel.
Conclusion: In patients with angiographic coronary artery disease but at least one vessel without detectable stenoses, paradox and thus pathologic vasoconstriction was observed when vasodilators such as acetycholine were infused into angiographically normal coronary arteries. Furthermore, intracoronary ultrasound detected intramural plaques in all angiographically normal vessels. In contrast to coronary disease in patients without diabetes mellitus, there is generalized atherosclerosis in diabetic patients which warrants not only aggressive treatment but also to take measures of "secondary prevention" even before the first event occurs.

P1695 Additive vascular effects of microalbuminuria and hypertension in patients with type 2 diabetes mellitus

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Diabetes mellitus (DM) is a strong risk factor for the progression of cardiovascular disease. Microalbuminuria (MA) and hypertension (HTN) are predictors of poor cardiovascular outcome in diabetic patients. However, the link between DM, MA and HTN and vascular damage was not fully established. The aim of our study was to assess the association between DM and the endothelial function and the aortic distensibility in patients with or without MA or HTN. Our cross-sectional analysis included 193 type 2 DM patients (pt), mean age 69 ± 7 yrs, evaluated during a 2 yrs period. MA was defined as urinary albumin excretion of 20-200mg/24h in 3 non-consecutive samples. Endothelial function was evaluated with flow-mediated vasodilatation (FMD) and the endothelium-independent Nitroglycerine vasodilatation. FMD was defined as percent change in brachial artery diameter at 1 min. after 5 min. of upper arm blood pressure cuff occlusion. Aortic distensibilty (AD, 10-3 mmHg-1) was defined as difference between end-systolic and end-diastolic aortic area divided by the product of brachial pulse pressure (PP) and end-diastolic aortic area. Aortic area was determined by echocardiography at 4 cm above aortic valves. Association of DM, HTN and MA with both FMD and AD was assessed by means of multivariate logistic regression (odds ratios-OD) using diabetics without MA and HTN as comparison. Presence of both MA and HTN in DM pt was significantly associated with both decrease in FMD (OR: 2.74, 95%CI: 1.32-5.36) and decrease in AD (OR: 2.65, 95%CI: 1.46-5.03). Presence of only MA was also associated with decreased FMD (OR:1.97, 95%CI: 1.20-2.53) and decreased AD (OR: 1.87, 95%CI: 1.17-3.10). A weaker association was noted between diabetics with HTN and the decreased FMD (OD: 1.47, 95%CI: 0.90-2.10). No significant association was detected between hypertensive diabetics and decreased AD. **Conclusion:** Association of MA or HTN in older diabetic patients has negative impact on the endothelial function and arterial distensibility. In these pt MA and HTN have additive deleterious vascular effects and could reflect a diffuse vascular disease.

P1696 C-type natriuretic peptide relaxes human coronary artery bypass graft vascular conduits preconstricted by endothelin-1

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Background: Endothelin (ET) is implicated in graft spasm after coronary artery bypass grafting (CABG). We assessed reversal by the endothelium-derived vasodilator C-type natriuretic peptide (CNP) of prior constriction of vessels commonly used for CABG surgery, and whether local vascular proteases limit CNP bio-availability.
Methods: Segments of human saphenous vein (SV), internal mammary artery (IMA) and radial artery (RA) were removed from patients undergoing cardiac surgery (n=34, 64±2 years), mounted in organ baths. Effects of increasing concentrations of CNP (with or without aprotinin [APRO], 1000U/ml) on contraction induced by ET 10^{-7}M: SV 44±7mN, n=33; IMA 23±2mN, n=30; RA 44±6mN, n=21)were compared with acetylcholine (ACH; 10^{-9} to 10^{-4}M), sodium nitroprusside (SNP; 10^{-9} to 10^{-5}M), and papaverine (PAP; 10^{-9} to 10^{-4}M). Responses were expressed as mean±SEM for % maximum relaxation to SNP (10^{-5}M, 100%), and data compared by 2-way repeated measures ANOVA.
Results: CNP significantly relaxed ET pre-constriction in all vessels studied (F=17.8, 36.3 and 48.4 respectively; $p<0.001$). Aprotinin did not significantly affect CNP dose response curves in SV (F=0.012, p=0.92), IMA (F=0.79, p=0.42) or RA (F=2.06, p=0.25). ACh relaxed SV weakly, with maximal relaxation at 10-8M and reconstriction at higher doses. The highest concentration of papaverine completely relaxed all vessels, but responses were less sensitive than to SNP or ACh.

Drug	SV	IMA	RA
CNP (10^{-6}M)	44±18 (5)	54±7 (5)	74±4 (4)
ACh (10^{-6}M)	9±16 (4)	67±9 (6)	71±6 (6)
PD2	6.7±0.4 (4)*	7.9±0.3 (6)*	8±0.1 (6)*
PAP (10^{-4}M)	95±1 (6)	97±2 (6)	98±1 (3)
PD2	5.4±0.1 (6)	6.2±0.2 (6)	6±0.4 (3)
SNP (10^{-5}M; mN)	-27±5 (5)	-21±2 (5)	-55±11 (4)
PD2	7.7±0.1 (5)*	7.9±0.3 (5)*	7.8±0.1 (4)*

PD2 (-log EC50), maximum (%) for vasorelaxation. N in parentheses. * $p<0.05$ for PAP vs ACh or SNP for PD2, t-test.

Conclusions: CNP reverses ET-induced constriction in arterial and venous conduits used for CABG. Proteolytic breakdown of CNP by local vascular enzymes appears of little importance. Strategies to induce CNP release in situ may improve graft function after CABG.

P1697 Oxidative stress induces PP2A-mediated dephosphorylation of the retinoblastoma family proteins

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Background: Oxidative stress induces Endothelial Cells (EC) death and growth arrest. Indeed, oxidative stress plays a causal role in numerous pathologies, including tissue ischemia and reperfusion, diabetic vasculopathy, and atherosclerosis. To cope with oxidative damage, cells deploy "adaptive responses" aimed at minimizing damage. Understanding at the molecular level these responses may allow the identification of new therapeutical targets. The retinoblastoma family proteins are an integral part of the mechanisms that regulate cell growth both in normal conditions and after exposure to genotoxic stimuli. It consists of three members: the retinoblastoma protein (pRb) and the related p107 and p130. They are the substrate of Cyclin Dependent Kinases (CDK) and, in their hypo-phosphorylated form, bind to selected cellular proteins, regulating cell growth and apoptosis.
Aim: Investigating the regulation and the functional role of pRb, p107 and p130 in the EC response to oxidative stress.
Methods and Results: Treatment of human umbelical vein EC (HUVEC) with H2O2 (>200 μM) induced rapid hypo-phosphorylation of the retinoblastoma family proteins. This event did not require p53 or p21Waf1/Cip1/Sdi and was not associated with Cyclin/CDK down-modulation. Four lines of evidence indicate that H2O2-induced hypo-phosphorylation of pRb, p107 and p130 was due to the activity of protein phosphatase 2A (PP2A): First, HUVEC treatment with two phosphatase inhibitors, okadaic acid (0.5 mM) and Calyculin-A (50 μM), prevented the hypo-phosphorylation of the retinoblastoma family proteins, at concentrations that specifically inhibit PP2A. Second, SV40 small t, that binds and inhibits PP2A, when overexpressed, prevented H2O2-induced de-phosphorylation of the retinoblastoma family proteins, while a SV40 small t mutant unable to bind PP2A was totally inert. Third, PP2A core enzyme physically interacted with endogenous pRb and p107, both in H2O2 treated and untreated cells. Fourth, a PP2A phosphatase activity was co-immunoprecipitated with pRb and the activity of pRb-associated PP2A was positively modulated by cell treatment with H2O2. Role of PP2A-dependent retinoblastoma family proteins de-phosphorylation was also investigated. DNA damaging agents inhibit DNA synthesis in a pRb-dependent manner. It was found that inhibition of PP2A by SV40 small t over-expression, prevented DNA synthesis inhibition induced by H2O2.
Conclusions: H2O2-induced the de-phosphorylation of pRb, p107 and p130 byPP2A. This de-phosphorylation is integral part of and S-phase checkpoint.

P1698 Vasomotor responses of human atherosclerotic radial artery

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The radial artery (RA) is increasingly used as coronary artery bypass graft because its long-term patency rates are expected to be superior to those of the saphenous vein. In rare cases, however, the RA exhibits macroscopically evident atherosclerosis at the time of harvest. As atherosclerotic changes can affect vasomotor responses, we examined how the regulation of vascular tone is altered in these RA. Macroscopically evident atherosclerotic lesions could be observed in 3 out of 429 RA isolated within 2 years. Histological analysis revealed that plaque formation was severe. However, immunohistochemical staining for von Willebrand Factor showed a morphologically intact endothelial layer. To assess functional properties, the vessels were cut into 3 mm rings and suspended in organ chambers for isometric tension recording. Endothelium-dependent relaxations to acetylcholine (10-5 M), which releases nitric oxide in the human RA, were reduced in atherosclerotic RA (31.77±5.71%; n=3) as compared to control (77.77±4.33%; n=10; p=0.0001). Receptor-independent contractions to KCl (100 mM) were reduced in atherosclerotic RA (33.19±5.06 mN; n=3) as compared to control (108.02±15.76 mN; n=9; $p<0.05$). Similar to the cation, receptor-mediated contractions to norepinephrine were reduced in atherosclerotic RA (27.64±12.48 mN) as compared to control (82.74±11.36 mN; n=9; $p<0.05$). Moreover, contractions to thrombin (1 U/ml) were reduced in atherosclerotic RA (3.02±1.58 mN) as compared to control (10.97±5.12 mN; n=8). These data demonstrate that both endothelium-dependent relaxations and vascular contractility are impaired in atherosclerotic RA, indicating that a dysfunction of endothelial cells as well as vascular smooth muscle cells is present in these vessels. Due to the reduced formation of nitric oxide, atherosclerotic RA may be prone to thrombus formation und should not be use for coronary artery bypass.

P1699 Vascular endothelial nuclear factor-κB inhibition by nitric oxide: inhibition of protein kinase A-dependent phosphorylation of RelA by nitric oxide

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Purpose: NO inhibits the expression of proinflammatory genes regulated by nuclear factor kappa B (NF-kappaB) in vascular endothelial cells (EC). The mechanisms are not completely understood. Since NO is unable to inhibit rapid nuclear translocation and DNA binding of NF-kappaB following cytokine stimulation, we investigated NO mechanisms independent of NF-kappaB promoter binding.
Methods: a possible role of the transcriptional repressor protein RBP was analyzed by screening NF-kappaB dependent genes for RBP binding sites. The effect of NO on the expression of the transcriptional coactivator CREB-binding protein (CBP) was studied by Western blotting, and the association of CBP with NF-kappa B was studied with coimmunoprecipitation in EC. Protein-kinase A (PKA) and phosphoinositol-3-kinase (PI3K) dependent phosphorylation of RelA was investigated in transient transfected EC with NF-kappaB reporter plasmids.
Results: RBP is not important for the NO effect on NF-kappaB. The NO donor S-nitroso glutathione (GSNO) has no effect on the protein expression of CBP. TNF-alpha induced association between NF-kappaB and the transcriptional coactivator CBP is not inhibited by NO. Phosphorylation of the NF-kappaB subunit RelA contributes significantly to the transcriptional activation of NF-kappaB dependent genes. Preincubation with 10 μM of the specific PKA-inhibitor H89 inhibits TNF-alpha induced, NF-kappaB dependent transcription of transient transfected EC by 53% (n=4, p = 0.01). GSNO (200 μM) significantly inhibits TNF-alpha induced transcription in transfected EC by 44%. GSNO has no additional effect, if EC are coincubated with H89. When the PI3K dependent phosphorylation of RelA is inhibited by the PI3K inhibitor LY294.002, cytokine induced NF-kappaB promoter activity is inhibited by 40% ($p < 0.01$). Coincubation with GSNO and LY294.002 results in an additional inhibitory effect on NF-kappaB promoter activity, indicating different pathways for the effect of NO and LY294.002 on endothelial NF-kappaB inhibition.
Conclusions: Our results suggest that inhibition of PKA dependent phosphorylation of RelA contributes to the NO effect on NF-kappaB in vascular EC.

PLATELETS AND THROMBOSIS

P1700 The membrane-bound chemokine fractalkine increases platelet activation and adhesion independent from ADP-costimulation

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Background: Chemokines released by the endothelium have pro-aggregatory properties on platelets. For pro-aggregatory action of most chemokines, costimulation with ADP is required. Therefore, we investigated whether fractalkine, a recently discovered membrane-bound chemokine with a transmembrane domain, which is expressed in vascular injury, requires ADP costimulation for platelet activation.
Methods and Results: Rat platelets were stimulated with recombinant fractalkine (FK), ADP or a combination of both in the presence and absence of apyrase ((Apy)mixed ADPase/ATPase). Surface-expression of P-selectin, a reliable marker of platelet activation, was assessed by flow cytometry. P-selectin expression was significantly enhanced by in vitro stimulation with recombinant rat fractalkine compared with baseline levels. This effect was only partly reduced by degradation of ADP, which completely inhibited the ADP elicited surface-expression of P-selectin. Specificity of the stimulation was shown by completely preventing platelet activation when antagonising recombinant fractalkine (anti-FK) or uncoupling the G-protein-coupled fractalkine-receptor by preincubation with pertussis toxin (PTX). In an adhesion flow chamber stimulation with fractalkine significantly enhanced platelet adhesion to collagen and fibrinogen by 20% and 60%, respectively. Similar to P-selectin expression, enhanced adhesion in platelets stimulated with fractalkine was not reduced by apyrase while ADP-induced adhesion was completely abolished.

Surface-expression of P-selectin

basal	FK	FK+anti-FK	FK+PTX	FK+Apy	ADP	ADP+Apy
23.2	60.9**	15.2#	19.8#	40.8*	52.4**	23.4¶
3.4	5.1	0.9	3.1	0.5	8.3	0.6

Data are expressed as mean fluorescence ± SEM; *=$p<0.05$ vs. basal, **=$p<0.01$ vs. basal, #=$p<0.01$ vs. FK, ¶=$p<0.05$ vs. ADP

Conclusion: The membrane-bound chemokine induces platelet activation and adhesion independent from ADP costimulation. As fractalkine is overexpressed in atherosclerosis and vascular injury it is likely to substantially contribute to increased thrombogenesis in vascular diseases.

P1701 Importance of adenosine 5-diphosphate receptor P2Y12 stimulation in three-dimensional platelet thrombus growth on the collagen surface under blood flow conditions

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Background: The effects of P2Y12 ADP receptor blockade on three-dimensional platelet thrombus growth under blood flow conditions and in He-Ne laser induced thrombosis was investigated. Materials and Methods. Blood samples were obtained from eight adult donors. Effect of various concentrations of specific anti-P2Y12 (AR-C69931MX) on platelet thrombi formed on the collagen and von Willebrand factor (VWF) surface under the controlled flow conditions were tested. On the collagen surface, effects of P2Y12 blockade on platelet adhesion and platelet cohesion was separately assessed by three dimensional imaging technique achieved by the ultra-fast laser confocal microscopy and piezo-motor control unit. Effect of the agent on He-Ne laser induced guinea pig thrombosis was also investigated. Results. AR-C69931MX inhibited collagen surface platelet thrombi in a dose-dependent manner. Two-dimensional surface coverage analysis revealed that the area covered by platelet decreased from 37.0±6.2% to 13.4±3.8% at 1,500 s-1 and 23.8±13.6% to 10.3±6.6% at 100 s-1 by AR-C6991MX (100 nM), respectively (both $p<0.01$). Stronger inhibition by the agent to the surface area coverage of 5.4±2.8% at 1,500 s-1 and 3.3±3.6% at 100 s-1, respectively, was seen on VWF surface. Three-dimensional structural analysis revealed that height of platelet thrombi formed on the collagen surface significantly decreased from 12.4±2.6 μm to single layer of 3.3±1.1 μm by blocking P2Y12 (AR-C69931MX: 100 nM). Those in vitro results were consistent with the results obtained in vivo thrombosis model. Conclusions. We demonstrate the importance of P2Y12 stimulation in stable platelet adhesion to immobilized VWF, which mediate platelet cohesion resulting three-dimensional growth of platelet thrombi.

P1702 Platelet responsiveness in vivo is altered one week following induction of diabetes in rats, independently of nitric oxide

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Introduction: Thrombotic disease is a major cause of morbidity and mortality in patients with diabetes. Previous in vitro studies have suggested an increase in platelet reactivity and a decrease in both endothelial- and platelet-derived nitric oxide in diabetes. In the present study we examined changes in platelet aggregation responses in vivo in a rat model of diabetes.
Methods: Male Wistar rats (175-200g) were rendered diabetic by a single intraperitoneal injection of streptozotocin 65mg/kg. Age-matched control rats were injected with the same volume of isotonic saline. Experiments were carried out one week later. At this time point blood glucose concentration(mmol/L) was 7.4±0.3 in control rats and 26.5±0.9 in streptozotocin-treated rats ($P<0.01$). Platelets were labelled with Indium-111 and pulmonary accumulation following intravenous administration of thrombin 10U/kg was determined, in rats pre-treated with either NG-monomethyl-L-arginine (L-NMMA, 30mg/kg intravenously) or vehicle, using an automated isotope monitoring system. Data are expressed as mean±SEM. Statistical analysis was by paired or unpaired Student's t test, as appropriate, with $P<0.05$ taken as significant (two-tailed).
Results: In both control and diabetic rats, thrombin induced a reversible accumulation of platelets in the pulmonary circulation. A peak in pulmonary radioactive counts was seen 10-30 sec after administration of thrombin and this was followed by a decrease in counts over the subsequent 30-180 sec corresponding to disaggregation of platelets. In both groups of rats, L-NMMA had no effect on peak height or disaggregation time. Peak response to thrombin was significantly lower in the diabetic rats as compared to controls, both in the absence of LNMMA (6.0±0.8 vs. 8.8±0.9% increase above baseline, $P<0.05$, n=12) and in the presence of LNMMA (5.8±1.3 vs. 12.2±1.4% increase above baseline, $P<0.05$, n=5). By contrast, disaggregation time following thrombin was significantly greater in the diabetic rats as compared to the controls, both in the absence of LNMMA (88±9 sec vs. 59±10 sec, $P<0.05$, n=12) and in the presence of LNMMA (102±9 sec vs. 39±5 sec, $P<0.01$, n=4).
Conclusion: Short term induction of diabetes in rats gives rise to important changes in platelet reactivity, with a reduction in peak response to thrombin but a prolongation of subsequent disaggregation. These effects are not related to alterations in nitric oxide and the underlying mechanism remains to be elucidated.

P1703 Prothrombotic mutations are associated with increased cardiovascular events in postmenopausal women receiving hormone replacement therapy

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Recent studies have suggested that hormone replacement therapy (HRT) in postmenopausal women (PMW) may be associated with an initial increased cardiovascular risk. Recent reports suggest that the prothrombin variant 20210G to A is associated with an increased risk of events in hypertensive PMW with a previous myocardial infarction. To this end 50 PMW with documented vascular event underwent prospective evaluation of antithrombin III, protein C, free and total protein S, activated protein C resistance, fibrinogen, factor VII:C and homocysteine levels. In all the presence of antiphospholipid antibodies was investigated by kaolin clotting time (KCT), diluted Russel's viper venom time (DRVVT) and by measurement of anticardiolipin antibodies IgG and IgM (ACA-G and ACA-M). Prevalence of factor V Leiden, prothrombin variant G20210A and homozygosity for thermolabile variant C677T of the metilenetetrahydrofolate reductase (MTHFR) were evaluated and compared with those of 50 normal matched controls.
Antithrombin III and protein C were normal in all cases. One patient (2%) showed free protein S deficiency and 3 patients (6%) had activated protein C resistance. Homocysteine levels above 15 μmol/L were found in 3 patients (6%). Antiphospholipids antibodies were found in 35 patients (70%). Among women receiving HRT 87% had combined inherited and acquired prothrombotic factors (OR = 37.3, 95% CI = 8.5-564.3) while no combined prothrombotic factors were found in control PMW receiving HRT.
In conclusion vascular events in women receiving HRT are associated with a high prevalence of combined inherited and acquired prothrombotic factors. Therefore screening for prothrombotic factors may be of help in identify those women at increased risk for cardiovascular events with HRT.

P1704 Polymorphonuclear leucocytes (PMNs) phagocytosis function is enhanced in plasminogen knockout mice

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Background: Animals lacking plasminogen require alternative pathways of fibrinolysis for survival, which may depend on polymorphonuclear leucocytes (PMNs). In plasminogen knock-out (PG-/-) mice, PMNs have augmented fibrinolytic activity, and enhanced retention in occlusive thrombi, but the mechanisms underlying these observations have not been elucidated. Phagocytosis of soluble and insoluble fibrin(ogen) is one of the major routes for clearance of fibrin(ogen) by PMNs. Mac-1, expressed on activated PMNs bind fibrinogen and may facilitate this phagocytosis. We postulated that PMNs in PG-/- mice would demonstrate increased phagocytic activity, and increased expression of Mac-1.
Methods and Results: Phagocytic activity of PMNs from PG-/- and wild type (PG+/+) were compared by chemiluminescence assay following stimulation with S. aureus particles; and the expression of Mac-1 by flow cytometric analysis. Resting PG-/- PMNs expressed 3.5 fold less Mac-1 than resting PG+/+PMNs. However, PMA(Phorbol 12-myristate 13-acetate) stimulation of PMNs resulted in a 10.9 fold increase in Mac-1 expression in PG-/- versus 2.1 fold in PG+/+ controls. Correspondingly, stimulation of PG-/- PMNs by S. aureus particles in the presence of PG-/- serum resulted in more than a 10 fold greater degree of activation than PG+/+ PMNs in PG+/+ serum, as detected by chemiluminescence ($p<0.001$). Incubation of PG-/- PMNs with PG+/+ serum gave intermediate results. Incubation with increased doses of PMA resulted in death of 33% of cells from PG-/- mice versus 68% in wild type control ($p<0.05$).
Conclusion: Our observation suggests that PG-/- PMNs may contribute to fibrin/ogen clearance through enhanced phagocytic capacity associated with increased uptake via Mac-1. This may be secondary to deficiency of plasminogen in serum rather than intrinsic to the neutrophil. In addition, resistance of PG-/- PMNs to cell death by high dose PMA stimulation may explain the greater numbers of viable PMNs observed within occlusive thrombi and may further augment PMN mediated clearance of fibrin(ogen) in the setting of plasminogen deficiency.

P1705 Increase in venous tissue-type plasminogen activator (tPA) by exercise predicts local endothelial tPA release in vivo in healthy men

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Background: High plasma levels of tissue-type plasminogen activator (tPA) at rest are related to increased cardiovascular risk. However, powerful tPA release from the endothelium is critical in activating endogenous fibrinolysis to counteract local clot formation and atherothrombosis. Impaired capacity for endothelial tPA release is also suggested to indicate endothelial dysfunction. To investigate endothelial tPA release, invasive studies in perfused organs have been required. This has been a limitation for performing larger studies on the importance of endothelial tPA release for prognosis. On the other hand patients with angina pectoris are known to have worse prognosis if their capacity to increase venous plasma tPA concentrations during exercise is impaired. The mechanism behind this is unknown. We therefore investigated if exercise-induced changes in venous plasma concentrations of tPA antigen predict stimulated tPA antigen release from the endothelium.
Methods: Eleven healthy male subjects completed a maximal exercise test. Venous plasma tPA concentrations were measured before, during and after exercise. Local endothelial tPA release was then studied in the perfused-forearm model with desmopressin stimulation. Forearm blood flow and samples from the brachial artery and vein were obtained repeatedly to decide net forearm tPA release before, during, and after stimulation.
Results: A significant increase in plasma tPA antigen (3-fold) and tPA activity (13 fold) was observed during exercise. Desmopressin induced a significant increase in forearm tPA antigen release (6-fold) and tPA activity (14 fold). Exercise-induced plasma tPA antigen concentrations predicted capacity to release tPA from the forearm endothelium, both regarding peak release rate ($r=0.75$, $p=0.007$) and the total amount (area under the curve) of tPA antigen released ($r=0.65$, $p=0.031$). The exercise-induced increase in plasma tPA antigen was also related to the increase in forearm tPA antigen release by desmopressin stimulation ($r=0.68$, $p=0.023$).
Conclusion: We have demonstrated, for the first time, that rise in venous plasma tPA antigen during exercise predicts the capacity to release tPA antigen locally from the endothelium in healthy humans. This may be used as a non-invasive method to determine capacity for endothelial tPA release.

P1706 Polymorphonuclear leukocytes and high endothelin concentrations in acute coronary thrombi

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Background: Acute coronary syndromes (ACS) are characterized by compromised coronary flow at the epicardial and the microvascular levels. No-reflow (NR) is an extreme variant of coronary flow deceleration in acute myocardial infarction (AMI), comprising an acute reduction in coronary flow (TIMI grade 0-1) that is thought to reflect severe microvascular dysfunction after reopening of the epicardial vessel. Acute thrombectomy has been shown to protect the coronary microvasculature by diminishing distal embolisation. Current concepts invoke vasoconstriction as a key factor in coronary NR and slow-flow. Therefore, we investigated the cellular and biochemical composition of coronary thrombus aspirates in AMI and measured the concentrations of the potent vasoconstrictor peptide endothelin (ET).
Materials and Methods: Acute coronary thrombus samples were harvested with the X-Sizer® Catheter System Thrombus Removal Device (Endicor Inc., ev3) in the course of acute coronary angioplasty for ST-elevation myocardial infarction. One part of the material was fixed in formalin and used for immunohistochemistry, the remaining thrombus was weighed, suspended in HBS-buffer, homogenized in a glass potter, sonicated, purified over C-18 SepPak® cartridges and used for ELISAs (ET 1-21 ELISA-kit, Biomedica). Peripheral blood samples were drawn from the femoral artery and EDTA-plasma was used for the experiments.
Results: The predominant cellular components of acute coronary thrombi were polymorphonuclear granulocytes (mean count 8.e+6 granulocytes per mm^3 thrombus, i.e., a 1000-fold concentration of leukocytes in the patients' whole blood), within a fibrin and platelet-containing meshwork. Serial analysis of thrombus sections (n=12) revealed that 46±18% of cells with segmented nuclei displayed cytoplasmatic staining for immunoreactive ET-1. Thrombus ET concentrations were increased to 118±111.9fmolET/ml compared with 0.27±0.66fmolET/ml in parent PPP (p=0.04).
Conclusion: The data show that coronary thrombi contain high concentrations of ET associated with polymorphonuclear granulocytes. Thrombus-derived ET and leukocytes could play an important role in microvascular impairment after thrombolysis or mechanical reopening of the culprit vessel.

P1707 Influence of vardenafil 20 mg on aspirin-induced prolongation of bleeding time in normal healthy males

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Background: Vardenafil is a potent, highly selective PDE5 inhibitor in development for the treatment of erectile dysfunction (ED). PDE5 is expressed in the penile vasculature and in platelets. We have previously shown that vardenafil 10 mg did not alter bleeding time when give alone or administered against a background of low-dose aspirin [Pharmacotherapy (in press)]. Here, the influence of vardenafil 20 mg alone, or in combination with aspirin, on bleeding time was evaluated in healthy male volunteers.
Methods: Twenty men first received single dose vardenafil 20 mg (Day 1), and were then randomized to a double-blind, two-way crossover period consisting of single dose vardenafil 20 mg or placebo, administered on Days 5 and 8 on the background of low-dose aspirin (162 mg/day for days 2-8). Bleeding time was measured 1 hour (vardenafil Tmax) and 4 hours (vardenafil $T\frac{1}{2}$ ~4-5 hours) after vardenafil dosing. Differences were analyzed using ANCOVA.
Results: Baseline bleeding time was 5.09 (25%)* minutes. Single dose vardenafil 20 mg did not alter bleeding time after one hour [5.70 (24%) minutes, geometric LS mean ratio (95% CI) of 1.12 (0.98-1.28)] or four hours [5.16 (29%) minutes, geometric LS mean ratio (95% CI) of 1.01 (0.89-1.16)], see table.

Vardenafil - aspirin Interactions

	Aspirin/placebo	Aspirin/vardenafil	Geometric LS mean ratio a (95% CI)
Predose	7.94 (42%)	8.53 (30%)	
1 hour postdose	8.44 (33%)	8.75 (32%)	1.01 (0.88-1.17)
4 hours postdose	8.23 (35%)	8.61 (31%)	1.03 (0.86-1.24)

* Bleeding time, minutes, data expressed as LS geometric mean (%CV); ratio is aspirin + vardenafil/aspirin + placebo

Aspirin-prolonged bleeding time, whether during vardenafil or placebo co-treatment, was indistinguishable. Vardenafil 20 mg was well-tolerated with headache being the most common adverse event reported.
Conclusion: In this study, vardenafil 20 mg did not alter bleeding time when given alone, or when given on a background of low-dose aspirin.

P1708 The omega-3 fatty acid docosahexaenoate increases tissue factor activity despite in surface expression in activated human endothelial cells

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Background and Objective: Tissue factor (TF) is expressed on the endothelium only in inflammatory conditions, and its activity is highly dependent on the presence of anionic phospholipids, chiefly phosphatidylserine (PS). Because omega-3 fatty acids have been associated with reduced incidence of thrombotic events, we investigated the endothelial effects of the most abudant omega-3 FA, docosahexaenoic acid (DHA, 22:6 n-3) on TF expression.
Methods and Results: We stimulated human umbilical vein endothelial cells (HUVEC) with interleukin-1 (IL-1), tumor necrosis factor (TNF-a) and lipopolysaccaride (LPS) for 4-6 h in the presence or absence of DHA (10-25-50 μM) for 72 h (or stearate as control). TF expression was measured by a surface EIA ± a blocking antibody and Western analysis and the mRNA of TF by RT-PCR analysis. Total and surface activity were measured by a TF-dependent clotting assay. All stimuli used induced TF activity and expression in a concentration- and time-dependent manner. DHA pre-incubation concentration-dependently reduced TF surface expression (-20% ± 10%, -36% ± 10%, at DHA 25 μM and 50 μM respectively, $P<0.005$). The reduced TF surface expression was not accompanied by a decrease of TF mRNA and total cellular protein, but was actually associated with an increase of the surface procoagulant activity. Flow cytometry showed that DHA treatment leads to PS externalization in the endothelial plasma membrane, thus accounting for the increased surface procoagulant acivity.
Conclusions: These results indicate that DHA inhibits TF surface expression in activated endothelial cells, probably through a post-translational mechanism. However, the increase of TF surface activity after DHA exposure of endothelial cells suggests a detrimental effect on the endotelial haemostatic balance.

P1709 Effects of clopidogrel on platelet calcium mobilisation in acute coronary syndrome patients

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Background: Anti-thrombotic agents clopidogrel and AR-C69931MX act as antagonists to the P2Y12 receptor which amplifies platelet activation and aggregation (PA), together with other responses e.g. procoagulant activity induced by thrombin receptor activating peptide (TRAP). Clopidogrel requires hepatic conversion to its active metabolite whereas AR-C69931 is an intravenous agent that is active in vitro. We compared the effects of clopidogrel ex-vivo and AR-C69931 in vitro on PA and Ca^{2+} mobilisation in patients with acute coronary syndromes (ACS).
Methods: 6 patients with ACS were studied before and the day after clopidogrel (300mg loading dose then 75mg daily). All patients were already taking aspirin and LMW heparin. Platelet rich plasma was prepared from hirudin anticoagulated blood. PA was measured by turbidimetry in response to ADP 3μM. Ca^{2+} mobilisation responses induced by TRAP 20μM, ADP 0.3μM or both stimulants combined was measured by flow cytometry using Fluo-3AM-labelled platelets.
Results: Both P2Y12 antagonists significantly inhibited PA ($p<0.01$) though AR-C69931 inhibited it to a greater extent (45% reduced to -1%) than by clopidogrel (45% reduced to 10%).
TRAP induced a large Ca^{2+} mobilisation response (33μM.sec) and this was not inhibited by either of the ADP antagonists. ADP alone induced a faster response, which was not significantly reduced by clopidogrel (29 to 26μM.sec), but was significantly reduced by AR-C69931 (29 to 16μM.sec $p<0.02$). Both TRAP and ADP together gave a larger Ca^{2+} response and this was reduced by clopidogrel (75 to 52μM.sec) and significantly reduced by AR-C69931 (75 to 35μM.sec, $p<0.01$).
Conclusion: Clopidogrel significantly inhibited PA but had a minor effect on Ca^{2+} mobilisation. AR-C69931MX significantly inhibited both these parameters. This reduction of Ca^{2+} mobilisation may contribute to some of the antithrombotic effect of ADP antagonists.

P1710 Strenous exercise, platelet and B-T lymphocytes CD39

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Purpose Strenous exercise may induce platelet activation in vivo and enhanced platelet reactivity in vitro. It has been demonstrated recently that CD39 (a membran-bound glycoprotein originally identified as a lymphoid activation marker) is the third thromboregulatory system in addition to eicosanoids and nitric oxide. The present study aimed to investigate the effects of strenous exercise on platelet function and CD39 expression both in sedentary and physically active subjects.
Methods For the study, platelet-platelet aggregates (PPAs), in vitro ADP-platelet aggregation, PAC-1 and CD62P platelet expression, CD39 platelets and B-T lymphocytes expression were assessed before and after a standardized treadmill exercise testing (Bruce protocol), both in 8 healthy sedentary subjects (not engaged in any regular physical activity for more than 1 year before the study) and in 8 physically active subjects (habitually engaged in strenous exercise, 30 minutes or more at least three times per week).
Results At baseline in vitro ADP-platelet aggregation, PPAs counts and platelets CD39 expression were higher in sedentary than in active subjects ($P<0.02$ or more). Platelet PAC-1 and CD62P and B-T lymphocytes CD39 expression did not statistically differ in the groups. In sedentary subjects strenous exercise significantly increased PPAs counts ($P<0.05$) and decreased in vitro ADP-platelet aggregation ($P<0.001$); a significant inverse correlation ($P<0.05$)exists between these two parameters. Platelet CD39 expression significantly decreased ($P<0.05$) and B lymphocytes CD39 expression significantly increased ($P<0.05$) after strenous exercise in sedentary subjects. In the active subject's group PPAs counts and B lymphocytes CD39 expression significantly increased after strenous exercise ($P<0.001$;$P<0.05$). In vitro ADP-platelet aggregation showed slight non significant increase.
Conclusion Our results demonstrate that strenous exercise induces multicellular activation, enhancing the platelet reactivity particularly. Most likely platelets CD39 expression decrease indicates its consumption in thromboregulation. The B lymphocytes CD39 expression increase may be hypothesized as an integrative pathway in thromboregulation mechanism.

EXPERIMENTAL MODELS OF THROMBOSIS, ISCHAEMIA, REPERFUSION AND INFARCTION

P1711 Enhanced susceptibility of reperfused myocardium to gap junction blockers

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Objective: Previous studies showed that gap junction-dependent intercellular communication may allow spreading of necrosis during myocardial reperfusion. However, the fact that gap-junction mediated cell-to-cell communication is essential for impulse propagation in normal myocardium limits the potential therapeutic interest of gap junction blockers. This study tested the hypothesis that the altered cytosolic and extracellular composition may render reperfused myocardium more susceptible to these drugs.
Methods: Developed tension, electrical tissue impedance with four electrode probes, conduction velocity assessed using transmembrane action potentials, and lactate dehydrogenase (LDH) release were monitored in normoxically perfused rat hearts exposed to different drug concentrations of heptanol, 18alpha-glycyrrhetinic acid (GA) or halothane. Concentrations that were found to lack any effect on myocardial electrical impedance, either on resistivity or on phase shift, were applied to additional hearts during the first 15 min of reperfusion (30 min) following 60 min of non-flow ischemia at 37°C under the same monitoring, and compared with control hearts (no drug added).
Results: Under normoxic conditions, myocardial resistivity was minimally affected by the studied gap junction blockers except at high concentrations: EC50 were (2.01±0.15)x10-3 M for heptanol (n=6), (7.99±5.95)x10-5 M for GA (n=4), and > 1 M for halothane (n=3). Heptanol 1 mM, GA 10 μM, or halothane 10 mM had no effect on myocardial impedance of normoxic tissue. However, at these concentrations all the three drugs significantly delayed the recovery of myocardial resistivity during reperfusion: after 3 min of reperfusion the recovery was reduced by 39.40%, 11.45%, and 13.94% respect to corresponding controls in hearts receiving heptanol, GA and halothane, respectively. This effect on resistivity was accompanied by significant reductions in reperfusion-induced hypercontracture as assessed by peak diastolic pressure (74.84%, 63.61%, and 17.64% for heptanol, GA and halothane, respectively), and in LDH release during the reperfusion period (81.23%, 54.64% and 67.40%, respectively).
Conclusions: Myocardial susceptibility to gap junction blockers is increased during the initial minutes of reperfusion. This allows concentrations of blockers lacking effects on electrical impedance of normal myocardium to be protective against gap-junction mediated propagation of post-reperfusion cell death.

P1712 Crucial role of p66ShcA in tissue damage induced by hindlimb ischaemia

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Background: Clarification of the molecular events underlying cell death pathways activated in response to ischemia is an important step toward the treatment of tissue damage occurring during arterial occlusion and organ transplantation. Reactive oxygen species formation is believed to play a causal role in tissue injury that follows ischemia and ischemia/reperfusion. p66ShcA adaptor protein plays a key role in oxidative stress response and p66ShcA-/- mice exhibit increased resistance to oxidative stress.
Aim: Assessing whether the vascular remodeling and muscle damage that follow acute hind limb ischemia were altered in p66ShcA-/- mice.
Methods and Results: Unilateral hind limb ischemia, was induced by femoral artery dissection in p66ShcA wt and -/- mice. The induced levels of ischemia, as assessed by Laser Doppler Perfusion Imaging, were similar in p66ShcA wt and -/- mice. However, significant differences in the damage to vascular and muscle tissue were found: in p66ShcA wt mice, capillary density rapidly decreased and never recovered to initial values; conversely, in p66ShcA -/- mice, capillary density never decreased, reaching a maximum at day 14 after ischemia. When tissue damage was examined, p66ShcA wt mice displayed marked muscle fibers apoptosis and necrosis, followed by myogenic regeneration. In contrast, minimal myofiber death, followed by faster regeneration was observed in p66ShcA -/- mice. Following ischemia, p66ShcA and p53 were activated and no differences in p53 activation were detected in mice of the two genotypes, indicating that p66ShcA may act down-stream of p53 activation. Normo-perfused muscles from p66ShcA wt and -/- mice were analyzed as well. It was found that capillary density was lower in p66ShcA-/- than in wt mice, suggesting that, in the absence of ischemia, p66ShcA may be involved in angiogenesis.
Conclusions: p66ShcA plays a crucial role in the cell death pathways activated by acute ischemia indicating p66ShcA as a potential therapeutical target for prevention and treatment of ischemic tissue damage.

P1713 The tubulin-binding agent Paclitaxel improves the recovery of post-ischaemic cardiomyocytes

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The development of Paclitaxel-coated stents in the treatment of coronary restenosis stresses the need to evaluate the possible cardiac side effects of this agent on the healthy and the diseased myocardium. Therefore we investigated the effects of Paclitaxel (10 μM) on the viability and the electromechanical parameters of neonatal rat cardiac myocytes (CM). Paclitaxel treatment induced after 1h an hyperpolymerization of microtubules, a loss of intercellular contacts, an increase in adhesion structures and an actin reorganization. Moreover, Paclitaxel treatment induced a lengthening of electromechanical time parameters suggesting disturbed calcium flux. Using an in vitro, substrate-free hypoxia-reoxygenation model of simulated ischemia-reperfusion (SI-R), we observed that Paclitaxel pretreatment (10 μM, 1h) improved postischemic recovery of functional parameters (action potential rate and excitation-contraction delay coupling). Moreover, Paclitaxel decrease both the release of the LDH and troponin I (29% and 49,5% respectively) and the expression of Hsp70 mRNA as a biomarker of cellular injury. Moreover, the combination of Paclitaxel and cyclosporine A enhanced this decreasing effect, suggesting a mitochondrial side effect of Taxol. These overall data suggested that, in spite of significant effects in basal conditions, the tubulin binding agent Paclitaxel displayed a beneficial influence on the metabolically challenged cardiac muscle cells. These observations may be of clinical interest in view of the recent surge of the Paclitaxel-releasing devices against restenosis.

P1714 A dual thromboxane inhibitor and thromboxane receptor antagonist prevents pig myocardial infarction induced by coronary thrombosis

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Objectives: to characterise the effects of BM-573 (N-terbutyl-N'-[2-(4'-methylphenylamino)-5-nitro-benzenesulfonyl] urea), a novel dual thromboxane A2 receptor antagonist and thromboxane synthase inhibitor, on myocardial infarction induced by topical ferric chloride (FeCl3) application to the left anterior descending (LAD) coronary artery in pigs.
Methods: Experiments were performed on 12 healthy pure pietran anaesthetised pigs of either sex weighing from 20 to 30 kg. After a 30 min stabilisation period, a tissue strip saturated with ferric chloride solution (50% w/v) was rolled around the LAD coronary artery for 45 min. The animals were randomised in two groups: a control group (n=6) intravenously infused with vehicle (propylene glycol-NaCl 0.9%, 50:50), and a BM-573-treated group (n=6) infused with BM-573 (10 mg.kg-1.h-1). The infusion started 30 min before ferric chloride application and was continuously infused till 6 hours after strip application. The strip was removed 45 min after its application.
Results: All control animals (n=6) developed an occlusive thrombus in the LAD coronary artery. The mean infarct size, revealed by triphenyl tetrazolium chloride (TTC) and the area at risk evidenced by Evans blue corresponded to 35.3 + 2.2% and 36.9 + 2.1% of the left ventricular (LV) mass, respectively. Among the BM-573 treated group, four pigs did not develop coronary artery thrombus and their myocardium appeared healthy. Histopathological examination of FeCl3-injured coronary artery revealed an occlusive and adherent thrombus in control group while pretreatment with BM-573 prevented thrombus formation. In infarcted zones, lack of desmin staining and muscle structure disorganisation were obvious. Depletion of myocardial ATP content was observed in the myocardial necrotic region of the control group, but not in myocardial samples of BM-573-treated pigs which did not develop myocardial infarction. When BM-573 prevented LAD artery occlusion, the area under the curve (AUC) of plasmatic troponin T was reduced by 77% over 6h.
Conclusions: These data suggest that BM-573 could be useful for the prevention of myocardial infarction.

P1715 Enhanced cyclooxygenase-2 expression at site of recent myocardial infarction is associated with increased myocardial apoptosis

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Background: Cyclooxygenase-2 (COX-2) is one of the two isoforms of cyclooxigenase catalyzing the conversion of arachidonic acid to prostaglandin H2. While cyclooxigenase-1 (COX-1) is present in most cells, COX-2 is only induced in myocardiocytes in response to stress, such as ischemia and it is therefore not expressed in healthy myocardium. Aim of this study was to assess whether COX-2 expression occurs at site of recent myocardial infarction (MI).
Methods: We thus evaluated COX-2 myocardial expression at time of autopsy in hearts of 23 subjects who died 10 days to 2 months after MI with no evidence of re-infarction. Since COX-2 myocardial expression is stimulated by ischemia and therefore may be associated with increased rates of myocardiocyte apoptosis at site of infarction, we also investigated whether COX-2 myocardial expression was associated with higher apoptotic rates (AR). Myocardiocyte apoptotic rate was defined as the number of muscle actin-positive cells co-expressing in situ end-labeling of DNA fragmentation (TUNEL) and immunostaining for activated caspase-3.
Results: COX-2 expression, which is a marker of cellular stress such as ischemia, was found in 9 of 23 cases (39%). The clinical characteristics of subjects were not different comparing cases with COX-2 myocardial expression vs the others, even if most of COX-2 positive cases had permanent infarct-related artery (IRA) occlusion at time of death (78%), while only 50% of cases had patent IRA in the COX-2 negative group (P=0.18 at chi-square test). COX-2 myocardial expression was associated with an approximatively six-fold higher AR (median 17.9% [IR 11.0-25.4%] vs 3.7% [0.6-12.8%], P=0.016 at Mann-Whitney U test for unpaired data. The link between ischemia, COX-2 expression, ischemia and apoptosis was further strenghtened by the finding of high concordance between hypoxia induced factor-alfa (HIF-alfa)(78%, P=0.021) and the observation of intense immunostaining for bax in COX-2 positive myocardial regions.
Conclusion: The inducible form of cyclooxigenase, COX-2, is expressed in almost 50% of cases at site of MI even late after the index event, and the expression of COX-2 at site of infarct is associated, in this model of late MI, with extremely high apoptotic rates. These findings suggests a potential link between myocardial ischemia, COX-2 expression and enhanced post-infarction myocardial apoptosis. Further studies are warranted in order to investigate the causal roles in this association and to assess the potentially beneficial role of therapeutic interventions capable to modulate the COX-2 system.

P1716 Functional and contrast enhanced magnetic resonance imaging for demonstrating the sensitivity of hypertrophied hearts to ischaemia

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Purpose: Myocardial hypertrophy is a risk factor for myocardial infarction and hypertrophied hearts are prone to greater susceptibility to ischemic injury. Therefore, accurate estimation of left ventricular (LV) mass and early detection of necrotic tissue are important. MRI has been successfully used to measure myocardial mass and function. Administration of MR contrast media enhances the potential of MRI in estimating myocardial infarction. Newly developed necrosis specific MR contrast agents provide accurate measurement of infarction size in normal hearts subjected to ischemia, but has not been tested in hypertrophied hearts. Purposes of the study were to compare the susceptibility of hypertrophied hearts to ischemia with that in normal hearts using functional and contrast enhanced MRI.
Methods: Ten rats were subjected to aortic banding to induce hypertrophy. Another 10 served as a control. After 8 weeks, all animals were subjected to 25min ischemia/3hours reperfusion. Gadophrin III (0.05mmol/kg, Schering AG, Berlin, Germany) was administered at the beginning of reperfusion. Multislice T1-weighted spin echo images (2.0T CSI-II, Bruker Instruments, TR=30ms, TE=12ms) were acquired in end-systole and -diastole to define infarcted regions in the entire heart and the effect of ischemia on LV function. After imaging, the area at risk and infarction were determined using histochemical staining.
Results: LV mass in rats subjected to aortic banding was significantly greater (803±16mg) than that in normal hearts (618±17 mg, P=0.001) and close correlation was found between MRI and postmortem measurements. Hypertrophied hearts showed larger infarction size (19.0±1.4% of LV) than normal hearts (9.8±1.7%, p=0.001). There was no significant difference between Gadophrin-enhanced region and histochemical staining at postmortem (19.0±1.5% in hypertrophied and 9.8±1.7%). The size of areas at risk was identical in both groups. Thus, difference in infarction size cannot be attributed to this factor. Ejection fraction was significantly lower in hypertrophied (39±4%) than normal hearts (49±2%, p=0.01). The difference in ejection fraction and EDV are most likely attributed to the larger infarction size. There was no significant difference in heart rate, arterial blood pressure or percent systolic wall thickening between the groups.
Conclusions: Functional and contrast-enhanced MRI accentuate the great sensitivity of hypertrophied hearts to ischemia. The necrosis specific contrast agent Gadophrin III accurately determines the size of infarction in hypertrophied hearts.

P1717 Cardiotrophin-1 augments tumour necrosis factor-alpha-induced expression of intercellular adhesion molecule-1 in endothelial cells

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Background: A concert of cytokines is responsible for endothelial activation. One of the most potent is TNFa, but effects of Cardiotrophin-1 (CT-1) a member of the IL-6 superfamily on endothelial cells are unknown. Increased CT-1 levels are found in sera of patients with congestive heart failure. The aim of our study was to examine the effect of CT-1 on the expression of intercellular adhesion molecule 1 (ICAM-1) as a marker of endothelial activation and its functional consequences.
Methods: Human umbilical vein endothelial cells (HUVECs) were stimulated with TNFa 0,1 ng/ml, CT-1 10 ng/ml and TNFa 0,1 ng/ml together with CT-1 10 ng/ml. ICAM-1 mRNA was determined by RT-PCR. Protein expression of ICAM-1, STAT3 and phosporylated STAT3 was determined by western blot analysis. U937 cells were used for adhesion assay after stimulation of HUVECs with TNFa and TNFa plus CT-1 for 24 hours.
Results: TNFa increased ICAM-1 mRNA after 4 and 8 hours and ICAM-1 protein after 24 and 48 hours significantly, whereas application of CT-1 did not change ICAM-1 mRNA or protein, significantly. Addition of CT-1 to TNFa augments TNFa induced ICAM-1 mRNA 1,4 fold after 4 h ($p<0,05$) and 1,7 fold after 8 h ($p<0,05$). After 24 h ICAM-1 protein expression increased 2,9 fold ($p<0,05$) and 1,9 fold ($p<0,05$) after 48 h compared to TNFa alone. Application of CT-1 caused STAT 3 phosphorylation dose dependently. Maximal STAT 3 phosphorylation was achieved with 10 ng/ml CT-1. TNFa had no effect on STAT 3 phosphorylation. Application of piceatannol, an inhibitor of STAT 3 phosphorylation, diminished CT-1 modulated ICAM-1 expression significantly ($p<0,05$). Adhesion of U937 cells was doubled after stimulation of HUVECs for 24 h with TNFa plus CT-1 compared to TNFa alone ($p<0,01$).
Conclusion: These data demonstrate that CT-1 augments TNFa induced ICAM-1 expression via STAT-3 phosphorylation. This mechanism may support chronic inflammation in failing myocardium and contribute to the heart's structural deterioriation seen in congestive heart failure.

P1718 Low molecular weight fucoidan prevents arterial thrombosis in the rabbit model

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Introduction: Arterial thrombosis is an important issue in acute coronary syndromes. We have previously developed an experimental model of arterial thrombosis mediated by endothelial cell apoptosis after local injection of staurosporin. Low molecular Weight fucoidan (LMWF), a sulfated polysaccharide from brown algae, is a new direct antithrombin agent. The aim of this study was to investigate the therapeutic potential of LMWF to prevent thrombosis and to compare its effect to enoxaparine and placebo.
Methods and Results: Arterial thrombosis was induced by local incubation of staurosporin (10-5M) in rabbit femoral arteries (n=18). In group A, LMWF (15 mg/kg/12 hours, n=6) was injected SC during 3 days. In group B and C, Enoxaparin (1 mg/kg/12 hours, n=6) or a saline solution (n=6) were injected SC, similarly. APTT was evaluated in each group one hour after the first injection and platelets were counted at day 3. Thrombosis occurrence was evaluated by angiography 3 days later. Thrombosis occurred in 5/12 and 7/12 arteries in groups B and C, respectively. In contrast, no thrombosis occurred in group A. aPTT slightly increased in group A and B (84 $\pm$27 and 78 $\pm$ 11 s, respectively) compared to group C (46 $\pm$ 9 s). Platelet count did not vary significantly in the 3 groups.
Conclusion: LMWF is a promising and well tolerated new antithrombotic agent as compared to enoxaparin to prevent experimental arterial thrombosis in the rabbit model.

P1719 The synthetic serine protease inhibitor FUT-175 (Nafamstat Mesilate) reduces leukocyte-endothelium-interaction after ischaemia-reperfusion injury

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Background: We studied the synthetic serine protease inhibitor FUT-175 (Nafamstat mesilate) on its ability to modulate leukocyte-endothelial cell interactions following ischemia and reperfusion. During the inflammatory response, leukocyte rolling, adherence, and subsequent transmigration through the endothelial wall in the microcirculation are key steps in the inflammatory cascade and lead to further tissue injury.
Methods: The effects of FUT-175 on leukocyte-endothelial cell interactions were observed by intravital microscopy in the rat mesenteric microcirculation. Additionally we performed immunohistochemical analysis. The inflammatory cascade (leukocyte rolling, firm adherence, and transmigration) was studied by thrombin (0.5U/ml) superfusion of the mesenteries or hemorrhage (60min) followed by reperfusion (90min).
Results: Systemic bolus administration of FUT-175 (1mg/kg) 5 min prior to reperfusion significantly reduced leukocyte rolling from 51$\pm$9 to 5$\pm$2 cells/min ($p<0.001$) and adherence from 8$\pm$1 to baseline conditions ($p<0.05$) along the venular endothelium of the rat mesentery during reperfusion. Similar, FUT-175 decreased leukocyte endothelium interaction following local inflammatory stimulation of the mesenteries with thrombin. Moreover, myeloperoxidase activity in ischemic reperfused mesenteries, a marker of neutrophil accumulation was significantly reduced following FUT-175 treatment.
Conclusions: Our data clearly demonstrate that FUT-175 can potently inhibit the recruitment of leukocytes in the microvasculature, and proved to be a potent endothelium protective agent in clinically relevant doses. Thus, FUT-175 treatment may be useful agent for primary prevention of inflammatory tissue injury mediated by ischemia-reperfusion like shock, trauma, open heart surgery, or sepsis

P1720 Chracteristics of post-infarct ventricular rupture in mice

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Ventricular rupture occurs in 1-6% of patients with acute myocardial infarction (AMI), accounting for 4 to 30% of all in-hospital deaths. The incidence of rupture following AMI appears not to have declined in recent decades. This is partly due to lack of animal models for research use because rupture does not occur in the commonly used laboratory species. We studied the onset of rupture in mice with surgically induced AMI, determined infarct size, measured the threshold-tension-to-rupture (TTR) in ventricular rings in vitro, and analysed myocardial collagen content by hydroxyproline assay. In infarcted mice that survived 24 hrs after surgery, the incidence of ventricular rupture was 18 to 33% (four batches of mice with n=20-45). All ruptures (n=30) occurred between 3-6 days after AMI with the peak onset time at day 4 (46.7%). Rupture accounted for 40 to 50% of total deaths within the first week. Both male and female mice developed rupture. At autopsy, large quantity of blood clots were found in the chest and the location of rupture was at the left ventricular (LV) free wall or the apex. Rupture was either at the centre or the board zone of an infarct with the size varying from a 3-mm tear to a small penetration. By histology, mice with rupture usually had a moderate infarct size that was usually smaller than mice died of acute heart failure within the first week (41% vs 55%, $P<0.01$). Infarct expansion, measured as reduced ratio of infarcted versus non-infarcted wall thickness, was more pronounced in hearts with rupture than that from mice either died of acute heart failure or survived to day 7. LV rings were freshly prepared from hearts without or with AMI for 4 days, matched for wet weight and used for TTR measurement. LV rings with infarct had a 60% reduction in TTG than that without an infarct (4.0$\pm$0.5 vs 11.5$\pm$0.8 g, $P<0.001$), indicating a significant decrease in the mechanical strength of the infarcted myocardium. In contrast, in LV rings from rats at day 4 after AMI or sham-operation, TTR in infarcted LV rings was similar compared with the non-infarct controls. Such between-species difference in the TTR might be due to a lower collagen content in mouse than in rat LV myocardium as judged by hydroxyproline levels (1.38$\pm$0.04 vs 2.32$\pm$0.04 ug/mg dry weight, $P<0.01$).
Conclusion: The mouse appears the only laboratory species that develops rupture following AMI. The colllegen content is a determinant of rupture. This mouse model will be useful for research on mechanisms and interventions of rupture.

IMPACT OF ATHEROSCLEROTIC DISEASE ON THE FUNCTION OF THE CORONARY CIRCULATION

P1721 Effect of preinfarction angina pectoris on microcirculation in patients with reperfused acute myocardial infarction

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Preinfarction angina pectoris (PA) has been suggested to have beneficial effect on microvasculature after acute myocardial infarction (AMI). The precise mechanisms of this protection is not known. Under the presence of MV dysfunction, pressure-derived collateral flow index (CFIp) may reflect the destruction degree of microvasculature and higher CFIp was shown to be associated with no-reflow phenemenon. In this study, we investigated the influence of PA on microvasculatory function by using ST-segment resolution and CFIp as a marker of microcirculatory perfusion.

Methods We studied 41 (25 had PA in the 24 hours before AMI) patients with a first AMI in whom Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the infarct related artery (IRA) was established by thrombolytic therapy. The percent resolution of ST-segment deviation (STD) after thrombolysis was determined. All of the patients had TIMI grade 3 flow in IRA at the coronary angiography. Intracoronary pressure measurements and stent implantation to the IRA were performed. After angiography, CFIp was calculated as the ratio of simultaneously measured coronary wedge pressure – central venous pressure (Pv) to mean aortic pressure – Pv.

Results Patients with preinfarction angina pectoris had greater percent STD than those without PA. ($67 \pm 18\%$ vs $44 \pm 24\%$, p= 0.03). The mean of coronary wedge pressure (23.2 ± 9.4 compared with 16.4 ± 7.4, $P<0.03$) and pressure derived collateral flow index (0.22 ± 0.08 compared with 0.15 ± 0.10, $P<0.03$) were significantly lower in patients with preinfarction angina compared to those without.

Conclusion Preinfarction angina is associated with a greater degree of ST-segment resolution and lower CFI-p in patients with TIMI -3 reflow after thrombolysis. These findings suggest that PA had protective effect against reperfusion injury as evidenced by greater ST resolution and lower CFIp after AMI.

P1722 Left-ventricular jeopardized myocardium remote from necrotic areas is extensively affected from apoptotic myocardiocyte loss after acute myocardial infarction

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Background: Myocardiocyte apoptosis early and late after acute myocardial infarction (AMI) is a major determinant of cell loss and progression to cardiac failure in addition to acute ischemic cell necrosis in the infarct region. However, the spatial distribution of post-infarction apoptosis, and in particular the presence and extent of myocardial apoptosis in non-necrotic but still jeopardized myocardium is uncertain. Aim of this study was thus to assess the three dimensional distribution of myocardial apoptotic rate (AR) after AMI.

Methods: 9 hearts were collected at autopsy 4 days to 6 months after AMI, without evidence of re-infarction. Areas of myocardial sampling were: 1) perinecrotic, 2) near border (approximately 2 cm farther from the necrotic area), 3) opposite unaffected regions and 4) right ventricle. Both patients with transmural or non-transmural AMI, as well as patients with anterior or non-anterior AMI were included to strengthen the analysis. Co-localization for and immunohystochemistry for cleaved caspase-3 was used to calculate the AR (median, 25-75% range). Correction for DNA synthesis and RNA splicing was also performed.

Results: Myocardial apoptosis affected the whole LV myocardium, including unaffected regions and right ventricle [1.8% (0.7-4.8%)]. Myocardial apoptotic loss was however significantly higher in peri-necrotic regions and near border regions [13% (6.6-17.2%), $P<0.001$ at Mann-Whitney U test]. Strikingly, when analysis was performed according to specific sampling areas, apoptotic rates in apparently unaffected but still jeopardized near border regions [10% (3.2-13%)] were significantly greater than those of unaffected regions [1.5% (1.1-5.0%), P=0.008], or right ventricular regions [1.0% (0.4-2.0%), P=0.028] yet being lower than apoptotic rates in peri-necrotic regions [17.0% (12.5-20.0%), P=0.008]. Comparison of anterior vs. non-anterior AMI or transmural vs. non-transmural AMI did not significantly affect the analysis.

Conclusions: Myocardial apoptosis after AMI assessed at post-mortem evaluations is a diffuse process, affecting the whole myocardium at risk in the distribution of the infarct-realted artery. Myocardiocyte apoptotic burden shows a gradient of LV involvement with increasing apoptotic rates from remote to peri-necrotic regions.

P1723 The chronic total occlusion of the infarct-related artery leads to profound microvascular obstruction. A morphometric study

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The results of clinical trials as well as studies on animal models have suggested a significant benefit in patients with sustained patency of the infarct-related artery (IRA). However, potential benefits in humans are still under investigation.

Aim of the study: The study was to assess the impact of the degree of residual stenosis of IRA on the microvasculature and the process of the infarct scar formation.

Material and Methods: We studied 31 clinical cases. A study group consisted of 21 patients after QMI with a typical infarct scar found during autopsy. Control group comprised 10 patients who died due to non-cardiac reasons (confirmed by autopsy). Coronary arteries were transected at 5 mm intervals and carefully examined for occlusive lesions. To assess the capillary network within the infarcted area and the free wall of the left ventricle (LV) we used immunohistochemical staining for CD34 (endothelial cell marker). Morphometric assessment was done with the use of digital image analyser.

Results: A significant reduction in capillary density within the infarcted area was noted when compared to the control group ($1525{,}6 \pm 378{,}5/mm^2$ vs. $2968{,}7 \pm 457{,}3/mm^2$; $p<001$). Such a decrease correlated to the degree of residual stenosis of IRA (Spearman correlation rs=-0,512; p=0,03). Conversely, a non-significant reduction in capillary density found in the free wall of LV ($2848{,}3 \pm 463{,}4/mm^2$ vs. $2968{,}7 \pm 457{,}3/mm^2$; NS) was related to the degree of myocytes hypertrophy (r=-0,569; p=0,009). The subdivision of the study group showed that total occlusion of IRA (cross-sectional area stenosis >98%) was associated with a significantly higher reduction of the capillary density ($1204{,}6 \pm 156{,}9/mm^2$ vs. $1676{,}67 \pm 245{,}8/mm^2$; p=0,0005). A 60%-reduction in capillary density observed in patients with persistently occluded IRA resulted in the extensive fibrosis within the infarcted area and the formation of left ventricle aneurysm.

Conclusions: (1) The persistent occlusion of IRA resulted in a profound microvascular obstruction that affected the process of infarct healing.
(2) The results of the study might explain one of the beneficial mechanisms of the sustained patency of IRA.

P1724 Distal microembolization in native coronary artery stenting with distal protection: clinico-pathological correlations

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Background: Distal embolization after percutaneous coronary interventions(PCI) has been considered particularly uncommon and of scarce clinical importance in native coronary arteries, while being of potential relevance only in degenerated saphenous vein grafts. Aim of our study was to evaluate the feasibility of using protection filter devices in native coronary artery during stenting procedures in patients with stable and unstable angina, to assess the magnitude of microembolization phenomenon by analyzing the debris captured by the filter and to make clinico-pathological correlations.

Material and Methods: elective coronary stent implantation with the use of a distal filter protection was attempted in 37 consecutive coronary arteries lesions with > 60% stenosis (mean $76.71 \pm 10\%$). Mean age of the patients was 66.5 ± 8.69 years; 72.2% were men, 44.4% had previous myocardial infarction, 55.6% had unstable angina, 55.6% had hypertension, 27.8% were dislipidemic.

Results: presence of debris was detected in 75.67% of the filters. The mean surface area covered with material was $26.30 \pm 20.17\%$. Particle size ranged from 128.03 to 2503.48 μm (mean 721.31 ± 306.64 μm) in the major axis and 43.4 to 1214.61 μm (mean 256.73 ± 119.74 μm) in the minor axis. Collected debris consisted mainly of thrombotic material and foam cells. In patients with unstable angina the maximum longitudinal diameter was 1180.77 μm while in patients with stable angina was 308.52 μm ($p<0.0001$); in patients with <75 years the percentage of poliuretane membrane covered by material was $29{,}89 \pm 4.2$ while in patients >75 years was 9.8 ± 2.1($p<0.0001$).

Conclusions: Distal protection during coronary artery stenting was feasible. Embolized debris were collected in a high percentage of cases. In patients with unstable angina particulate debris larger than 1000 μm could be captured in the filters, suggesting that, at least in this subgroup of patients, filter protection should be recommended to reduce myocardial injury.

P1725 Relationship of coronary flow pattern to myocardial blush grade in patients with first acute myocardial infarction

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Background: Analysis of myocardial blush grade and coronary flow velocity pattern after PTCA for acute myocardial infarction (AMI) have been used to obtain information about microvascular reperfusion. The association between myocardial blush grade (MBG) and coronary flow velocity pattern immediately after PTCA for AMI has not been evaluated.
Methods: The coronary blood flow velocity pattern was determined immediately after PTCA in 35 patients with first AMI using a Doppler guide wire. Measurements were related to microvascular function of the infarct zone determined by the MBG.
Results: Coronary flow velocity patterns were different between patients with absent myocardial blush (MBG:0/1; N=14), patients with reduced blush (MBG:2; N=7) and patients with normal myocardial blush (MBG:3;N=14) (see table). In a multivariate analysis the MBG was the only variable with significant impact on the diastolic deceleration rate (P=0.034) while age, infarct location, time to revascularization, infarct vessel diameter and maximal creatine kinase level had no significant impact.

Coronary flow related to MBG

	MBG 0/1 (N=14)	MBG 2 (N=7)	MBG 3 (N=14)	P
Systolic peak velocity (cm/sec)	7.1 ± 4.0	12.7 ± 6.0	15.7 ± 9.6	0.011
Systolic flow duration (msec)	198 ± 99	360 ± 109	289 ± 25	<0.001
No. of early systolic flow reversal	8/14	0/7	0/14	0.043
Diastolic deceleration rate (cm/s2)	103+/58	80 ± 65	50 ± 19	0.025
Diastolic-systolic velocity ratio	4.1 ± 2.2	2.0 ± 0.6	1.9 ± 1.0	0.002

Conclusion: The coronary flow velocity pattern immediately after PTCA for AMI relates to myocardial perfusion determined by the angiographic MBG. Depressed reperfusion on the myocardial tissue level is the strongest predictor of an abnormal coronary flow velocity pattern in the infarct related artery.

P1726 Earlier exhaustion of atrial compared to ventricular coronary flow reserve at stress

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Purpose: As human atrial myocardial perfusion data are lacking, the purpose of this study was to compare atrial and ventricular coronary flow reserve (CFR).
Methods: Twenty-two patients with suitable coronary anatomy underwent coronary blood flow velocity (APV) measurements, using a 0.014 inches Doppler guidewire in the proximal left circumflex coronary artery (LCx) and in the left atrial circumflex branch (LACB), after the completion of programmed routine cardiac catheterization. Measurements were recorded at baseline (b) and at maximal hyperemia (h) after adenosine administration. CFR was calculated as h-APV/b-APV. All measurements were done at resting heart rate and pacing-induced stress at 120 bpm.
Results: Please see Table 1.

Table 1

	Rest			120 bpm		
	LCx	LACB		LCx	LACB	
b-APV cm/sec	15.9 ± 4.8	16.8 ± 5.3	p = NS	20.3 ± 5.1	27.1 ± 8.2	p < 0.05
h-APV cm/sec	47.3 ± 14.9	46.8 ± 12.5	p = NS	44.3 ± 13.6	51.8 ± 12.4	p < 0.05
CFR	3.0 ± 0.6	2.9 ± 0.5	p = NS	2.3 ± 0.5	1.9 ± 0.3	p < 0.05

Conclusions: Although atrial and ventricular CFR show no significant differences at rest, differences in atrial compared to ventricular myocardial perfusion regulation lead to earlier exhaustion of CFR at stress. Thus, the currently used cut-off value for CFR in assessing the physiologic significance of intermediate severity lesions may need to be re-evaluated for proximal LCx lesions, in order to avoid the consequences of left atrial ischemia.

P1727 Does wall shear stress correlate to wall shear stress gradient in left coronary artery tree? Implications to atherogenesis

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Introduction: Apart from the well-established role of the local low Wall Shear Stress (WSS) in the atherogenesis and the localization of atherosclerotic lesions, the Wall Shear Stress Gradient (WSSG) is recently considered to be an atherogenesis factor, probably as local modulator of endothelial gene expression. Purpose of this study is to investigate a possible correlation between these two factors in the normal human Left Coronary Artery tree (LCA) and to further elucidate their implications to atherogenesis.
Methods: The geometry used for the artery model construction was based on data compiled from several sources. Physiological steady flow velocity, under resting conditions, is incorporated as inflow boundary condition, while the outflow discharges were set analogous to the third power of the corresponding vessel diameters. The numerical results shed light into the 3D, non-Newtonian nature of the flow patterns and quantified the correlation between WSS and WSSG throughout the entire LCA tree model (21616 nodes). The correlation coefficients between WSS and WSSG were also separately calculated for the LAD (15368 nodes) and LCxA (6248 nodes) vessels.
Results: 1) The correlation coefficient between WSS and WSSG referring to the entire LCA tree was 0.555 ($p<0.001$). The mean WSS and WSSG values were 6.75 ± 0.036 N/m^2 and 860.02 ± 6.37 N/m^3, respectively. The WSS ranged between 0.75 and 46.39 N/m^2, while the WSSG ranged between 7.30 and 15863.30 N/m^3. 2) The corresponding correlation coefficient referring to the LAD was 0.579 ($p<0.001$). The mean WSS and WSSG values were 7.09 ± 0.05 N/m^2 and 884.06 ± 7.98 N/m^3, respectively. 3) The corresponding correlation coefficient referring to the LCxA was 0.444 ($p<0.001$). Mean WSS and WSSG values were 5.90 ± 0.046 N/m^2 and 800.91 ± 9.99 N/m^3, respectively.
Conclusion: A strong correlation between Wall Shear Stress (WSS) and Wall Shear Stress Gradient (WSSG) exists throughout the entire Left Coronary Artery. As it is apparent from the analysis results, these two flow parameters exhibit a similar distribution. Dominant low WSSG (7.30 N/m^3 to 348.23 N/m^3) regions appear opposite the flow dividers where low WSS (<10.00 N/m^2) prevails and atherosclerosis usually occurs. Lower WSSG values are also encountered at the proximal regions (compared to the distal ones), which are particularly prone to atherosclerosis. Important low WSS and WSSG regions mainly appear at the vicinity of the left main coronary artery bifurcation and around the origin of the first diagonal branch. The significant role of WSSG distribution is emerging.

P1728 Changes of coronary microvascular resistance before and after percutaneous coronary intervention

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Purpose: It is generally assumed that coronary microvascular resistance during maximal hyperemia is not only minimal but also constant. We used a novel dual-sensor equipped guide wire (pressure and Doppler flow) to assess a velocity-based index of hyperemic microvascular resistance (h-MRv) before and after percutaneous coronary intervention (PCI) to test this hypothesis.
Methods: 15 patients (16 target lesions) were included. Simultaneous measurements were performed after induction of maximal hyperemia with i.c. adenosine in an angiographically normal reference vessel, and in the target vessel at baseline, and after each treatment step (PTCA, stenting and ultrasound guided upsizing of stent). Hyperemic distal flow velocity (h-APV), aortic pressure, distal pressure (h-Pd) and ECG were recorded. H-MRv was calculated as mean h-Pd divided by mean h-APV per beat. Linear regression analyses were performed between h-MRv and h-Pd per patient. A Wilcoxon signed ranks test was used to test the significance of the slopes. Pre- and post-PCI hemodynamic data were compared by ANOVA.
Results: The pre-treatment value of h-MRv was significantly higher than that of the reference vessel (Table). PCI increased both h-APV and h-Pd. H-MRv significantly decreased after PCI. Post-treatment h-MRv was lower than that of the reference vessel, although the difference did not reach significance. Per patient, there was a significant inverse relationship between h-MRv and h-Pd in the target vessel (p = 0.026).

Table: hemodynamic measurements

	pre treatment	post PTCA	post stent	post upsize	reference
h-IPV	29±18	44±9.4a	56±16b	63±19b	57±15b
h-Pd	57±16	68±13a	78±13b	77±14b	90±15b
h-MRv	2.6±1.4	1.6±0.4b	1.5±0.4b	1.3±0.4b	1.7±0.4b

a. $p < 0.05$, b. $p < 0.005$ vs. pre-treatment

Conclusions: H-MRv is not homogeneously distributed between perfusion areas distal to stenotic and non-stenotic vessels. After PCI, restoration of distal perfusion pressure leads to a decrease of h-MRv. Hence, also in humans, hyperemic microvascular resistance is pressure dependent.

P1729 Role of non-angiographically evident collateral flow on left-ventricular function after primary percutaneous coronary intervention

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Background: The prompt restoration of good flow in the infarct related artery (IRA) with thrombolysis or primary percutaneous transluminal coronary angioplasty (PCI)is determinant for myocardial salvage in a patient (Pt) with acute myocardial infarction (AMI). However, recent observations suggest that time to treatment may be less important with primary PCI performed after 2 hours from the onset of symptoms and factors other than time to reperfusion may play a crucial role.
Aim: to assess the influence of non-angiographically evident collateral flow on contractile recovery and left ventricular remodeling in pts with AMI.
Methods: We studied 12 Pts with first anterior AMI treated with primary PCI, with a time to reperfusion of 2-4 hours. All Pts showed the proximal occlusion of left descending anterior coronary artery. Pressure-derived fractional collateral flow (PDCF) was measured in all subjects. PDFC was determined with a pressure-wire, before revascularization by simultaneous measurement of mean aorta pressure, distal coronary pressure during balloon occlusion and central venous pressure, which was substituted for by 5 mm Hg. All Pts underwent echocardiographic exam within six hours from the procedure and at one month follow up in order to assess the variations of regional wall motion score index (WMSI) and of left ventricular end diastolic volumes (EDV).
Results: PDCF measurement was safe and feasible in all Pts. The mean value of PDCF was 0.231. The results of canonical correlation analysis showed that PDCF was significantly correlated to the improvement of WMSI (r=-0,672; $p<0.05$), and to the increase of the left ventricular end diastolic volume (r = -0.783; p=0.02) at one month follow up. No significant correlation was found between PDCF and time to reperfusion (r=-0.110; $p>0.20$). The increase of left ventricular end diastolic volume was shown to be strongly correlated to the peak of creatine-kinase.
Conclusions: The presence of adequate collateral flow seems to positively influence contractile recovery and to prevent left ventricular remodeling in patients with acute myocardial infarction submitted to primary PCI.

P1730 Assessment of coronary arterial stents by multislice-computed tomography angiography

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Purpose: The aim of this study was to assess patency, lumen visibility and stenoses of coronary artery stents by Multislice-CT-Angiography (MSCTA) in comparison to conventional coronary angiography as the standard of reference.
Methods: 47 stents of 13 different types were evaluated in 29 patients. MSCTA was performed on a four slice scanner with a standard coronary protocol (detector collimation 4x1 mm; table feed 2 mm/rotation, 300 mAs, 120 kV). Original axial images and multiplanar reformations were evaluated regarding contrast distal to the stent as an indirect sign of patency, stent lumen visibility and in-stent stenosis (>50%) detection in three different window settings (700/200 HU, 1000/300 HU, 1200/400 HU).
Results: Of 38 interpretable stents, 37 were correctly classified as patent, one was correctly classified as obstructed. Partial residual of the stent lumen could be visualized in 29 cases (window 700/200 HU). On average, 20-40% of the stentlumen diameter could be visualized. Regarding stenosis evaluation 20 stents were correctly classified as having no significant stenosis, one was falsely classified as stenosed and one was correctly classified as occluded. In 20 stents lumen visibility was not sufficient for stenosis evaluation (all window settings combined).
Conclusion: Coronary four-slice CT angiography may provide important indirect information on the patency of stents but does not allow sufficient visibility of the stent lumen for stenosis evaluation.

INJURY, PROTECTION AND REPAIR OF THE VESSEL WALL

P1731 The in-hospital prognostic value of vascular endothelial growth factor in patients with acute myocardial infarction

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Background: Vascular Endothelial Growth Factor (VEGF) is an angiogenic factor which is probably released because of acute inflammation, or/and endothelial damage, or/and hypoxia, or/and thrombus formation, during acute myocardial infarction (AMI). All situations mentioned above, if persistent, could be associated with poor prognosis of AMI. The aim of this study was to determine whether serum VEGF levels are of any prognostic value for patients with AMI during hospitalization.
Methods: The study included 78 patients (52 men, mean age 63.7 $\pm$ 16.7 years) who presented with AMI and were given thrombolysis with 20 U of reteplase, within 6 hours from the onset of the chest pain. Serum VEGF levels were measured (by ELISA method) at admission (prior to the start of thrombolysis) and 7 days later. The elevation rate of serum VEGF levels (VEGF levels on day 7/VEGF levels on admission) was also estimated. The patients were divided into two groups: group A included 14 patients who had an in-hospital event such as death, re-infarction, post-infarction angina and life-threatening arrythmia (after the 1st 24hours from the onset of the AMI) and group B included 64 patient who had no complications during hospitalization.
Results: Serum VEGF levels at admission had no statistically significant difference between the two groups (115.6 $\pm$ 46.3 vs 98.3 $\pm$ 34.3 ng/ml, p=0.114). Serum VEGF levels at day 7 were much higher in group A than in group B (268.3 $\pm$ 83.3 vs 147.6 $\pm$ 48.7 ng/ml, p=0.000) and the same stood for the elevation rate of VEGF levels (2.42 0.3 vs 1.49 $\pm$ 0.62 ng/ml, p=0.000)
Conclusions: Whereas VEGF level on admission is of no prognostic value for in hospital events for patients with AMI, VEGF level of the 7th day and the elevation rate of its value from baseline levels (on admission) are associated with serious complications. This could be explained by the fact that in these cases there is probably a continuous process of inflammation, or/and endothelial damage, or/and hypoxia, or/and thrombus formation after the acute face of myocardial infarction.

P1732 Augmentation of vascular endothelial growth factor synthesis by gene transfer of copper-zinc superoxide dismutase: the role of hydrogen proxide and involvement of heme oxygenase-1

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Background: Nitric oxide (NO) and reactive oxygen species (ROS) are emerging as important regulators of angiogenesis as they increase VEGF synthesis and are mediators of its activity. Recently we showed that carbon monoxide (CO) a product of heme oxygenase-1 (HO-1) augment VEGF generation. Interestingly, the expression of HO-1, a stress-induced and vasculoprotective gene, is enhanced both by NO and H2O2. Here we examined the possibility of augmentation of VEGF synthesis by overexpression of copper-zinc superoxide dismutase (SOD1), an enzyme dismutating superoxide radical to H2O2 and molecular oxygen.
Methods and Results: VEGF production in vascular smooth muscle cells and 3T3 fibroblasts was concentration-dependently potentiated by exogenous H2O2 (50-400 mM; up to 3-fold increase), while superoxide, generated intracellularly by LY83583 or extracellularly by xanthine oxidase was ineffective. Transfer of pcSOD1 expression plasmid resulted in increased SOD1 activity (determined in non-denaturating gel) and enhanced generation of ROS, as evidenced by dichlorodihydrofluorescein fluorescence (1,95$\pm$0,16 fold increase over cells transfected with control plasmid, n=10). Overexpression of SOD1 strongly enhanced VEGF promoter activity in a reporter-gene assay (3,1$\pm$0,3 fold over control, n=5) and augmented VEGF expression and protein synthesis (175,8$\pm$12,9% of control, n=11). Increased SOD1 activity stimulated hypoxia responsive element (7,5$\pm$0,5 fold over control, n=5) and SP-1 responsive element (3,3$\pm$0,4 fold over control, n=6) of VEGF promoter, as evidenced by reporter gene assay, indicating for the role of HIF-1a and SP-1 transcription factors in ROS-induced VEGF synthesis. The effect of H2O2 stimulation or SOD1 overexpression was respectively reverted by addition of exogenous catalase protein (1 U/ml) or by tranfection with catalase expression plasmid. Both treatment with H2O2 and SOD1 gene transfer induced HO-1 expression. Accordingly, H2O2-dependent VEGF generation was abolished by treatment with tin protoporphyrin, an inhibitor of HO activity.
Conclusions: H2O2 can potently increase VEGF production. Similarly to the effect of NO, its influence seems to be mediated by the activity of HO-1. Augmentation of SOD1 expression can result in enhanced VEGF synthesis what may add to the beneficial effects of free radicals scavenging by SOD. The data support the potential application of SOD1 gene transfer for stimulation of angiogenesis via enhancement of VEGF expression.
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P1733 Changes in fibrilar versus network forming collagens during smooth muscle cell cycle reentry allow adaptive arterial remodelling

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Purpose: The response of arterial vessel wall morphology to processes such as balloon angioplasty, arteriosclerosis and hypertension involves changes in vessel wall mass, extracellular matrix expression and smooth muscle cell (SMC) proliferation. We have recently shown that the SMC-specific expression of SV40 large T-antigen (TAg) induced smooth muscle cell cycle reentry that resulted in fundamental vessel wall thickening in the presence of adaptive arterial remodeling featuring an increased luminal area. The present study aimed to investigate the extracellular matrix expression that allowed the vessel to respond in an adaptive rather than constrictive fashion.
Methods: We established a transgenic mouse line with smooth muscle-specific expression of a temperature sensitive SV40 TAg (MHC-tsA58). This approach enabled us to generate SMC-lines for in vitro studies of the expression of type I collagen and type VIII collagen, matrix metalloproteinase-2 and -9 (MMP2 and MMP9) and furthermore of tropoelastin under smooth muscle cell cycle reentry and cell cycle exit, respectively. Northern blotting was employed using riboprobes recognizing the various transcripts of type I collagen and type VIII collagen, respectively. MMP2, MMP9 and tropoelastin were studied by quantitative RT-PCR.
Results: Smooth muscle specific expression of TAg at the permissive temperature resulted in ongoing cell cycle reentry, while SMC underwent cell cycle exit when TAg was switched off. These experiments revealed that smooth muscle cell cycle reentry resulted in substantially elevated levels of type I collagen RNA while the levels of type VIII collagen RNA were suppressed. This elevation of type I collagen RNA was caused by an increase in its longer transcripts. In contrast, the levels of MMP2 and MMP9 were not considerably affected by the cell cycle reentry, while tropoelastin was slightly suppressed in proliferating SMC.
Conclusions: These results in conjunction with our previous studies indicate that smooth muscle cell cycle reentry is not a sufficient cause of vascular stenosis but is rather capable of inducing adaptive remodeling which is made possible by alterations in the expression of fibrilar versus network forming collagens. This insight into vascular remodeling may help to improve the understanding of pathophysiological mechanisms during early atherosclerosis. Our results may also pave the way to the development of new therapeutic paradigms based on the directional rather than absolute control of SMC proliferation in vascular diseases.

P1734 Vascular injury response is controlled by p130 but not by the related p107

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Purpose: Recent studies have revealed the role of pRb family proteins in the response to vascular injury. We have previously shown that the inactivation of pRb-proteins (pRb, p130 and p107) and p53 in transgenic mice resulted in enhanced smooth muscle cell cycle reentry with resulting vessel wall thickening and spontaneous neointima formation. The present study was designed to evaluate the arterial injury response in the absence of p130, formerly referred to as pRb2, and p107, which shares a high degree of homology with p130.
Methods: Unilateral carotid artery ligation was applied to either, mice with targeted disruption of the p130 gene (p130-/-), or targeted disruption of the p107 gene (p107-/-). Mice were allowed to recover for 3 weeks after ligation and then perfusion fixed for histologic and cross-sectional morphometric analysis.
Results: Non-instrumented arteries (aorta, carotid and femoral arteries) of p130-/- mice and of p107-/-mice were indistinguishable from +/+ control littermates. Following carotid artery ligation, we found p130-/- mice (n=8) to develop a significant thickening of the vessel wall compared with controls (n=9). Mean vessel wall area ranged from 3.07 ± 0.20 to $3.56 \pm 0.62 \times 10^{-2}$ mm^2 for p130-/- mice versus 2.26 ± 0.13 to $2.57 \pm 0.26 \times 10^{-2}$ mm^2 for controls (p=0.02) along the lesion studied. This increase in vessel wall area was primarily due to a 7-fold mean increase in neointima in p130-/- mice yielding mean values in the range of 0.43 ± 0.18 to $1.19 \pm 0.70 \times 10^{-2}$ mm^2 along the lesion. Remarkably, despite the increase in vessel wall area, the lumen area was not statistically different for both groups. In contrast, the p107-/- mice did not display an enhanced injury response. Neointima formation, vessel wall area and lumen area following carotid artery ligation were comparable for p107-/- mice (n=9) and for controls (n=12).
Conclusions: The data indicate that the loss of the cell cycle inhibitor p130 - but not of p107 - leads to an enhanced injury response in the presence of perfect adaptive remodeling. This provides evidence that smooth muscle cell cycle regulation and remodeling following vascular injury is not a general effect of all proteins of the pRb family but rather a specific effect found at least for p130. Further studies on p130 specific pathways and investigations on functional domains of p130 with focus on proliferation and differentiation are required to illuminate the pathophysiology of injury response.

P1735 Arginine supplementation and oxidative processes: in vivo model

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L-arginine, an endogenous amino acid, is a precursor of endothelium- derived nitric oxide. It was revealed that supplementation with arginine improves endothelial function by nitric oxide synthesis augmentation. Nitric oxide, a free radical with pro- and antioxidant properties is capable to modulate the direction of the oxidative reaction. Ca^{2+}-dependent NO synthases at the low arginine concentration can generate superoxide and hydrogen peroxide. Arginine supplementation may therefore determine synthesis of NO without excessive reactive oxygen species production. The aim of the study was to investigate the influence of arginine administration on the nitric oxide generation and oxidative processes (assessed by selected markers) as well as on the urea synthesis (L-arginine is a precursor of the urea).
L-arginine "in substantia" at the dose of 85mg/kg of body weight was administered (by gastric tube) to the healthy rabbits during 21 days. Urine and plasma samples, taken from animals, were analysed for: (1) nitrite (NO2-) concentration (an indicator of NO generation), (2) total antioxidant status, (3) thiobarbituric acid reactive species (TBARS– lipid peroxidation products), (4) protein carbonyl groups and (5) sulfhydryl groups (protein oxidation products), (6) nitrotyrosine (protein nitration product, a potential biomarker for oxidative stress), and (7) urea concentration.
Arginine administration induced a significant increase in plasma nitrite concentration (2.90 ± 0.72 vs 6.81 ± 0.87, $p<0.001$) and plasma total antioxidant concentration (0.51 ± 0.08 vs 0.63 ± 0.08 mmol/l; p=0.001), decrease in plasma (4.67 ± 1.2 vs 2.67 ± 0.53 μmol/l; $p<0.001$) and urine (23.9 ± 3.2 vs 20.5 ± 4.4 μmol/l; p=0.002) TBARS concentration, and decrease in plasma carbonyl groups concentration (2.62 ± 0.61 vs 1.53 ± 0.24 nmol/mg protein; $p<0.001$). No influence of arginine supplementation on plasma (0.377 ± 0.1 vs 0.354 ± 0.07 nmol/mg protein) and urine (0.0304 ± 0.002 vs 0.0325 ± 0.003 nmol/mg protein) nitotyrosine, and blood sulfhydryl groups concentration (4.45 ± 0.92 vs 4.39 ± 0.69 mmol/l) was found. Plasma urea concentration was not also affected by arginine treatment (45.6 ± 10.1 vs 46.3 ± 9.7 mg/dl).
Conclusions: L-arginine supplementation diminishes significantly oxidative stress and improves nitric oxide generation, that can affect endothelial function. An average administrated arginine doses not have any influence on the urea synthesis.

P1736 Oestrogen downregulates Rac-1 GTPase mediated free radical production

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Background: Rac1 GTPase is essential for the activation of the NAD(P)H oxidase complex and, thereby, regulates the release of reactive oxygen species (ROS) in the vessel wall. 17β-estradiol (E2) inhibits vascular ROS production. To elucidate the underlying molecular mechanisms we investigated the potential regulation of Rac1 by E2 in vascular smooth muscle cells (VSMC).
Methods and Results: Treatment of VSMC with angiotensin II as well as overexpression of the constitutively active mutant RacL61 increased ROS release as assessed by DCF fluorescence, whereas inhibition of Rac1 by Clostridium sordellii lethal toxin or overexpression of dominant-negative RacN17 inhibited ROS production. Treatment with E2 (100 nM) completely prevented angiotensin II induced NAD(P)H oxidase activity and ROS production. E2 time- and concentration-dependently decreased angiotensin II induced and basal Rac1 mRNA and protein expression as well as Rac1 activity. Downregulation of Rac1 expression by E2 was mediated by inhibition of gene transcription (nuclear run-on assays), but E2 had no effect on Rac1 mRNA stability. Regulation of Rac1 was mediated by estrogen receptors since co-incubation with ICI 182.780 prevented downregulation of Rac1.
To test these observations in vivo, ovariectomized spontaneously hypertensive rats were treated with E2 or vehicle. Real-time PCR and western blotting showed reduction of aortic Rac1 mRNA and protein by 32% and 58%, respectively. Furthermore, downregulation of Rac1 by E2 was observed in human mononuclear cells of women with elevated E2 levels after controlled ovarian hyperstimulation.
Conclusion: Rac1 GTPase gene-transcription and activity is regulated by 17β-estradiol, which may be an important molecular mechanism contributing to the cardiovascular effects of estrogens.

P1737 Transcriptional control of telomerase reverse transcriptase in normal endothelial cells. Differences between stimulation by fibroblast growth factor-2 and vascular endothelial growth factor

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Objective: Telomerase plays a major role in the control of replicative capacity, a property critical to successful angiogenesis and maintenance of endothelial integrity. We have previously demonstrated that in normal human endothelial cells telomerase is differentially regulated by fibroblast growth factor-2 (FGF-2) and vascular endothelial growth factor (VEGF), two major pro-angiogenic growth factors. Here we examined the transcriptional control of the catalytic subunit of telomerase, telomerase reverse transcriptase (hTERT), by these endothelial mitogens and report the functional consequences of these differential effects on the onset of senescence.
Methods and Results: In cultured human umbilical vein endothelial cells (HUVEC) both telomerase activity and mRNA levels of hTERT decreased reversibly upon induction of quiescence. Treatment of quiescent HUVEC with FGF-2 restored telomerase activity in a time and dose-dependent manner, whereas VEGF had no such effect, though both factors induced comparable mitogenic responses. FGF-2, but not VEGF, up-regulated the mRNA levels for hTERT and for the hTERT gene transactivation factor Sp1. In contrast, mRNA levels for c-Myc, a second important hTERT transactivation factor, were equally up-regulated by FGF-2 and VEGF, whereas Max and Mad1 mRNA levels were not influenced by the proliferative status of endothelial cells. Finally, serial passage of HUVEC in the presence of individual growth factors accelerated the accumulation of senescent cells in VEGF-treated cultures compared to cultures treated with FGF-2.
Conclusions: In human endothelial cells FGF-2, but not VEGF, up-regulates telomerase activity, telomerase reverse transcriptase and its transactivation factor Sp1, while c-Myc is induced equally by both growth factors. These findings are consistent with a model of cooperation between Sp1 and c-Myc in the transcriptional control of hTERT. FGF-2 was more effective than VEGF in maintaining the replicative capacity of endothelial cells.

P1738 Involvement of phosphorylation in hypoxia-induced heme oxygenase-1 expression in neonatal rat cardiomyocytes

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Background: Hypoxia has been previously shown to induce expression of heme oxygenase-1(HO-1),a stress protein and the rate-limiting enzyme in heme degradation, however, the underlying mechanism is poorly understood. We sought to examine the notion that protein kinases and phosphatases through phosphorylation and dephosphorylation, respectively, modulate the hypoxia-induced HO-1 expression in cardiomyocytes.
Methods: Cultured neonatal rat cardiomyocytes were exposed to normoxia or hypoxia and HO-1 expression was assessed by Northern blot, Western blot and transfection assay.
Results: Exposure of cardiomyocytes to hypoxia markedly induced the HO-1 expression. The hypoxia-induced HO-1 induction was blocked by staurosporine, a broad spectrum inhibitor of protein kinases, and SB202190, a specific inhibitor of p38 kinase, in a dose-dependent manner. Interestingly, hypoxia also caused a decrease in the activity of protein phosphatase-1 (PP-1). To examine the effect of PP-1 inhibition on the HO-1 expression, we utilized the phosphatase inhibitor okadaic acid (OA) or an antisense PP-1 expression vector. OA treatment or overexpression of the antisense PP-1 transcript markedly induced the HO-1 expression. Furthermore, transfection assay using reporter constructs that contain different lengths of the HO-1 promoter revealed the involvement of the NF-kB and AP-1 in the hypoxia-induced activation of the HO-1 gene. The HO-1 promoter activity was markedly increased by OA under normoxic conditions and downregulated by nonselective protein kinase inhibitor staurosporine under hypoxic conditions.
Conclusions: Our results suggest that both activation of protein kinases and downregulation of PP-1 activity contribute to the hypoxia-induced HO-1 expression in cardiomyocytes and that this hypoxic response is likely to be mediated through activation of NF-kB and AP-1.

P1739 JNK and p53 as mediators of nitric oxide-induced apoptosis in cardiomyocytes

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AP-1 has been characterized as a mediator of NO-induced apoptosis in isolated adult cardiomyocytes. The aim of this study was the identification of down- and upstream targets in this signaling cascade of NO-induced apoptosis in ventricular cardiomyocytes of rat.
Since the promotor of the p53 gene has a AP-1 binding site and p53 is involved in several apoptotic processes, we tested if p53 is a downstream target of AP-1 in NO-induced apoptosis. As analyzed in retardation assays, the NO-donor SNAP (100 μM) increased p53-binding activity in cardiomyocytes within 2 h to 151 $\pm$ 17% ($p<0.05$ vs. control, n=9). The induction of p53 by SNAP could be blocked by intracellular scavenging of AP-1 binding activity with AP-1-decoy-oligos (109 $\pm$ 13%, n.s. vs. control, n=9), as well as induction of apoptosis by SNAP was inhibited. Preincubation of cardiomyocytes with p53-decoy oligonucleotides, which scavanged p53 intracellularly, also prevented NO-induced apoptosis (5.0 $\pm$ 1.1% apoptotic cells vs. 10.2 $\pm$ 1.1%, $p<0.05$, n= 5). As an upstream activator of this pathway JNK was identified, since activation of AP-1 and also apoptosis induction by SNAP was inhibited by the JNK-inhibitor D-JNK1 (1 μM). Incubation of cardiomyocytes with D-JNK1 alone did not alter the basal rate of apoptosis.
In conclusion, nitric oxide induces apoptosis in isolated adult cardiomyocytes via activation of JNK, AP-1 and p53.

P1740 The cytochrome P450 2C9 epoxygenase induces angiogenesis via cross-talk with the epidermal growth factor receptor

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Cytochrome P450 (CYP) epoxygenase products, such as 11,12-epoxyeicosatrienoic acid (EET), exert a proliferative effect on endothelial cells. We set out to identify the signal transduction cascade linking EET generation to enhanced proliferation and to determine whether or not EETs are angiogenic factors.
In human umbilical vein endothelial cells (HUVEC) over-expressing CYP 2C9, cell number as well as bromodeoxyuridine incorporation into DNA were increased compared to cells over-expressing a control vector. Both effects were sensitive to the selective CYP 2C9 inhibitor sulfaphenazole. CYP 2C9 overexpression was associated with the activation of Akt and an increase in cyclin D1 expression, effects which were abolished by AG1478, a specific inhibitor for the EGFR tyrosine kinase. AG1478 also prevented the CYP 2C9-induced increase in cell proliferation. Furthermore, stimulation with 11,12-EET or transfection with CYP 2C9 enhanced the release of EGF/HB-EGF by HUVEC. Additionally, exogenous application of EETs led to an increase of the tyrosine phosphorylation of the EGFR, indicating that CYP 2C9-derived EETs activate the EGFR via induction of EGF-secretion.
Since activation of the EGFR tyrosine kinase with EGF induces angiogenesis, we determined whether or not the over-expression of CYP 2C9 induced angiogenesis in an in vitro assay. HUVEC were infected with adenoviral constructs encoding CYP 2C9 or antisense CYP 2C9 and seeded on a fibrin gel. The control virus did not induce endothelial tube formation whereas CYP 2C9 overexpression markedly stimulated tube formation (by more than 6-fold). A similar effect was observed in endothelial cells treated with exogenous 11,12-EET and was comparable with the tube formation induced by EGF. In an in vivo angiogenesis assay (chick chorioallantoic membrane), 11,12-EET stimulated vessel formation (2 to 3-fold) and induced vessel convergence. These results indicate that CYP 2C9-derived EETs stimulate endothelial cell proliferation and angiogenesis. The signalling pathway involves the activation of Akt and the enhanced expression of cyclin D1 and is initiated by activation of the EGFR.

SIGNALLING PATHWAYS IN VASCULAR CELLS AND CARDIAC FIBROBLASTS

P1741 GNB3 polymorphisms is associated with plaque burden in coronary artery disease patients

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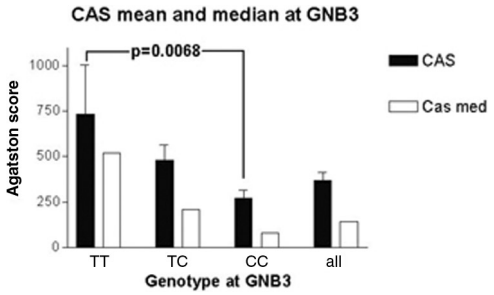
Coronary artery disease (CAD) is a multifactorial disease yet genetic predisposition is under debate. We investigated whether coronary calcium plaque burden (CPB) as an established risk assessment tool for Coronary artery disease (CAD) risk profile is associated with 825T allele of the GNB3 polymorphism. Risk factors of CAD like obesity and hypertension are associated with the polymorphism of the G-protein subunit GNB3.

Methods: 203 male patients (mean age 59 ± 2 years) without history of AMI, with angina or suspicion of CAD were included. Calcium score was measured using EBCT. GNB3 polymorphism (CC (wild), TC, TT; T represents the mutated allele) was detected by standard methods. Age, smoking habits, cholesterol levels and other risk factors were equal in the groups.

Results: Genotyping revealed CC in 105 patients (52%), TT in 16 (8%), and TC in 82 (40%). There was no difference in age and major risk factors between the groups. The mean CAS score was 272.6 ± 445.8 in the CC group, 733.4 ± 978.8 in the TT group, and 478.6 ± 726.1 in the TC group ($p < 0.008$). 72% of the T-allele carriers (n = 85) had a CAS score above the 50th percentile (OR 3,3) compared to 54,2% of CC carriers.



CAS at GNB3 polymorphism.

Conclusion: The 825T allele is associated with CPB in a heterozygos manner. Primary risk evaluation for CAD can be assessed using EBCT calcium score in combination with genotyping for the GNB3 polymorphism.

P1742 Acute manipulation of atherosclerotic plaque characteristics by caspase inhibition should contribute to plaque stability

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Apoptosis is commonly observed within advanced atherosclerotic plaques. Macrophage apoptosis contributes to enlarging lipid core and smooth muscle cell (SMC) apoptosis results in fibrous cap attenuation. Further, significant apoptosis of inflammation cells in fibrous caps leads to cap rupture and acute coronary event. Since apoptosis contributes to plaque vulnerability and rupture, we hypothesize that inhibition of apoptosis in atherosclerosis should be of benefit.

Methods: Atherosclerosis was induced in 27 NZW rabbits by deendothelialization of the abdominal aorta and hyperlipidemic diet (HD) (0.5% cholesterol+6% peanut oil); 5 unmanipulated rabbits were fed normal chow (NC) and used as controls. Animals were randomized as below: Gr.2 (n=6) HD 4 mo; Gr.3 (n=6) HD 3 mo+NC 1 mo; Gr.4 (n=7) HD 4 mo+ Simvastatin (po 1mg/kg/day) last mo; Gr.5 (n=6) HD 4 mo+ ZVAD-fmk (polycaspase-inhibitor, iv 1 mg/kg) 6 and 1 H before imaging on last day; Gr.6 (n=2) HD 4 mo+ YVAD-CHO (caspase1-inhibitor, iv 1 mg/kg) 6 and 1 H before imaging on last day. Tc-99m labeled Annexin-V was used for noninvasive imaging of the extent of apoptosis in atherosclerotic lesions.

Results: Visualization of atherosclerotic lesions by gamma imaging was best in Gr.2 with mean % injected dose/g Annexin uptake of 0.051 ± 0.009, Gr.1: 0.006 ± 0.001, $P<0.05$. HD withdrawal and Simvastatin treatment reduced Annexin uptake significantly, 0.03 ± 0.006 and 0.029 ± 0.007 respectively, $P<0.05$. Short term ZVAD-fmk and YVAD-CHO treatment reduced apoptosis even moreso than diet withdrawal and statin therapy (0.021 ± 0.006; 0.024 ± 0.007, respectively, $P<0.05$). Histopathologic characterization revealed stabilization of plaque with decreased inflammation and increased SMC in diet withdrawal and statin treatment; apoptosis was significantly reduced. In caspase treated groups, although histology characteristics were not altered, apoptosis was completely abrogated. Moreso prevalence and apoptotic index directly correlated with Annexin uptake.

Conclusion: Conventional management strategies in atherosclerosis lead to reduction in apoptosis. Apoptosis can also be acutely manipulated in plaques and is expected to contribute to plaque stabilization.

P1743 Beta2-adrenergic receptor stimulation increases human cardiac fibroblast proliferation via an endothelin 1-dependent autocrine mechanism

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In heart failure patients, myocardial sympathetic nervous activity is increased, resulting in elevated levels of catecholamines that in the long-term are detrimental to cardiac function. Beta-adrenergic receptor (beta-AR) antagonists significantly reduce the remodelling and mortality associated with heart failure. Although catecholamines induce myocyte death and/or hypertrophy, their effects on cardiac fibroblasts, the cells that maintain normal cardiac structure, are less well studied. We recently demonstrated that beta2-AR stimulation increases human cardiac fibroblast proliferation. Since catecholamines are not "classical" growth factors, we hypothesised that beta2-AR stimulation increased proliferation by up-regulating secretion of growth factors that act in an autocrine manner. Human cardiac fibroblasts were cultured from biopsies of right atrial appendage. Conditioned media (CM) were prepared by treating the cells for 48 h with medium containing 2.5% FCS alone to generate C-CM, or 2.5% FCS plus 1 μM isoproterenol, a beta-AR agonist, to generate ISO-CM. When added to other populations of fibroblasts in the presence of a beta-AR antagonist, ISO-CM significantly increased proliferation compared with C-CM ($P=0.007$, n=5), indicative of an autocrine mechanism. The proliferative capacity of ISO-CM was abolished by heat-treatment (80°C), suggesting that the autocrine factors are heat-sensitive.

Cardiac fibroblasts secrete a number of growth factors, including endothelin-1 (ET-1), that have potential to stimulate proliferation in an autocrine manner. We therefore determined the effect of specific ET receptor antagonists on ISO-CM-induced proliferation. Both an ET-A/B receptor antagonist (PD142893, 10 μM) and an ET-A receptor antagonist (BQ123, 1 μM) completely abolished ISO-CM-induced fibroblast proliferation ($P=0.0129$ and 0.0196 respectively, n=5). In contrast, an ET-B receptor antagonist (BQ788, 1 μM) had no effect ($P=0.3699$, n=4). Using an ELISA assay we determined that the median concentration of ET-1 in C-CM was 11.8 pM (range 1.1-15.4). Surprisingly, we observed similar levels in ISO-CM (12.9 pM, range 2.8-16.8), demonstrating that ET-1 is not the autocrine factor itself, but an essential co-factor in this mechanism.

In conclusion, beta2-AR stimulation increases proliferation of human cardiac fibroblasts via a mechanism involving increased secretion of heat-sensitive autocrine growth factors. Although ET-1 is not the autocrine growth factor, it plays an essential role in the mechanism of beta2-AR-induced proliferation.

P1744 Ratjadone is a potent inhibitor of vascular smooth muscle cell proliferation

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Ratjadone was isolated as an orphan ligand from the bacterium Sorangium cellulosum at Cala Ratjada, Spain, in 1994. It exhibits growth advantage towards yeasts and bacteria, and recently, it could be chemically characterized and synthesized. In the present study, the antiproliferative effects of ratjadone (ratj) on human coronary (HCASMSs) and rat aortal vascular smooth muscle cells (rVSMCs) were examined and compared with the effect of rapamycin.
Results: 48 hours after addition of 10 nM Ratjadone to growing cultures of HCASMCs and rVSMCs, cell number was significantly reduced (to 18±4% and 20±3 of control, respectively). MTS-Assays demonstrated a dose dependent effect, starting at remarkably low concentrations (2.5 nM). BrdU-incorporation assays showed that ratjadone suppresses DNA synthesis; no cytotoxicity was observed. Flow cytometric (FACS) analysis revealed that ratjadone induced specifically a cell cycle arrest in G0/1-phase in the vascular smooth muscle cells (10% serum control: G0/1-phase 60%, S-phase 30%; 10 nM ratj: G0/1 75%, S 12%; 100 nM ratj: G0/1 93%, S 1%) without any signs of apoptosis up to 96 hours. In contrast, as a negative control the enantiomeric molecule of ratj (consisting of 3 stereoisomeric, flipped molecule centers) did not exert any growth inhibiting effects. Comparison with rapamycin, another antiproliferativ agent, revealed an approximately 2-3 times stronger inhibitory effect on cell proliferation on a molar base. Western blot analysis did not result in any apparent change in the protein levels of p21, p27 or p53 expression. Concordantly, ratj exhibited a strong antiproliferative effect on p21- and p53-knock out cells. However, immunofluorescence studies revealed an inhibition of the intracellular export shuttle from the nucleus to the cytosol, resulting in an intranuclear accumulation of cell cycle inhibiting proteins as the putative mechanism of the antiproliferative effect of ratj.
Conclusion: The new orphan ligand ratjadone is a potent inihibitor of coronary and aortal smooth muscle cells by inducing cell cycle arrest in G0/1-phase without cytotoxicity. It therefore represents a promising therapeutical substance for drug eluting stents in the treatment of instent restenosis.

P1745 Different cell death rates determine growth of vascular smooth muscle cells from human aortocoronary bypass vessels: implications for radial artery grafts

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Long-term patency of aortocoronary bypass grafts is determined by vascular smooth muscle cell (VSMC) proliferation leading to neointima formation. As long-term patency rates of MA grafts are higher than those of SV, alternative arterial grafts such as the radial artery (RA) are used increasingly. Radial artery (RA) patency rates seem to be in between those from mammary artery (MA) and saphenous vein (SV). In the present study, we investigated how growth of VSMC in response to PDGF-BB is regulated in RA and how this compares to MA and SV. After 6 days of serum stimulation, RA-VSMC number (51'520±7'538) was lower than SV (69'750±11'588), but higher than MA (28'365±6'324) (SV vs. MA: $p<0.01$; SV or MA vs. RA: p=n.s.; n=4). In contrast, RA-VSMC exhibited only minimal proliferation to PDGF-BB, (15'493±2'116), which was comparable to MA (15'446±2'768; MA vs. RA: p=n.s.) and differed from SV (33'094±3'028; SV vs. RA or MA: $p<0.01$; n=4). Consistent with growth rates, 3H-thymidine incorporation was significantly lower in RA (150±21 DPM/1000 cells) and MA (138±20) as compared to SV (269±14) (RA vs. MA: p=n.s., RA or MA vs. SV: $p<0.001$; n=4. As determined by FACS analysis, PDGF receptor alpha expression was similar (p=n.s.; n=5), whereas PDGF receptor beta expression was higher in RA as compared to MA or SV (RA vs. MA or SV: $p<0.05$; MA vs. SV: p=n.s.; n=5). Western blotting confirmed these findings. Propidium iodide incorporation after PDGF stimulation showed identical cell cycle distribution in VSMC from all three vessels. Similarly, Western blotting for cell cycle proteins after PDGF treatment revealed identical expression: the cyclin-dependent kinase inhibitor (CKI) p27 was downregulated, the CKI p21 was slightly induced, while the CKI p57, cyclin-dependent kinase 2 (cdk2) and cyclin E did not show any change. Cdk2 kinase assay confirmed that G1 progression was identical in VSMC from all three vessels. The percentage of dead cells in each population was determined by counting the floating cells using FACS analysis. There occurred more cell death in MA (27.9±6.8%) and RA (28.9±7.7%) as compared to SV (20.5±6.0%; n=4). Similarly, LDH release was higher in MA and RA as compared to SV (MA vs. SV: $p<0.05$; RA vs. MA or SV: p=n.s., n=5). Thus, cell cycle progression is identical in VSMC from human bypass vessels, while different cell death rates determine growth, suggesting that VSMC death rather than proliferation may account for the different patency rates of bypass grafts. The weak effect of PDGF in RA as compared to SV encourages the clinical use of RA grafts.

P1746 Promoter region polymorphisms of matrix metalloproteinases and their influence on plaque rupture

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Background – The rupture of the fibrous cap which protects the atherosclerotic plaque from the bloods thrombogenic particles is a key event in precipitating acute coronary syndromes (ACS). Matrix metalloproteinases (MMPs) may accentuate weakening of the plaque and therefore favour plaque rupture. Interstitial collagenase, a member of the MMP family specifically cleaves fibrillar collagens I, II and III. These collagens are tightly coiled, have a highly cross-linked structure and are usually extremely resistant to most proteinases. This suggests that MMP1 may have important role in plaque rupture. A common variant (G/GG) in the promoter of the MMP 1 gene has been identified. The polymorphism involves a guanine (-G-) addition/deletion at the position -1607bp relative to the start codon. This has been shown to increase levels of expression of MMP1 in vitro. The functional significance of the MMP1 promoter polymorphism has not been addressed in cardiovascular disease.
Methods and Results: We investigated the relationship between the G/GG polymorphism and plaque rupture by conducting a case-case study. We compared the frequency of MMP promoter polymorphisms in 200 patients presenting for the first time with either stable angina (stable plaque, n=85) or ACS (unstable plaque, n=115). Genotypes were identified by nested PCR and restriction enzyme digestion. There was a trend towards increased prevalence of the G/G + G/GG genotype in the stable cohort (81%), compared with the ACS cohort (75%) which was independent of other traditional risk factors (p=0.07).
Conclusion – This data suggests that the genetic variation influences MMP1 gene promoter activity in an allele specific manner. Patients who are homozygous or heterozygous for the single G allele may benefit from a stabilising effect of reduced enzyme expression. This in turn could influence the phenotypic expression of patients with coronary artery disease. On-going studies, with a larger cohort are required to clarify MMP 1's role in atherogenesis and plaque rupture.

P1747 Peroxisome proliferator-activated receptor gamma inhibits expression of minichromosome maintenance proteins in vascular smooth muscle cells

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Partial agonists for the peroxisome proliferator-activated receptor gamma (PPARg) have a weaker transcriptional activation activity for the receptor than full agonists but have equal or greater potency in inhibiting vascular smooth muscle cell (VSMC) proliferation. Using a cDNA array consisting only of cell cycle genes, we found that a novel non-thiazolidinedione partial PPARg agonist (nTZDpa) inhibited expression of minichromosome maintenance (MCM) proteins 6 and 7 in rat aortic VSMC. MCM proteins are required for the initiation and elongation stages of DNA replication and are regulated by the transcription factor E2F. Mitogen-induced MCM6 and MCM7 mRNA and protein expression was potently inhibited by nTZDpa (100%, 97.6 ± 6.1% inhibition vs. PDGF+insulin after 24 h (10 mM), respectively, n=3, $p<0.05$) and to a lesser degree by the full PPARg agonist, rosiglitazone (RSG) (44.3 ± 4.1%, 64.1 ± 5.4% inhibition vs. PDGF+insulin after 24 h (10 mM), respectively, n=3, $p<0.05$). Inhibition of MCM6 and MCM7 expression by nTZDpa and RSG paralleled their effect to inhibit phosphorylation of the retinoblastoma protein and cell proliferation. Transient transfection experiments revealed that the nTZDpa inhibited mitogen-induced MCM6 and MCM7 promoter activity implicating a transcriptional mechanism (82.1 ± 7.9%, 84.7 ± 7.3 inhibition, n=3, $p<0.005$). Adenoviral-mediated E2F overexpression reversed the suppressive effect of nTZDpa on MCM6 and MCM7 expression. Furthermore, activity of a luciferase reporter plasmid driven by multiple E2F elements was inhibited by nTZDpa indicating that their downregulation by nTZDpa involves an E2F-dependent mechanism (86.9 ± 6.8% inhibition vs. PDGF+insulin after 24 h (10 mM), n=3, $p<0.005$). Overexpression of dominant-negative PPARg or addition of a PPARg antagonist, GW 9662, blocked nTZDpa inhibition of MCM7 transcription. Adenovirus-mediated overexpression of constitutively-active PPARg inhibited MCM7 expression in a similar manner as the nTZDpa. These findings provide strong evidence that nTZDpa attenuates MCM7 transcription by binding to and activating PPARg and support the important role of this nuclear receptor in regulating VSMC proliferation.

P1748 HIV protease inhibitor ritonavir inhibits platelet-derived growth factor-BB-induced migration and proliferation of vascular smooth muscle cells

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HIV protease inhibitors (PIs) such as Ritonavir have dramatically decreased HIV-related morbidity and mortality. However they exhibit significant side-effects such as hyperlipidemia, hyperglycemia and obesity, which yield patients to increased risk for atherosclerosis. Direct effects on the vessel wall may further increase or counteract the vascular risk but have not yet been investigated. Platelet-derived-growth-factor (PDGF) is an important contributor to atherogenesis. Here we evaluated the effects of Ritonavir on PDGF-BB-induced responses of vascular smooth muscle cells (VSMCs).
Pretreatment of VSMCs with Ritonavir resulted in a significant concentration- and time-dependent inhibition of PDGF-BB-dependent cellular responses. At a therapeutic concentration of Ritonavir (10 μg/ml) PDGF-induced DNA-synthesis and -chemotaxis were significantly reduced by 34,7±9,4% and 42,1±12,2%, respectively ($p<0.05$ each). These inhibitory effects were not due to cytotoxicity or apoptosis, as measured by LDH-release- and apoptosis-assays, whereas higher concentrations (100 μg/ml) exhibited cytotoxic effects. Instead, western-blot-analyses revealed, that Ritonavir inhibited the ligand-induced tyrosine phosphorylation of the betaPDGF-receptor (betaPDGFR) and PDGF-induced downstream events such as activation of MAP kinase (Erk 1/2), whereas it did not alter betaPDGFR expression.
We conclude, that the HIV PI Ritonavir has direct effects on VSMCs at therapeutic concentrations in vitro, as it inhibits betaPDGFR activation and PDGF-dependent proliferation and migration of VSMCs. Although the metabolic side effects of Ritonavir may increase the risk of vascular disease, it may exert beneficial effects against atherogenesis on the cellular level.

P1749 The regulation of the bFGF-induced cell cycle progression of human cSMC depends on distinct functions of the serine/threonine phosphatases PP1 and PP2A

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The growth factor induced proliferation of human coronary smooth muscle cells (cSMC) contributes to the pathogenesis of restenosis and arteriosclerosis. Basic fibroblast growth factor (bFGF) has been shown to be a powerful mitogen for cSMC by switching on the mitogen activated protein kinase (MAPK) pathway. The extend of protein phosphorylation within the signalling pathways is controlled by the opposing actions of protein kinases and protein phosphatases. To elucidate the cascades of phosphorylation and dephosphorylation we investigated the role of the serine/threonine phosphatases PP1 and PP2A in the bFGF-induced cell cycle progression of cSMCs.
Preincubation of cSMC with the PP1 and PP2A specific inhibitor calyculin A leads to a decrease in bFGF-induced DNA synthesis demonstrated by [3H]-thymidine incorporation assay. However phosphorylation of the MAPK is increased compared to cSMC that have been stimulated with bFGF alone. To distinguish between the role of PP1 and PP2A in bFGF-induced proliferation of cSMC we preincubated the cells with the PP1 specific inhibitor tautomycin and the PP2A specific inhibitor fostriecin, respectively. Preincubation of cSMC with tautomycin effectively blocks the bFGF-induced DNA synthesis and reduces the expression of the proliferation marker proliferating cell nuclear antigen (PCNA), but has no effect on the bFGF-induced MAPK phosphorylation level. In contrast, fostriecin treatment leads to an increase in bFGF-induced proliferation accompanied by an increase in MAPK phosphorylation. Fostriecin does neither affect the activation of the MAPK stimulating Ras-Raf-MEK cascade nor does it influence the bFGF-induced stimulation of PKC activity, demonstrating that the enhancement of the MAPK phosphorylation is due to the inhibition of MAPK dephosphorylation by PP2A.
These results demonstrate that the serine/threonine phosphatase PP2A is a negative regulator of the bFGF-induced proliferation whereas the positive regulator PP1 has no effect on this signalling pathway. In this regard, the PP1 specific enzyme activity may be involved in processes downstream of the MAPK cascade regulating cell proliferation.
Taken together, our results suggest that the phosphatases PP1 and PP2A play an important role in the growth factor stimulated cell cycle progression and are interesting therapeutic targets for preventing the progression of arteriosclerosis and restenosis.

INFLAMMATION AND ATHEROSCLEROSIS: FOCUS ON C-REACTIVE PROTEIN, CD40 LIGAND AND ADHESION MOLECULES

P1750 Increased C-reactive protein and adhesion molecule levels in stable angina patients with rapid coronary artery disease progression

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Background: Studies have shown that endothelial activation and inflammation play a significant role in atherogenesis and may determine atherosclerotic plaque vulnerability. There is also evidence that subclinical episodes of disruption of vulnerable coronary plaques with local thrombus formation and subsequent healing may represent a mechanism for coronary artery disease (CAD) progression. The aim of this study was to investigate the association between C-reactive protein (CRP) and endothelial adhesion molecule levels, and rapid angiographic CAD progression in patients with chronic stable angina (CSA).
Methods: We studied 131 CSA patients (87 men, mean age: 60.5±9.6 yrs) who were on a waiting list for routine coronary angioplasty and underwent coronary angiography on two occasions: the first (diagnostic) angiogram was carried out at study entry and the second immediately prior to coronary angioplasty. Differences in stenosis diameter between the two angiograms were assessed using a digital quantitative angiographic analysis system and CAD progression was determined by the following criteria: >10% diameter reduction of a pre-existing stenosis >50%, >30% diameter reduction of a stenosis <50%, progression of any lesion to total occlusion and the development of a new lesion >30% in a previously normal segment. CRP was measured using a high sensitivity ELISA immunoassay, whilst soluble Intracellular and Vascular Cell Adhesion Molecule-1 (sICAM-1 and sVCAM-1) were assessed by a quantitative sandwich immunoassay technique.
Results: During the time on the waiting list (4.8±2.4 months) rapid CAD progression occurred in 36 (27.5%) patients according to the above criteria: Baseline demographic, clinical and angiographic data were similar in patients with and those without progression. CRP levels were found significantly increased in patients with CAD progression compared to those without (1.34[0.73-4.01] μg/ml vs 0.84[0.52-1.74] μg/ml; P=0.008). sICAM-1 was also significantly higher in these patients (305.4±57.5 ng/ml vs 261.5±42.5 ng/ml; $P<0.005$). sVCAM-1 levels, although higher in CAD progression patients, did not differ significantly between groups. Logistic regression analysis also revealed that patients with CRP levels >3μg/ml had almost a 3-fold higher risk (Odds ratio 2.9, 95% CI: 1.1-7.0) to develop rapid CAD progression.
Conclusions: Our findings indicate that inflammatory mechanisms involving endothelial activation may play a significant role in rapid coronary artery disease progression in patients with chronic stable angina.

P1751 Predictors of serum C-reactive protein concentrations in patients with chronic stable angina

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Purpose: The acute-phase reactant C-reactive protein (CRP) is an independent predictor of future cardiovascular events. Whether raised CRP levels represents a response to inflammation within atheromatous plaques or whether they are the result of systemic inflammation leading to atherogenesis, or both, is speculative at present. We compared the impact of extent and severity of coronary artery disease (CAD) versus established CAD risk factors, particularly those encompassed by the metabolic syndrome, on CRP levels. **Methods:** We studied 700 consecutive patients (mean age 63±10 years, 75% men) with chronic stable angina (CSA). High sensitivity serum CRP (hs-CRP) was measured on the COBAS Integra (Roche Diagnostics Limited, Lewes, East Sussex, UK). Multivariate analysis used linear regression analysis for continuous dependent variables and binary logistic regression analysis for discrete variables.
Results: Baseline hs-CRP concentrations were higher in the elderly (P=0.001), in patients with a history of myocardial infarction (P=0.03) and smokers (P=0.002). A significant correlation was also found between hs-CRP levels and hypertension (P=0.004), body mass index (BMI) (r= 0.16, $P<0.0001$) and serum triglyceride levels (r= 0.15, P=0.003). Hs- CRP levels, however, were not significantly associated with total cholesterol concentrations (P=0.08), CAD severity, as assessed by the number of coronary vessels with ≥50% stenosis or treatment with aspirin or HMG-CoA reductase inhibitors. Multiple regression analysis showed that only age (P=0.02), gender (P=0.009), BMI ($P<0.0001$), smoking (P=0.02) and serum triglyceride levels (P=0.004) were independent predictors of serum CRP concentrations, in this study.
Conclusion: CRP concentrations raise with increasing age, smoking, female gender, BMI and serum triglyceride levels. The relationship found here between hs-CRP and components of the metabolic syndrome suggests that inflammation could be the common link between obesity, metabolic abnormalities and cardiovascular disease.

P1752 C-reactive protein is related to impaired endothelium dependent relaxation and increased angiotensin II response

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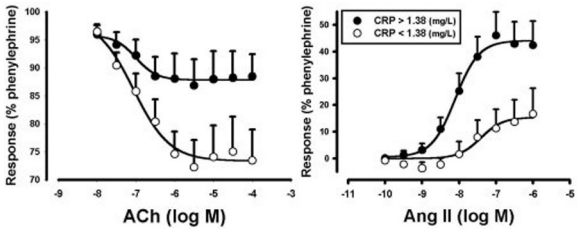
Objective Inflammation is thought to play a central role in the aetiology and outcome of atherosclerosis. C-reactive protein (CRP), a sensitive marker of inflammation, is an important risk indicator for cardiovascular disease. However, the mechanisms underlying this association are not completely understood. We hypothesised that elevated levels of serum CRP are related to impaired endothelium dependent relaxation and increased angiotensin II (Ang II) response.
Methods The study group consists of 23 patients, from who blood samples and segments of the internal mammary artery were obtained during coronary bypass surgery. Measurements of endothelium dependent relaxation were performed in organ baths by adding acetylcholine (ACh, 10nM-100μM). After a washing and stabilisation period constriction to cumulative doses of Ang II was evaluated (0.1nM-1μM). High-sensitive CRP was determined by nephelometry.
Results As shown in the figure, CRP levels above median (>1.38mg/L) are associated with decreased relaxation to ACh and increased constriction to Ang II, respectively (both $p<0.05$).



Conclusion Elevated serum CRP levels are related to decreased endothelium dependent relaxation and increased constriction to Ang II. These findings could be the link between CRP and the development of atherosclerosis. In addition, these data suggests a potential beneficial role of ACE-inhibitors in patients with elevated CRP levels.

P1753 Children with familial hypercholesterolaemia express inflammatory markers. Pravastatin effect on neopterin but not on C-reactive protein

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Background: Atherosclerotic disease involves inflammatory and immunologic mechanisms, but the sequence of immunomodulatory steps and which molecule(s) having key roles early in atherogenesis is not clear. High sinsitive C-reactive protein (hsCRP) is established as an inflammatory marker of atherosclerosis. Neopterin, a marker of cellular immune activation, is produced by human macrophages. HMG-Co A reductase inhibitors, statins, have been recognized as immunomodulators and reduce cardiovascular events and mortality.
Objectives: In this study we examined the levels of neopterin and mikroCRP in children with familial hypercholesterolemia (FH) because FH has been regarded as a model of atherosclerosis. We evaluated the impact of pravastatin.
Methods: Children aged 8-18 years, with FH (n=157) and 74 unaffected siblings, were randomised in a double blind fashion and given pravastatin 40 mg bid (n=77) or placebo (n=80) and followed for 2 years.
Results: There were no differences between the the groups concerning demographic data. The children with FH had a significant ($p<0.009$) elevated level of neopterin compared to normal siblings (4.89$\pm$0.21 nmol/L vs 4.33$\pm$0.14 nmol/L respectively). Furthermore, 2 years of pravastatin therapy reduced the neopterin level with 15% ($p<0.001$) to 4.23$\pm$0.13 nmol/L compared to placebo which had a 7% reduction (4.6+0.18 nmol/L). There were no difference between the FH-children (0.11$\pm$0.02 mg/L), siblings (0.10$\pm$0.03 mg/L) and controls (0.07$\pm$0.03 mg/L) concerning hsCRP at baseline. Furthermore, hsCRP increased in both FH-children receiving pravastatin (0.25$\pm$0.09 mg/L) and placebo (0.17$\pm$0.095 mg/L) after 2 years.
Conclusion: Our findings suggest that children with FH are characterized by an inflammatory element (m-CRP) with enhanced immun activity (neopterin) and that pravastatin modifies the cellular immune respons, neopterin, but not m-CRP.

P1754 Atorvastatin suppress the expression of CD40 ligand and P-selectin on platelet in patients with hypercholesterolaemia

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Background: Hypercholesterolemia (HC), a risk factor for cardiovascular disease, is associated with inflammation and the prothrombotic state. Recently CD40-CD40 ligand interaction and the activation of platelet was claimed to play a major role in the pathogenesis in atherosclerosis. The aim of this study was to characterize the in vitro expression of CD40 ligand (CD40L) and p-selectin in patients (pt) with HC, and to investigate whether atorvastatin (ATOR) - a potent lipid-lowering agent can influence the level of these molecules and TNF-α.
Methods: 22 patients with polygenic HC (total cholesterol > 220 mg/dl or LDL > 130 mg/dl) without other associated inflammatory disease and 18 normal controls were enrolled in this study. Blood samples were obtained before and after 8 weeks of ATOR (10 mg/day) therapy in patient group. After isolation, half of the platelets were stimulated by the addition of ADP (5 μmol/L). Flow cytometry was used to analyze the expression of CD40L and p-selectin. TNF-α was measured by ELISA.
Results: Befoer treatment, there was no signeficent differences of CD40L and P-selectin between control and pts group inspite of with or without ADP stimulation. However, after Lipopolysaccharide stimulation, the levels of TNF-α and IL-1B were higher in the pts group. In addition, there was a significant correlation between CD40L and P-selectin, in spite of with or without ADP stimulation. There was a negative correlation between P-selectin level and HDL-C ($p=0.025$, $r=-0.476$). After 8 weeks of ATOR, the levels of LDL, LDL/HDL and total-cholesterol decreased significantly ($p=0.001$, $p=0.001$, $p=0.001$, respectively). After treatment, the level of P-selectin, whether with or without ADP stimulation,all decreased significantly ($p=0.008$, $p=0.018$, respectively). The levels of CD40L decreased significantly after ADP stimulation ($p=0.009$).
Conclusions: In this short term study, ATOR not only decreased the cholesterol levels, but also can down-regulated the expression of CD40L and P-selectin on platelet in patients with HC. We supposed that in HC pts, in addition to its effect on decreasing the cholesterol level, ATOR can intervene the interaction of CD40-CD40L and the expression of P-selectin which may alleviate the prothrombotic potency of platelets in pts with HC.

P1755 Role of superoxide anion in inducing CD40 ligand expression by human platelets

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Background: CD40 ligand, a transmembrane protein structurally related to the cytokine, is an important mediator of inflammation involved in the atherosclerotic process.CD40 ligand is expressed by a variety of inflammatory cells and by platelets. Circulating levels of CD40 ligand are prevalently of platelet origin and are predictors of cardiovascular events. Several platelet agonists such as ADP, thrombin and collagen elicit CD40 ligand expression,but the intrinsic mechanism is still to be fully elucidated.
Methods: a cytofluorimetric analysis of CD40 ligand expression was performed on washed human platelets stimulated at 37C° for 10 min with collagen (n=5) in presence or not of AACOCF3(15 mM)(an inhibitor of PLA2), DPI (50 mM)(an inhibitor of NADPH oxidase), SOD (300 U/ml) and ascorbic acid (100 mM)(O2- scavengers), catalase(500 U/ml)(H202 scavenger), manni tol (5mM) (OH scavenger) and vitamin E (250 mM)(an inhibitor of lipid peroxidation).
Results: AACOCF3 significantly inhibited CD40ligand expression induced by collagen and arachidonic acid, suggesting a role for arachidonic acid pathway activation as stimulus for CD40ligand expression. Platelets incubated with DPI and stimulated with collagen, showed a significant inhibition (-78% $p<0.05$) of CD40L expression. Incubation of platelets with several antioxidant agents demonstrated that SOD (-75% $p>0.05$) and ascorbic acid (-68% $p<0.05$) but no vitamin E, mannitol and catalase, inhibited collagen induced CD40L expression
Conclusions: The results of the present study show for the first time a role for superoxide anion (O2-) in inducing platelet CD40 ligand expression and suggest that specific scavenger of O2- may be useful for decreasing CD40 ligand plasma levels in human.

P1756 Soluble CD40l and cardiovascular risk in patients with asymptomatic carotid plaque

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Purpose: Inflammation is a key feature of the development of atherosclerotic plaque. CD40 ligand (CD40L) mediates several processes in atherogenesis and can be released from activated platelets. Soluble CD40L (sCD40L) levels may predict patients with features suggestive of high-risk plaque. We tested the hypothesis that sCD40L may prospectively predict the risk of cardiovascular (CV) events in patients with asymptomatic carotid plaques.
Methods: . We enrolled 42 outpatients with asymptomatic carotid stenoses greater than 15% in either internal or common carotid artery and 21 control subjects without any carotid stenosis matched for age, sex and smoking habit. All subjects had at least a major cardiovascular risk factor (CRF). Plasma levels of CRP, IL-6, TGF-b1, and sCD40L were measured. Subjects underwent follow-up examinations every 12 months, or when they experienced a clinical CV event, such as myocardial infarction, angina, stroke, transient ischemic attack, carotid endarterectomy, or intermittent claudication. Planned duration of follow-up was in median 8 years.
Results: Patients with asymptomatic low-grade carotid stenosis had significantly higher levels of CRP ($p<0.0001$), IL6 ($p<0.0001$), TGF-b1 ($p<0.0001$) and sCD40L ($p<0.0001$) than controls. Soluble CD40L significantly correlated with CRP (Rho=0.59, $P<0.0001$). Moreover, sCD40L plasma levels were higher in patients compared to controls irrespectively of any CRF. During follow-up, 14 (33%) patients experienced a CV event. Only high sCD40L levels [Hazard Ratio: 5.96; 95% confidence interval, 1.83 to 19.42, p=003] independently predicted the risk of CV events.
Conclusions: High levels of sCD40L may prospectively predict the risk of CV events in patients with asymptomatic carotid plaque.

P1757 Leukocyte but not endothelial cell adhesion molecules are increased in patients with hypercholesterolaemia: the effect of atorvastatin treatment

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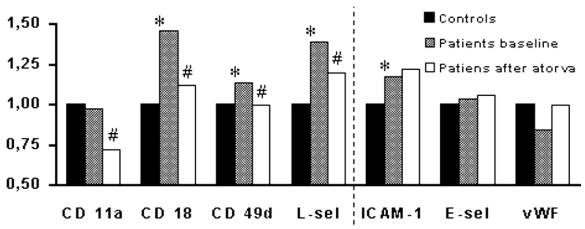
Background: Leukocyte infiltration into subendothelial space plays an important role in atherogenesis. Transendothelial migration of leukocytes is mediated by endothelial and leukocyte cell adhesion molecules (CAM). Endothelial expression of CAM can only be assessed indirectly, through measurement of their serum levels; leukocyte CAM, however, can be measured directly. We have therefore hypothesised that leukocyte CAM are more altered than serum endothelial CAM in patients with hypercholesterolemia.
Methods: We examined 32 otherwise healthy subjects with severe hypercholesterolemia and 26 age-matched controls. Patients were examined at baseline and after 12 weeks of atorvastatin treatment (20 mg/day). Expression of beta 1 and 2 integrins (CD11a,b, CD18, CD49d) and of L-selectin on peripheral blood leukocytes was quantitated by flow cytometry. Serum ICAM-1, E-selectin and vonWillebrand factor (vWF) were measured by ELISA.
Results: Expression of leukocyte CAM (left) and serum levels of endothelial CAM (right) are shown in a Figure; results are normalised to the values in controls (* $p<0.05$ patients at baseline vs. controls; # $p<0.05$ patients after atorvastatin vs. baseline).



Conclusion: Leukocyte CAM (except for CD11b) were significantly increased in patients with hypercholesterolemia. Atorvastatin significantly decreased expression of all leukocyte CAM tested; this may have an important role in the protective effect of atorvastatin. In contrast, there was nearly no effect of hyperlipidemia and/or atorvastatin treatment on the endothelial CAM. Leukocyte expression of CAM may therefore be a more sensitive marker of atherogenesis than endothelial CAM. Supported by research project J 13/98 11110000 2-1.

P1758 Ethanol inhibits monocyte adhesion and monocyte chemotactic protein-1 expression in interleukin-1β-activated human endothelial cells

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Moderate alcohol consumption is associated with a reduced incidence of cardiovascular disease, but the precise mechanisms involved are unknown. Monocyte chemotactic protein-1 (MCP-1) plays a key role in the pathogenesis of atherosclerosis by recruiting monocytes to the subendothelial space. The aim of this study was to determine the effect of ethanol (EtOH) on the endothelial production of MCP-1. **Methods:** Human umbilical vein endothelial cells (HUVEC), passages 3-5, were used in all experiments. HUVEC were pretreated with or without EtOH (1.0-100 mM) for 2 h before being stimulated with interleukin 1-beta (IL-1b, 1 ng/ml), in the absence or presence of EtOH, for various periods of time (0.5 – 24 h). MCP-1 levels in culture supernatant were determined by ELISA, and MCP-1 mRNA was measured by Northern blot analysis. Monocyte adherence experiments were performed using 3H-thymidine labeled THP-1 cells, a human monocytic cell line. **Results:** EtOH treatment decreased monocyte adhesion to IL-1b-activated HUVEC, when compared to control (untreated but activated) cells; ~25 and 50% inhibition for 10 mM and 100 mM EtOH, respectively. IL-1b increased the production of MCP-1 by HUVEC in a time-dependent manner from an undetectable level to approximately 900 pg/ml within a 24 h time period. EtOH dose-dependently inhibited IL-1b-stimulated MCP-1 secretion; 25±1%, 35±7% and 65±5% inhibition for 1, 10 and 100 mM EtOH, respectively, at 2 h (n=3, $p<0.05$ vs control). Similarly, EtOH dose-dependently inhibited IL-1b-stimulated MCP-1 mRNA expression; 37±8% and 45±1% inhibition for 20 mM and 100 mM EtOH, respectively (n=3, $p<0.05$ vs control), in the absence of any effect on mRNA stability. As determined by nuclear run-on assay, IL-1b stimulated MCP-1 gene transcription ~30 fold at 30 mins. EtOH (20 mM) inhibited this transcriptional activity by 63%. **Conclusion:** In conclusion, ethanol inhibited IL-1b-induced MCP-1 mRNA gene expression and protein secretion, and decreased monocyte adhesion to activated endothelium. These data suggest that ethanol could inhibit atherogenesis by blocking the crucial early step of monocyte adhesion and subsequent recruitment to the subendothelial space. These actions of ethanol may underlie, in part, its cardiovascular protective effects in vivo.

EXPERIMENTAL STUDIES OF VASCULAR INFLAMMATION

P1759 Rabbit foam cell media induce collagenase-1 and -8 expression in human monocyte/macrophages independently of CD40 ligand

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Matrix metalloproteinases (MMPs) contribute to the destruction of the extracellular matrix at the shoulder regions of atherosclerotic plaques, leading to plaque instability and aneurysm formation. The interstitial collagenases (MMPs-1, -8, –13 and -14) are the principal enzymes capable to cleave fibrillar collagens types I and III, the major load bearing collagens in the fibrous cap. Loss of these collagens and neoepitopes of degraded collagens have been detected in rupture-prone atherosclerotic plaques and are associated with macrophages. We previously demonstrated that human monocyte derived macrophages secrete MMP-9 constitutively and MMP-1 in response to CD40 Ligand (CD40L). On the other hand, rabbit foam cell macrophages constitutively secrete high levels of MMP-1, which implies the presence of unidentified endogenous regulators. To determine whether soluble autocrine factors produced by rabbit foam cells stimulate MMP-1 secretion we incubated conditioned medium with human monocyte derived macrophages. Human MMP-1 expression was determined using species selective RT-PCR and specific ELISAs. Attention was extended also to the other interstitial collagenases (MMP-8, -13 and -14).
CD40L substantially increased MMP-1 mRNA from undetectable levels in human monocyte derived macrophages and this increase was inhibited (98±5% n=3, $p<0.0009$) by a CD40L blocking antibody. Interestingly rabbit foam cell conditioned medium also stimulated MMP-1 mRNA levels to (117±11.5%, n=3) of the level with CD40L but this was not inhibited (5±2.3%, n=3) by anti-CD40L. ELISA confirmed these observations at the protein level. Similarly to MMP-1, upregulation of MMP-8 mRNA and protein was enhanced by CD40L and foam cell conditioned medium and was blocked competently by anti-CD40L in cells treated with CD40L (100%, n=3) but only partly in foam cell conditioned medium (58±3%, n=3). In contrast, no enhancement of MMP-13 expression could be observed by CD40L or conditioned medium and constitutive expression of MMP-9 and -14 was not enhanced either. These results imply that 1) rabbit foam cells secrete a soluble stimulatory factor or factors that selectively increase the expression of MMP-1 and -8 in human monocyte derived macrophages; 2) this factor is not soluble CD40L 3) this factor has no affect on MMP-9 or -14 expression. The nature of the factor(s) stimulating secretion of MMP-1 and MMP-8 in foam cell media is under investigation.

P1760 Local macrophage accumulation in atherosclerotic rabbit aortas as determined by a novel three-dimensional histology technique

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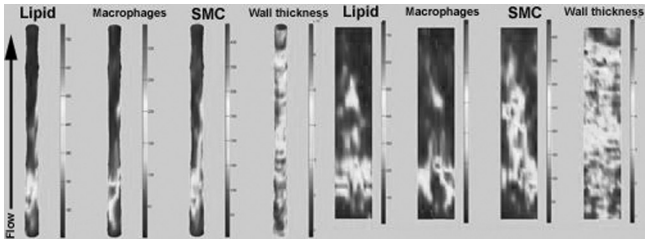
Background: Plaque rupture has been reported to occur mainly upstream of the plaque. As a high activity of macrophages has been implied in plaque rupture, we have developed a novel 3D histology technique which enables to evaluate whether macrophages accumulate specifically upstream of the plaque, and whether this is accompanied by less smooth muscle cell accumulation, or a high lipid accumulation.
Methods: The plaque was generated in abdominal rabbit aortas by feeding a high cholesterol diet for two months in combination with denudation. At the day of sacrifice, a pull back was performed applying a standard IVUS imaging system (40 MHz, CIVUS, Boston Scientific). The vessel segments was isolated, dissected, and frozen. 3D histological reconstructions were performed by i) cutting the frozen blood vessel in well defined 2mm segments, ii) sectioning (cryostat) and staining (smooth muscle cell (SMC), lipids (L), and macrophage cell (MF) densities (%)), iii) applying a longitudinal external marker, iv) reconstruct the slices in 3D with in house developed software, and v) project the 3D histological reconstruction on a 3D reconstruction of IVUS derived lumen contours.
Results: All rabbits displayed clear cellular heterogeneity of plaque composition (figure). Clearly, macrophage accumulated upstream of the plaque. In addition, a positive relationship between macrophage number and lipid accumulation and an inverse relationship between smooth muscle cell accumulation and macrophage accumulation was found.



Conclusions: A novel 3D histological technique demonstrated a predominant macrophage accumulation upstream of the plaque. This might be result from an increased lipid accumulation, leading to a decreased smooth muscle cell accumulation.

P1761 Crucial role for both chemokines receptors CCR2 and CXCR3 in atherogenesis

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Recruitment of mononuclear leukocytes (macrophages and T lymphocytes) within atherosclerotic lesions is a critical feature of the chronic inflammatory and fibroproliferative response central to the process of atherosclerosis. Attraction of leukocytes to tissues is controlled by chemokines, which have been implicated in the early phases of atherosclerosis. The role of CCR2, highly expressed on macrophages, but also on SMCs and T lymphocytes, especially on Th1 T cells, is of a major impact for inflammatory processes during atherogenesis. Indeed, mice lacking CCR2 receptor have a striking reduction of atherosclerotic lesion extent. The chemokine-receptor CXCR3 has been identified on several cells of hematopoietic lineage, including T and B lymphocytes, and natural killer cells. In addition, expression of CXCR3 has been indicated as a marker of polarization of the T helper subset of T cells toward a Th1 phenotype, the principal T lymphocyte type detected within atheroma. To investigate whether the deletion of the two major receptors expressed on the two principal inflammatory cell types present within atheroma could have additional effects on atherogenesis in vivo, we crtossed ApoE-/- mice either with CCR2-/- or CXCR3-/- mice, or crossed ApoE-/- CCR2-/- mice with the CXCR3-/- mice in order to obtain the triple knockout line. Mice of 8 weeks old were fed for 10 weeks with a high-cholesterol diet (0% cholate) to induce atherosclerotic lesions. All mice remained alive and displayed normal behavior. The triple knockout mice displayed a reduced atherosclerotic development on aortic valves and abdominal aortas compared to ApoE-/- mice as well as to both double knockout lines ApoE-/- CCR2 -/- and ApoE-/- CXCR3-/-. These results were associated with a reduced number of inflammatory cells within the lesion as well as to the expression to some important pro-inflammatory molecules such as CCR5, MIP-1a, MIP-1b and MIP-2.

In conclusion, blocking chemokine signalling in vivo through deletions of the chemokine-receptors CCR2 and CXCR3 have additional effects on the development of atherosclerotic lesion. Due to the increasing role of inflammation during atherogenesis, these findings indicate that blocking chemokine receptor/ligand interactions through multiple combinations may lead to effective therapeutic strategies to reduce the evolution of this common disease.

P1762 Effect of fish oil supplementation on the development of atherosclerosis in murine models

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Intake of fish oils is associated with protection against coronary heart disease and sudden death, but their effect on atherosclerosis is controversial. We explored the effects of supplementing fish oil (rich in n-3 PUFAs) or corn oil (rich in n-6 PUFAs) in two different models of atherosclerosis.
69 apoE-/- mice and 63 LDLR-/- mice, each randomized in 3 groups, were fed experimental diets supplemented with either 1% fish oil (FO;Omacor), 1% corn oil (CO), or no oil; alfa-tocopherol content was matched in all preparations. Fresh diets were provided daily. After 20 weeks on experimental diet, mice were sacrificed and plaque burden evaluated both at the aortic root and en face. Perigonadal fat pads were analyzed for fatty acid (FA) content.
In gonadal fat, C18:3 and C20:5 were unchanged while C22:5 and C22:6 increased the FO groups compared to controls.
Plaque burden was unchanged in the apoE-/- strain. In the LDLR-/- strain, plaque burden was reduced both at the aortic root and in the whole aorta in the FO and CO group vs. the untreated group($p < 0.01$ in both cases). There was a trend towards a stronger reduction of plaque burden in the FO group vs the CO group that reached statistical significance when plaque burden was evaluated regionally, namely in the aortic arch area, as evaluated by en face analysis (% area stained by Red Oil O: FO = 32.4 $\pm$ 9; CO = 37.9 $\pm$ 9 $p < 0,05$ by unpaired T-test, untreated = 48.0 $\pm$ 12). Such reduction might be related to the significant reduction in LDL cholesterol observed in the FO group at the end of the study.

Group/Diet		Aortic root (mm^2)	En Face plaque burden			
			Arch	Des. aorta	Inf. Aorta	Total
LDLR-/-						
1. Untreated	n=20	1.23 $\pm$ 0.4	48.0 $\pm$ 12	22.3 $\pm$ 8	2.6 $\pm$ 3	23.3 $\pm$ 6
2. Fish oil	n=21	0.74 $\pm$ 0.3**	32.4 $\pm$ 9***	12.0 $\pm$ 4 **	1.6 $\pm$ 2	13.9 $\pm$ 4**
3. Corn oil	n=21	0.87 $\pm$ 0.4**	37.9 $\pm$ 9**	14.9 $\pm$ 6**	2.2 $\pm$ 2	16.6 $\pm$ 5**
ApoE-/-						
1. Untreated	n=23	2.57 $\pm$ 0.5	2.57 $\pm$ 0.5	21.3 $\pm$ 7	2.9 $\pm$ 2	6.0 $\pm$ 2
2. Fish oil	n=23	2.68 $\pm$ 0.5	2.68 $\pm$ 0.5	21.0 $\pm$ 8	3.6 $\pm$ 2	6.8 $\pm$ 2
3. Corn oil	n=23	2.81 $\pm$ 0.6	2.81 $\pm$ 0.6	19.1 $\pm$ 6	3.9 $\pm$ 3	6.5 $\pm$ 2

Thus, both n-3 and n-6 PUFAs supplementation appear to reduce the atherosclerotic burden in LDLR-/- mice, with some larger effect seen with n-3 PUFAs. There is an important strain-dependency of the effect, with no protection against atherosclerosis in apoE-/- mice.

P1763 Toll-like receptor 4 is involved in outward arterial remodelling

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Background: Toll like receptor 4 (Tlr4) is the receptor for exogenous lipopolysaccharides (LPS), endogenous heat shock protein 60 (Hsp60) and extra domain A of fibronectin (EDA). Expression of endogenous Tlr4 ligands, Hsp60 and EDA, has been observed in arthritic and oncological specimens in which tissue breakdown and repair are important features. In atherosclerosis, outward arterial remodeling prevents lumen loss and is associated with an unstable plaque phenotype. Outward arterial remodeling is characterized by a structural change in total arterial circumference. Since Tlr4 ligands are expressed during tissue turnover, we hypothesized that Tlr4 is involved in arterial geometrical remodeling.
Methods and Results: Using a femoral artery cuff model in the atherosclerotic ApoE3 (Leiden) transgenic mouse, Tlr4 activation by LPS stimulated plaque formation and subsequent outward remodeling (EEL area -LPS 28227 $\pm$ 2217 μm^2 and EEL area +LPS 38705 $\pm$ 2416 μm^2, p = 0.009). Using the same cuff model in wildtype mice, neointima formation and outward remodeling occurred (EEL area -LPS 30881 $\pm$ 3788 μm^2 and EEL area +LPS 44381 $\pm$ 3244 μm^2, p=0.019). In Tlr4 deficient mice, however, no outward arterial remodeling was observed (EEL area -LPS 23263 $\pm$ 2114 μm^2 and EEL area +LPS 22480 $\pm$ 2905 μm^2). Carotid artery ligation in wildtype mice resulted in outward remodeling without neointima formation in the contralateral artery (table). This was associated with an increase in Tlr4 expression and EDA and Hsp60 mRNA levels. In contrast, outward remodeling was not observed following carotid ligation in the Tlr4 deficient mice.

	EEL area baseline (μm^2)	EEL area 4 wk after ligation (μm^2)
Wt	117839 $\pm$ 19577	141169 $\pm$ 5644
Tlr4 deficient	133173 $\pm$ 13300	140125 $\pm$ 5509

Toll-like receptor 4 and outward arterial remodeling in a flow cessation model (contralateral artery).Values depict EEL area (mean $\pm$ SEM).

Conclusion: These findings provide genetic evidence that Tlr4 is involved in outward arterial remodeling probably via upregulation of Tlr4 and Tlr4 ligands.

P1764 Granulocyte-macrophage colony-stimulating factor regulates the transcription of tropoelastin in the vascular extracellular matrix

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Background: GM-CSF is a prominent member of colony stimulating factors. Besides its various effects regarding immunological processes GM-CSF has a profound influence on the metabolism of the vascular extracellular matrix (ECM). GM-CSF-knock out (KO) mice show reduced levels of fibrilar collagens. Here we report that GM-CSF-KO and overexpressing mice develop alterations in the elastic components of the vascular extracellular matrix.
Methods: Elastica von Gieson staining was used to show the elastic system of the aorta of GM-CSF-KO and overexpressing mice. Additionally, smooth muscle cells (SMC) were cultured for various periods in the presence or the absence of anti-GM-CSF antibodies (AB) or GM-CSF antisense oligonucleotides (AS-ODN). The mRNA expression of tropoelastin was shown by RT-PCR.
Results: Distinct alterations were observed in the elastic components of the aorta of both mouse models. The elastic fibers of the aorta of GM-CSF-KO mice are characterized by a hypertrophied phenotype. In comparison, GM-CSF overexpressing mice are featured by a strikingly reduced elastic system. This is reflected on the mRNA level by a reduced transcription of tropoelastin. The mRNA expression is age dependent, since it is gradually downregulated in GM-CSF overexpressing mice during the first 24 weeks. This phenomenon can be reproduced in vitro. In long-term cultured GM-CSF overexpressing aortic SMC the transcription of tropoelastin is downregulated. In cell culture studies an addition of anti-GM-CSF AB or GM-CSF AS-ODN resulted in a stimulation of tropoelastin mRNA production.
Conclusion: Our data demonstrate that besides its effects on the collagenous matrix GM-CSF plays a profound role in the regulation of the elastic fiber system of the arterial wall. Particularly, the transcription of tropoelastin is definitely altered due to the presence or absence of GM-CSF. Consequently, GM-CSF is an important factor involved in the maintenance of the vessel wall integrity.
IZKF P10 Sindermann/Plenz

P1765 MCP-1 simultaneously induces arteriogenesis and atherogenesis in ApoE −/−− mice

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Background: Local infusion of Monocyte Chemoattractant Protein-1 (MCP-1) accelerates arteriogenesis via increased attraction of monocytes/macrophages to proliferating arteries and potentially could be applied to treat peripheral obstructive arterial disease. However, accumulation of monocytes/macrophages is also the hallmark of atherogenesis and therefore the longterm effects of peripheral MCP-1 infusion on systemic atherogenesis have to be determined.
Methods: The right femoral artery was ligated in 16 ApoE -/- mice. Mice were treated for a period of seven days with 4,5 μg/kg/day MCP-1 or PBS as a control. Substance was infused via an osmotic minipump attached to a catheter that was positioned in the distal femoral artery. 2 months after femoral artery ligation, animals were killed and the aorta was harvested. Aortas were stained with Sudan IV and the percentage of plaque was quantified using planimetry. In addition, hindlimb perfusion was measured using fluorescent microspheres and FACS-analysis.
Results: Plaque percentage of the total aorta had increased significantly in the MCP-1 treated animals (control; 24.3 $\pm$ 5.2 vs. MCP-1; 38.2 $\pm$ 9.5, p=0.009). This increase was attributed mainly to the abdominal and thoracic aorta (control; 14.8 $\pm$ 5.1 vs. MCP-1; 30.9 $\pm$ 7.8, p=0.016) and less to the aortic arch (control; 52.4 $\pm$ 3.9 vs. MCP-1; 60.1 $\pm$ 7.8, p=NS). 2 months after femoral artery ligation, hindlimb perfusion was restored to 52.1% $\pm$ 8.7% in the MCP-1 treated mice and 47.5% $\pm$ 8.4% in control mice (p=NS).
Conclusion: The local infusion of MCP-1 in the ApoE -/- mice leads to systemic acceleration of atherogenesis, mainly in the thoracical and abdominal aorta. This study stresses the necessity to search for an optimal local dosing of MCP-1. Such dose should act arteriogenically at a local level without causing systemic atherogenic 'spill-over'. In addition we show that in ApoE mice the arteriogenic effects of MCP-1 do not persist over a period of two months.

P1766 Inhibition of nuclear factor-κB activation attenuates inflammation, and enhances neointima formation in rat and mouse models of carotid artery injury

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Transactivation of specific genes controlled by NF-kappaB is essential in inflammation and tissue repair. On the contrary, excessive activation of NF-kappaB may also lead to various diseases. Recently, NF-kappaB has been implicated in the process of neointimal formation of the vessel wall in response to injury, which is relevant to restenosis, a clinical problem in treatment of atherosclerosis by percutaneous transluminal angioplasty.
Aim: To clarify the role of NF-kappaB for vascular inflammation and neointimal formation using rhodent models of arterial injury.
Methods: Carotid arteries were de-endothelialized in rats. Subsequently pyrrolidine dithiocarbamate (PDTC), a pharmacological NF-kappaB inhibitor, or vehicle was delivered perivascularly or injected intraperitoneally for 2 weeks. In a second model, carotid arteries were ligated in wild type and NF-kappaB p50-precursor p105 knockout mice. NF-kappaB activation was also studied after carotid artery ligation in a NF-kappaB -luciferase reporter mice enabling a quantitative estimate of NF-kappaB activity.
Results: In the rat model, NF-kappaB was rapidly activated in the injured vessel wall as assessed by electrophoretic mobility shift assay and by immunostaining for nuclear NF-kappaB p65 signal. A similar kinetic pattern of NF-kappaB activation was observed in the reporter mice. Using real time RT-PCR and immunohistochemistry we demonstrated that NF-kappaB activation was accompanied by markedly increased expression of tumour necrosis factor alpha, interleukin 1 beta and inducible nitric oxide synthase after injury. Our results indicate that inhibition of NF-kappaB by local application of PDTC in rats for 3 days or by deletion of the NF-kappaB p105 gene in mice substantially suppressed the expression of inflammatory genes while enhancing neointimal formation 2 weeks post-injury.
Conclusions: NF-kappaB plays a pivotal role in regulating the inflammatory reaction and neointimal hyperplasia in the injured vessel. NF-kappaB activation, as a response to arterial injury, is essential for tissue repair.

P1767 Secreted IL-1Ra exerts a protective effect on atherosclerotic lesion development in apolipoprotein E-deficient mice

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A large body of evidence implicates Interleukin (IL)-1, a proinflammatory cytokine, in the pathogenesis of a variety of human inflammatory disorders such as rheumatoid arthritis (RA). RA patients experience a markedly increased frequency of cardiovascular disease. IL-1 is expressed within the endothelium of atherosclerotic plaques and may participate to inflammatory mechanisms of atherogenesis. IL-1 receptor antagonist (IL-1Ra) is a natural IL-1 inhibitor. IL-1Ra exists in four different isoforms, one as a secreted form (sIL-1Ra) and the other three are intracellular (icIL-1Ra1, 2, 3). sIL-1Ra competitively inhibits receptor binding of IL-1. In patients with RA, the administration of recombinant human sIL-1Ra ameliorates the clinical parameters of disease activity and decreases the progression of joint damage. The purpose of this study was to determine whether sIL-1Ra influences the formation of atherosclerotic plaques in vivo.

Transgenic mice expressing high amounts of human sIL-1Ra were crossed with Apolipoprotein E-deficient mice (ApoE-/-), which develop atherosclerotic lesions when fed a high cholesterol diet, in order to obtain ApoE-/- IL-1Ra-wild type and ApoE-/- IL-1Ra-transgenic mice of identical genetic background. Twelve week old males of both groups (n=6 per group) were fed a cholesterol-rich diet (1.25%) for 10 weeks. Increase in serum lipid profiles (total cholesterol, triglycerides) did not differ between both groups. Atherosclerotic lesion development was measured as the extent of sudanophilic lesions by computer image analysis.

The average lesion area within aortic roots was significantly decreased (47%, $p<0.001$) in transgenic mice (0.49 ± 0.06 mm^2) as compared to controls (0.93 ± 0.05mm^2). The extent of sudanophilic lesions was also reduced within the thoraco-abdominal aorta in transgenic mice (-36%). Preliminary analysis of the cellular composition of atherosclerotic plaques showed a decrease in the percentage of macrophage-positive areas (- 49%) in IL-1Ra transgenic mice as compared to control mice.

Our results show that sIL-1Ra exerts a protective effect on the progression of atherosclerosis in mice. These findings suggest that the administration of IL-1Ra may also exert beneficial effects on cardiovascular complications in patients with RA.

P1768 Cobalt increases adhesion of human vascular smooth muscle cells by proteinkinase C dependent activation of β1-integrin

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Hypoxia plays an important role in vascular remodeling and directly affects vascular smooth muscle cell (VSMC) functions. Interactions between VSMCs and extracellular matrix (ECM) proteins are mediated by the integrin family of cell-surface receptors. Regulation of integrin functions involve changes in cell surface expression and changes in affinity/avidity.

In the present study, we used cobalt as hypoxia mimicking molecule to study the effects of hypoxia on cell-matrix interactions of human VSMCs. Pretreatment with cobalt (200 μM) induced a time-dependent (maximum after 6 h stimulation) increase in VSMC adhesion to the ECM proteins collagen type I (Col I) (145% of control, $p<0.01$) and fibronectin (Fn) (149% of control, $p<0.01$). Inhibition of protein kinase C (PKC) with calphostin (100 nM) blocked cobalt-induced cell adhesion. Pretreatment with the MAPK kinase pathway inhibitor PD98059 (30 μM) significantly reduced cobalt-induced increase in adhesion. Activation of PKC by phorbol 12-myristate 13-acetate (PMA, 100 nM) caused an increase in adhesion of VSMCs to Col I and Fn, indicating a critical role for PKC in the regulation of cell adhesion. Cobalt induced a rapid activation of ERK1/2 MAPK (3.2-fold induction, $p<0.05$), focal adhesion kinase (FAK) (2.1-fold induction, $p<0.05$) and PKCepsilon (2.1-fold induction, $p<0.05$). PD98059, that blocked cobalt-induced ERK1/2 MAPK phosphorylation, had no effect on FAK activation. In contrast, calphostin significantly inhibited cobalt mediated activation of ERK1/2 MAPK and FAK, demonstrating that ERK1/2 MAPK and FAK are activated downstream of PKC. Using specific blocking antibodies (10 μg/ml) against different integrins revealed, that the effect of cobalt was mediated essentially by β1-integrin. However, β1-integrin mRNA levels and cell surface expression were not affected by cobalt, as demonstrated by RT-PCR and flow cytometry. As evidenced by flow cytometry, cobalt induced a time-dependent activation of β1-integrins by exposing an conformationally-sensitive epitope (9EG7) on the β1-subunit. However, immunofluorescence showed that during early adhesion β1-integrin aggregated in focal complexes either with or without cobalt stimulation.

In conclusion, our data indicate that cobalt-induced increase in adhesion of VSMCs on Fn and Col I, involving signaling through PKC, is mediated by an activation of β1-integrin through conformational change rather than through clustering of integrins or up-regulation of cell surface expression. ERK1/2 MAPK and FAK activation downstream of PKC are involved in cobalt-induced β1-integrin mediated cell adhesion.

UPS AND DOWNS OF GENE THERAPY

P1769 Inhibition of transforming growth factor-β by local intravascular gene transfer of a soluble transforming growth factor-β type II receptor inhibits stent-induced neointima by decreasing extracellular matrix accumulation

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Purpose: Extracellular matrix (ECM) accumulation is an important finding in coronary stent-induced neointima, and TGF-beta, implicated in ECM formation, is expressed abundantly in this tissue. We assessed the hypothesis that inhibition of TGF-beta by local delivery of an adenovirus expressing a soluble form of TGF-beta type II receptor (AdTb-ExR) inhibits stent-induced neointima in porcine coronary arteries.

Methods: Two coronary arterial segments (n=20) per pig randomly received 1x10E9 pfu of either AdTb-ExR or adenovirus expressing beta-galactosidase (AdLacZ)/PBS using an Infiltrator. Stents (n=20) were deployed after gene transfer in each segment of 10 pigs. Localized transgene expression was confirmed by RT-PCR and immunohistochemistry. Computer-based morphometric assessment was performed in stented arteries 4 weeks after gene transfer.

Results: There was significantly less intimal area (1.57 ± 0.49 vs 2.13 ± 0.34 mm^2) and area ratio of intima/media (0.84 ± 0.44 vs 1.32 ± 0.48), and higher neointimal cell density (3121 ± 330 vs 2812 ± 183 cells/mm^2) in arteries treated with AdTb-ExR compared with controls (all, $p<0.05$). Neither cell proliferation rate assessed by PCNA nor injury score was significantly different between two groups. The distribution of hyaluronan in intima was less in 4 of the 6 AdTb-ExR treated arteries compared to the controls. Cultured rat arterial smooth muscle cells transfected with AdTb-ExR showed a decreased expression of connective tissue growth factor (CTGF) mRNA, assessed by RT-PCR, compared with AdLacZ, suggesting that CTGF may be affected in the downstream pathway of TGF-beta signaling by AdTb-ExR.

Conclusion: Blockade of TGF-beta by local in vivo gene transfer of a soluble TGF-beta type II receptor inhibits stent-induced neointima probably by inhibiting ECM accumulation in porcine coronary arteries, and may have a therapeutic potential in the inhibition of restenosis after stenting.

P1770 Safety and feasibility of catheter-based local intracoronary vascular endothelial growth factor gene therapy in the prevention of post-angioplasty and in-stent restenosis and in the treatment of myocardial ischaemia

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Catheter-based intracoronary VEGF gene transfer is a potential treatment for coronary heart disease (CHD). In preclinical studies VEGF has reduced restenosis and shown proangiogenic activity. However, only limited data are available about local intracoronary VEGF gene transfer.

Purpose The purpose of this study was to evaluate the safety and feasibility of local intracoronary VEGF gene transfer given during angioplasty (PTCA) and stenting.

Methods One hundred and three patients with CHD (CCS II-III, mean age 58±6 yrs) were recruited in this randomized, placebo-controlled, double-blinded phase II study. PTCA was performed with standard methods, followed by gene transfer with perfusion-infusion catheter. 37 patients received VEGF-adenovirus (VEGF-Adv, $2x10^10$ pfu), 28 patients VEGF-plasmid-liposome (VEGF-P/L, 2000 μg of DNA with 2000 μl of DOTMA:DOPE (1:1 w/w)) and 38 control patients Ringer lactate. 90% of the patients were stented after the gene transfer. The primary end points were minimal lumen diameter and percent of diameter stenosis measured by Quantitative coronary angiography (QCA) at the 6 months follow-up. Secondary end points included myocardial perfusion and exercise tolerance in a subgroup of patients. Safety laboratory tests were screened during the follow-up. A questionnaire survey was performed 14 to 47 months after the gene transfer to evaluate the late outcome of the treatment.

Results Gene transfer to coronary arteries was feasible and well tolerated. The overall clinical restenosis rate was 6%. In QCA the minimal lumen diameter and percent of diameter stenosis did not significantly differ between the study groups (2.0 ± 0.8 mm vs. 2.2 ± 0.5 mm vs. 2.1 ± 0.6 mm and 34 ± 20% vs. 29 ± 13% vs. 26 ± 15%, VEGF-Adv vs. VEGF-P/L vs. placebo, respectively). However, myocardial perfusion showed a significant improvement in the VEGF-Adv treated patients after the 6 months follow-up. Some inflammatory responses were transiently present in the VEGF-Adv group but no increases were detected in the incidences of serious adverse events or new cancers in any of the study groups.

Conclusions Gene transfer with VEGF-Adv or VEGF-P/L during PTCA and stenting shows that: (i) intracoronary gene transfer can be performed safely and no major gene transfer -related adverse effects were detected, (ii) no differences in clinical restenosis rate or minimal lumen diameter were present after the 6 months follow-up, and (iii) a significant increase was detected in myocardial perfusion in the VEGF-Adv treated patients.

P1771 Endothelial nitric oxide synthase gene transfer does not increase nitric oxide release from atherosclerotic human carotid artery

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As nitric oxide (NO) inhibits thrombus formation and vascular smooth muscle cell proliferation, endothelial nitric oxide synthase (eNOS) gene transfer seems to be a reasonable strategy for the local treatment of vascular diseases. However, normal enzyme function depends on the availability of several cofactors, which are reduced in atherosclerotic tissue. We therefore investigated whether NO release is enhanced after eNOS transfection in human atherosclerotic carotid arteries ex vivo. Alkaline phosphatase staining revealed that human atherosclerotic arteries can be transfected in an efficient manner using an adenoviral vector. Consistent with this observation, eNOS expression was enhanced after transfection. Indeed, enzyme expression was detected immunohistochemically in endothelial and subendothelial cells. However, neither nitrite production nor NO release was enhanced in transfected tissue as compared to control conditions. In contrast to the atherosclerotic specimens, nitrite formation was significantly higher after eNOS transfection of human saphenous vein or native rat aorta. Treatment of transfected atherosclerotic specimens with L-arginine, NADPH, FAD, FMN, tetrahydrobiopterin did not alter NO release. Superoxide formation was not different in transfected atherosclerotic specimens as compared to control conditions. Thus, eNOS gene transfer in human atherosclerotic carotid arteries results in high expression of the recombinant protein; however, the enzyme is inactive and NO formation remains unaltered. In contrast, in non atherosclerotic vessels, transfection enhances NO release. The defect in the atherosclerotic vessels is not related to an enhanced superoxide production nor to deficiency of cofactors for eNOS. Since balloon dilatation is performed in severely atherosclerotic arteries, gene therapy for restenosis by eNOS transfection is unlikely to provide clinical benefit.

P1772 Molecular evidence of efficient lentiviral vector-mediated gene transfer into differentiated cardiovascular cells and undifferentiated mesenchymal stem cells for the cardiovascular gene therapy

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Human immunodeficiency virus type-1 (lentivirus) based vectors have a number of attractive features for gene therapy including the ability to transduce non-dividing cells and long term transgene expression. We have investigated the efficiency of foreign gene delivery using a new generation lentiviral vector into HeLa cells, human umbilical vein endothelial cells (HUVECs), primary cultured rat aorta smooth muscle cells (VSMCs), pleuripotent mesenchymal stem cells (MSCs) obtained from rat bone marrow and non-dividing well-differentiated cells including postmitotic beating neonatal rat cardiomyocytes (CMs). Using lentiviral vectors containing a variety of strong promoters and pseudotyped with the vesicular stomatitis virus-G glycoprotein, we successfully generated versatile high-titer lentivirus at titers of up to 50,000 infection unit (IU)/ml, and improved transduction efficiency in various cell types. This lentiviral system was able to deliver enhanced green fluorescence protein (GFP) and beta-galactosidase reporter genes with high transduction efficiency into HeLa cells (97% by FACS analysis), HUVECs, MSCs and CMs (80%, 30%, 30% by IF, respectively). While both lentiviral and retroviral vectors effectively transduce HeLa cells, HUVECs and MSCs, lentiviral vectors at titers of 2,000,000 IU/ml also efficiently transduce CMs but retroviral vectors showed very low transduction efficiency. Lentiviral vectors also mediate efficient delivery of therapeutic genes (ecNOS or hVEGF121 gene) into VSMCs or MSCs, and NO and VEGF were secreted into the supernatant of cultured cells. When lentiviral vectors encoding reporter genes were directly injected into the hind legs or myocardium of rat, transduction of nondividing skeletal or cardiac myocytes could be demonstrated until 10 weeks after gene delivery, which was not the case when retroviral vectors were used. Taken together, these results demonstrate that lentivirus-based vectors can efficiently transduce both undifferentiated and well-differentiated cells in vitro and in vivo. Therefore, lentivirus-mediated gene transfer strategies provide an efficient tool for in vivo gene therapy and ex vivo modification of MSCs to provide a new tool for research and therapy for cardiovascular diseases.

P1773 Semliki Forest virus is a highly efficient and selective vector for cardiac gene delivery

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Gene therapy is emerging as a realistic addition to the therapeutic arsenal in heart failure, but the search for suitable vectors for cardiac transfection is still ongoing. In this study, we explore the applicability of recombinant Semliki Forest Virus (SFV) for gene therapy in heart failure. To this end we used a method for intracoronary delivery of viral solution in the rat myocardial infarction model for heart failure. We administered SFV-lacZ to eight rats two weeks after induction of myocardial infarction, and determined the organ distribution of the virus in vivo by histochemical, biochemical, and RT-PCR methods. In addition, we compared the organ selectivity of SFV to that of adenovirus (Ad).

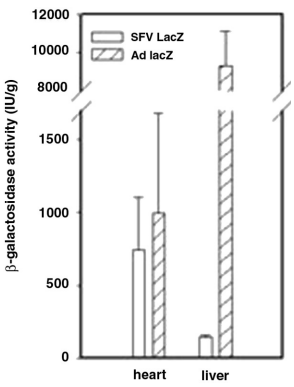

Figure 1: SFV vs. adenovirus.

We found that intracoronarily administered SFV efficiently and selectively transfects the cardiac wall. Histologically, large numbers of lacZ-positive cardiomyocytes were observed, corresponding with high levels of beta-galactosidase activity (740 ± 360 IU/mg) and lacZ RNA in the heart, whereas brain, kidneys, liver, lung, spleen, and testis showed no lacZ expression. In comparison, intracoronarily administered Ad-lacZ yielded equally high levels of transfection in the heart (990 ± 690 IU/mg), but was more vastly expressed in the liver at levels ~10 times higher (9250 ± 1890 IU/mg) than in the heart (Figure 1). Expression duration of SFV-mediated transfection in the heart was relatively short, reaching its maximum after 48 to 72 hours and subsiding within a week. In conclusion, intracoronarily delivered SFV has a favourable distribution pattern, showing expression of the transgene restricted to the heart. Preferably its relatively short duration of expression is to be modified to obtain a sustained therapeutical effect.

P1774 Postinfarct remodelling can be attenuated by intramyocardial adenovirus-mediated delivery of Inhibitor kappa Balpha gene

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Introduction: One of the key factors in the inflammatory response following myocardial infarction is the transcription factor nuclear factor kappa B (NF-kB). We hypothesized that NF-kB- blockade in an animal model of acute ischemia reduces the inflammatory response and therefore improves myocardial function. **Methods:** NF-kB - blockade was achieved by an overexpression of inhibitor kappa Ba (IkBa) using adenoviral (AV) - mediated gene transfer. Myocardial infarcts (MI) were produced in male Sprague-Dawley rats by ligation of the left descending coronary artery and followed by AV-mediated intramyocardial delivery of IkBa-gene (394±17,1g, n=6) respectively the delivery of a LacZ-reporter-gene (392 ± 25,3g; n=6). Sham-operated animals (385±17,6g, n=6) received neither ligation nor gene transfer. In vivo cardiac function was assessed 7 weeks after MI by transthoracic echocardiography(Vingmed Sound). In vitro cardiac function was evaluated by pump function curves on a red-cell-perfused isolated working heart. Only animals with MI involving more than 30% of the left ventricle were included. **Results:** There was no difference in myocardial infarction (45% ± 0,09) and left-ventricular-body-weight-ratio (0,0033 ± 0,0007 versus 0,0032 ± 0,0002) between the infarct groups. However this value was significantly elevated compared to sham-rats (0,0025 ± 0,0002; $p<0,05$). Concerning in vivo hemodynamics Ikba treated hearts showed reduced systolic and diastolic left ventricular dimensions compared to the LacZ MI group (systolic 0,52 ± 0,084 cm versus 0,66 ± 0,031 cm; diastolic 0,7 ± 0,081 cm versus 0,82 ± 0,073 cm; $p<0,05$). Consequently fractional shortening was preserved in Ikba hearts compared to LacZ MI hearts (0,26 ± 0,037 versus 0,19 ± 0,042; $p<0,05$). In vitro hemodynamics showed a similar picture: both infarct groups showed a significant left-and-downward-shift compared to the sham-operated hearts, this shift was less pronounced in the Ikb group ($p<0,05$) compared to the LacZ MI group. Data are given as mean ± SD.
Conclusion: It can be concluded that the overexpression of IkBa leads to an improved cardiac function thereby attenuating post-infarct-remodeling.

P1775 Helper-dependent adenoviral vectors devoid of all viral genes provide efficient in vivo gene transfer and decreased toxicity in rat myocardium

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Adenoviral (Ad) vectors have been used in many heart gene therapy studies and a few clinical trials due to high efficiency of myocardial gene transduction. However, first and second-generation Ad vectors are limited by tissue toxicity, mainly due to the residual production of immunogenic viral proteins. Recently, third-generation Ad vectors devoid of all viral genes ("gutless") have been developed. These HD vectors require a "helper" adenovirus for vector production. They can carry much larger transgenes (up to 30 Kb) than standard Ad vectors. HD vectors have not been tested in heart gene transfer models.
Methods: HD vectors expressing the EGFP reporter gene under the transcriptional control of the CMVie promoter were produced in 293Cre-recombinase cells using a helper adenovirus in which the packaging signal was flanked by two loxP sites to prevent its packaging. Multiple rounds of virus production and purification resulted in increased HD vector concentrations (up to 2x10E9 TU/ml), with minimized helper virus contamination (<0.2%). HD vectors were compared to Ad vectors after in vivo intramyocardial injection in rats (n = 30 and 14, respectively). Control rats received PBS (n=6). Myocardial EGFP expression was measured by ELISA in cardiac extracts at varying time points (3 days to 10 weeks) after gene transfer. Tissue toxicity was assessed immunohistochemically with mAbs against ED1-like (monocyte/macrophages), TCR, CD4 and CD8 (T cells).
Results: HD and standard Ad vectors achieved comparable peak myocardial EGFP expression at 1 week post-gene transfer. However, EGFP sharply declined by 2-4 weeks using either vector. At 10 weeks, significant EGFP expression was detected in only 1 out of 7 hearts with HD and none with Ad vectors. To test for transgene silencing, 3 additional hearts injected with HD vectors received intramyocardial retinoic acid (RA) and trichostatine (TSA) to stimulate promoter activity 3 days before harvest (at 10 weeks). EGFP expression was detected in 2 out of these 3 hearts treated with RA/TSA. Immunohistologically positive-staining myocardial areas (%) were as follows (HD vs Ad vectors): ED1-like: 6 ± 4 vs 32 ± 5; TCR: 6 ± 3 vs 30 ± 4; CD4: 6 ± 4 vs 43 ± 4; CD8: 5 ± 3 vs 30 ± 5 (all $p<0.05$; PBS <2% with all markers).
Conclusions: HD and Ad vectors are equally efficient at expressing genes in rat hearts in vivo. HD vectors achieve a marked decrease in tissue toxicity which, however, is not accompanied by prolonged transgene expression. Detectable expression after RA/TSA treatment suggests that transgene silencing may be involved.

P1776 A new method of prostacyclin synthase gene transfer ameliorates monocrotaline-induced pulmonary hypertension in rats

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Continuous intravenous prostacyclin infusion is the only one clinically established treatment for primary pulmonary hypertension (PH). We examined whether naked DNA encoding prostacyclin synthase (PGIS) into a remote skeletal muscle ameliorates monocrotaline (MCT)-induced PH in rats. One week after administration of MCT (60mg/kg, SC), either PGIS or control gene was transfected using the naked DNA method into the bupivacaine-treated thigh muscle of rats every week. Hemodynamic and morphological studies were performed 21days after MCT administration. Survival rate was determined by Kaplan-Meyer survival curves. Muscle tissue levels of 6-keto-PGF1a, a stable metabolite of prostacyclin, were significantly higher for 7 days after a single transfer of PGIS expression plasmid (day 2: PGIS, 2785 ± 607; control, 1823 ± 354pg/g tissue, $p<0.01$; day 7: PGIS, 2160 ± 319; control, 1551 ± 379pg/g tissue, $p<0.05$). The lung tissue content of cAMP, a second messenger of prostacyclin, was significantly greater (day 2: PGIS, 2785 ± 607; control, 1823 ± 354pmol/mg protein, $p<0.01$). RV systolic pressure was significantly lower in PGIS group versus control group (44.3 ± 9.0 vs 68.1 ± 9.2mmHg, $p<0.01$), whereas aortic pressure was similar in the two groups. RV hypertrophy was attenuated in PGIS group (RV weight/LV+S weight: PGIS, 0.38 ± 0.05; control, 0.44 ± 0.07, $p<0.05$). % wall thickness of the peripheral pulmonary arteries was significantly smaller in PGIS than control group (28.6 ± 0.6, 33.7 ± 0.3%, $p<0.01$). Survival rate was significantly improved in PGIS group as compared with control group (Log-rank, $p<0.05$). In conclusion, PGIS gene transfer into the skelton muscle not only attenuated PH and the resultant cardiovascular changes but also improved the prognosis of MCT-induced PH rats. This study may provide an insight into the new treatment strategy for PH.

HORMONES, VASCULAR FUNCTION AND HYPERTENSION

P1777 Long-term thyroxine administration results in heat shock protein 27 (HSP27) overexpression and protects the heart from ischaemia

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Thyroxine treated hearts are found to display a phenotype of cardioprotection through mechanisms not fully characterized. HSP27 is associated with enhanced tolerance of the heart to ischaemic stress. Hormones have recently shown to regulate heat shock proteins. We investigated the possible role of HSP27 in thyroxine induced cardioprotection.
Methods: L-thyroxine was administered in Wistar rats (25μg/100g/day sc) for 2 weeks (THYR), while normal animals served as controls (NORM). NORM and THYR isolated hearts were perfused in Langendorff mode and subjected to: 1) 20 min of stabilization; NORM-base, n=5 and THYR-base n=5; 2) 10 or 20 min of zero-flow global ischaemia (I) only; NORM-10I, n=5 and THYR-10I, n=5, NORM-20I, n=5 and THYR-20I, n=5; and 3) 20 min of I followed by 45min of reperfusion (R); NORM-I/R, n=8 and THYR-I/R, n=8. Total and phospho-HSP27 expression was assessed at the different time points of the experimental setting in the Triton-soluble (cytosol-membrane), S fraction and Triton-insoluble (cytoskeleton-nucleus) fraction, P fraction. Postischaemic recovery of left ventricular developed pressure at 45 min of R was expressed as % of the initial value.
Results: 1. Baseline: In THYR hearts, the levels of total HSP27 and phospho-HSP27 in P fraction were 1.5 fold and 1.55 fold higher as compared to normal, respectively. 2. Ischaemia (I): In NORM, at 10 min of I the amount of total HSP27 sligthly increased in P fraction (1.25 fold more in NORM-10I vs NORM-base $p>0.05$) whereas a significant increase occurred at 20 min of I (1.9 fold more in NORM-20I vs NORM-base $p<0.05$). In THYR hearts, total HSP27 in P fraction was significantly increased at 10 min of I (1.45 fold more in THYR-10I vs THYR-base $p<0.05$) and no further increase was observed at 20 min of I (1.5 fold more in THYR-20I vs THYR-base $p<0.05$). In P fraction, phospho-HSP27 increased at 20 min of I in NORM hearts (1.8 fold more in NORM-20I vs NORM-base, $p<0.05$) and at 10 min of I in THYR hearts (1.75 fold more in THYR-10I vs THYR-base, $p<0.05$) without further increase at 20 min of I (1.7 fold more in THYR-20I vs THYR-base, $p<0.05$). LVDP% was 74.9 (4.4) for THYR-I/R and 55.7(4.4) for NORM – I/R, $p<0.05$.
Conclusion Thyroxine pretreatment results in an increased basal expression and phosphorylation of HSP27 and in an earlier and sustained redistribution of HSP27 from the S to P fraction in response to I. This can partially explain the fact that hyperthyroid hearts are found to be more resistant to ischaemic stress.

P1778 Growth hormone releasing peptide ghrelin is synthesized and secreted by cardiomyocytes in culture

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Purpose: Ghrelin is an acylated-peptide gastric hormone acting mainly on the pituitary and hypothalamus to stimulate growth hormone (GH) release, adiposity, and appetite. Recent evidences indicate that ghrelin features a variety of cardiovascular activities, including increase of myocardial contractility, vasodilation, and protection from myocardial infarction-induced heart failure. Although ghrelin is essentially a gastric hormone, it is expressed ubiquitously at low level, and ghrelin mRNA has been detected in myocardium, although it is unknown the cardiac cell type in which this peptide is synthesized. Our purpose was to clarify whether cardiomyocytes synthesize and secrete ghrelin.
Methods and results: RT-PCR showed that adult mouse cardiomyocyte cell line HL-1 and human primary cultures of cardiomyocytes express ghrelin mRNA. Immunocytochemistry with specific antibodies confirmed cytoplasmic localization of ghrelin peptide in HL-1 cell line and isolated human primary cardiomyocytes in culture. Radioimmunoassay showed that ghrelin was secreted by HL-1 cardiomyocytes into the culture medium. Moreover, in HL-1 cardiomyocytes, gene expression and secretion of ghrelin to culture medium were regulated by apoptosis inducers and serum deprivation. The active form of ghrelin receptor (GHSR-1a) is usually expressed in heart and vessels, suggesting direct cardiovascular effects of ghrelin. GHSR-1a was detected by RT-PCR in HL-1 as well as in human cardiomyocytes in culture; and in competitive binding studies with 125I-labelled ghrelin to HL-1 cardiomyocytes, 125I-Tyr4-ghrelin recognized specific binding sites (Kd=4.29 nM; Bmáx=78.6 pM) at plasma membrane level.
Conclusions: This study provides the first evidence of the synthesis and secretion of ghrelin by isolated and purified mouse and human cardiomyocytes, and supports the hypothesis that ghrelin could work directly as a cardioprotective factor in the cardiovascular system in an paracrine/autocrine fashion.

P1779 Prevalence of primary aldosteronism among hypertensive patients

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Aim: There is increasing evidence that primary aldosteronism (PA) may be common in patients defined as "essential" hypertensive. Aim of this study was to evaluate the incidence of primary aldosteronism in a primary-care hypertensive population.
Methods: Seven hundred and fifty unselected hypertensive patients (399 female and 351 male, 316 untreated and 434 treated, age 25-75 yr) attending to our hypertensive unit, had ambulatory measurements for plasma aldosterone and plasma renin activity (PRA); electrolyte measurements were obtained simultaneously. Subjects with renal insufficiency and those treated with glucocorticoids or spironolactone were excludes. Antihypertensive medication was stopped for 7 days in the treated patients before the blood sample collecting for aldosterone and PRA evaluation.
The aldosterone to PRA ratio was used as an initial screening test to identify potential patients with PA. The patients with an elevated ratio ($>$ 25) were admitted for the salt loading suppression test (two litres saline venous infusion in 4 hours). Adrenal computed tomographic scansion was performed in biochemically confirmed cases.
Results: Eigthy-seven of the 750 hypertensive patients had an aldosterone/renin ratio greater than 25; in 85 of them confirmatory studies were carried out. Using an aldosterone concentration above 7.5 ng/dl after saline infusion as the diagnostic cut-off, 46 patients had biochemically confirmed primary aldosteronism. Among these individuals, only six were hypokaliemic; an adrenal mass was detected in 15 patients.
Conclusion: primary aldosteronism has been traditionally regarded as a rare cause of hypertension. However the availability of the aldosterone-renin ratio as a screening test and its application to a wider population of hypertensive has resulted in a marked increased detection rate. Our data suggest that primary aldosteronism occurs in at least 6.1% of the adult hypertensive patients.

P1780 Testosterone dilates isolated human pulmonary and mesenteric arteries and veins

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Testosterone replacement therapy improves exercise duration and peripheral vascular resistance in men with heart failure (1,2). Pulmonary and systemic vasodilator drugs are used in the treatment of heart failure, but it is unknown whether testosterone dilates human systemic or pulmonary arteries. Male patients were recruited from cardiothoracic and gastrointestinal operating lists in Sheffield Teaching Hospitals and gave full written informed consent. 2mm lengths of pulmonary conduit artery (PCA; diameter = 986 $\pm$ 168μm), pulmonary conduit vein (PCV; diameter = 841 $\pm$ 78μm), pulmonary resistance artery (PRA; diameter = 329 $\pm$ 19μm) and pulmonary resistance vein (PRV; diameter = 372 $\pm$ 17μm) and mesenteric resistance artery (MRA; diameter = 393 $\pm$ 31μm) were dissected and loaded in a wire myograph at in vivo pressure. Vessels were maintained in physiological saline solution at 37° C and pH 7.4. Vessel viability was confirmed by contraction to noradrenaline (10μM) or U46619 (1μM) and endothelial integrity was confirmed by dilatation to acetylcholine (1μM). Vessels were then exposed to increasing concentrations of KCl (0.1-100mM) followed by cumulative additions of ethanol vehicle (Eth). Vessels were then washed, the addition of KCl repeated and exposed to increasing concentrations of testosterone (T, 1nM-100μM). Testosterone dilated pulmonary resistance arteries and veins at concentrations greater than 100nM and pulmonary conduit arteries and veins at concentrations greater than 3μM. A significantly greater response was seen in mesenteric resistance arteries (table).

Vessel Type	n (vessels)	n (patients)	Emax KCl (mN)	Emax Eth (%)	Emax T (%)
PCA	12	8	10.56 (1.74)	10.6 (3.3)	-42.5 (3.2) **
PCV	12	8	6.76 (1.06)	10.6 (5.2)	-40.7 (4.7) **
PRA	16	12	3.51 (0.53) *	19.6 (3.7)	-51.5 (4.5) **
PRV	16	10	2.92 (0.64) *	19.9 (6.2)	-53.0 (5.1) **
MRA	16	8	15.98 (2.96) ***	9.7 (2.8)	-95.0 (8.1) ** ***

Mean (S.E.M.) responses to KCl, Eth and T in PCA, PCV, PRA, PRV and MRA. *p$<$0.01 cf conduit vessels, ** p$<$0.001 cf ethanol vehicle *** p$<$0.0001 cf PRA via Mann-Whitney U Test.

This vasodilatory action may underlie the beneficial effects seen with testosterone replacement therapy in men with heart failure.
References: [1] Pugh PJ et al. (2002a) Heart 87, p5; [2] Pugh PJ et al. (2002b) End. Abs. 4, 37.

P1781 Oestrogen receptor alpha mediates the acute vasodilative effects of 17β-oestradiol

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The atheroprotective properties of estrogen can be explained in part by vasodilative effects. Infusion of 17beta-estradiol (17beta-E) causes an acute dose-dependent vasodilation with a rapid onset, which is not typical for an action mediated by estrogen receptors (ER). Thus it remains unclear whether the haemodynamic effects of 17beta-E are mediated by ER. To study the role of ER on the 17beta-E-induced haemodynamic effects we examined the gender-specific effects of 17beta-E and investigated whether the non-selective ER-antagonist ICI 182,780 (ICI) can block these effects. To study which receptor subtype (ERalpha or ERbeta) is involved, we tested further in female rats the haemodynamic effects of the predominant ERbeta agonist genistein (about 20 times higher affinity to ERbeta than to ERalpha). **Methods:** The gender-specific effects of i.v. 0.2 μg/kg 17beta-E without and with selective ER-blockade (1 mg/kg ICI) were compared in open-chest rats vs. control. Additionally in experiments with female rats 0.2 μg/kg and 200 μg/kg genistein was infused. **Results:** 17beta-E causes an acute gender-specific vasodilation with a consecutive increase of the cardiac output and of the ejection fraction. These effects are more pronounced in female than in male rats. ER-blockade with ICI reduces these effects in both gender. Infusion of 0.2 μg/kg genistein causes (in contrast to 17beta-E) no vascular effects and even a very high dose of 200 μg/kg genistein causes only a slight vasodilation (TPR: -7.7% vs. control, p$<$0.05).

	Female rats			Male rats		
	17beta-E	ICI+17beta-E	control	17beta-E	ICI+17beta-E	control
CO	167±10#	133±4*	108±5	145±5#	123±4*	111±1
EF	127±3#	125±3#	98±3	115±3*	107±4	102±2
TPR	71±4#	81±2#	96±4	80±2#	87±3*	94±1

Mean $\pm$ SEM in % of preinfusion values; *=p$<$0.01, #=p$<$0.001 vs. control.

Conclusions: The 17beta-E-induced vasodilation is more pronounced in females than in males and can be attenuated in both gender by the selective ER-antagonist ICI. Since the ERbeta agonist genistein causes no relevant vasodilation the gender-specific vasodilative effect of 17beta-E seems to be mediated by ERalpha.

P1782 Castration of male SHRSP upregulates angiogenic molecules and endothelial nitric oxide synthase in the frontal cortex: an implication for the pathogenesis of attention deficit/hyperactivity disorder

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Purpose: Attention deficit/hyperactivity disorder (AD/HD) is a common psychiatric disorder in childhood, manifested by behavioral abnormalities based on inattention, hyperactivity and impulsivity. The pathogenesis of AD/HD is not fully understood, however, the frontal cortex is arguably considered to be one of the critical brain regions and the reduction of cerebral blood flow has been implicated. We have recently reported that juvenile stroke-prone spontaneously hypertensive rats (SHRSP) exhibit behavioral abnormalities similar to AD/HD. In addition, male but not female SHRSP show cognitive impairment assessed by spontaneous alternation behavior, implying gender difference observed in AD/HD patients. The present study was aimed to clarify the molecular mechanisms underlying male predominance in cognitive dysfunction in SHRSP.
Methods: We evaluated the expression of angiogenic molecules, vascular endothelial growth factor (VEGF), its angiogenic receptor, KDR, and endothelial nitric oxide synthase (eNOS) in the frontal cortex by using Western blotting, immunohistochemistry, real-time PCR and in situ hybridization.
Results: VEGF and KDR expressions were significantly downregulated in 6 week-old male SHRSP compared to age-matched Wistar Kyoto rats (WKY). In 6 week-old male SHRSP castrated at 3 weeks of age, VEGF and KDR expressions were significantly upregulated. Testosterone (Tes) replacement (TR) to the castrated SHRSP did not reverse the upregulated VEGF and KDR expression. Changes in eNOS expression were in parallel to the VEGF expressions in sham-operated, castrated and Tes-replaced SHRSP. Androgen receptor (AR), estrogen receptor (ER)-alpha and aromatase P450 expressions were decreased in sham-operated SHRSP; which were all upregulated after castration, but were not reversed by TR. ER-beta was not modified by any treatments. In WKY, VEGF, KDR and eNOS were downregulated after castration, supporting a positive correlation between Tes and angiogenic molecule expressions under normal condition as reported previously.
Conclusions: These findings suggest that downregulations of VEGF, its receptors and eNOS specific to male SHRSP cause reduction of cerebral blood flow, which in turn leads to cognitive impairment. Failure of TR to modify changes induced by castration in SHRSP indicates that Tes per se may not be responsible for the impaired blood flow and/or cognitive behavior in SHRSP. The fact that ER-alpha, AR and aromatase P450 expressions were changed in SHRSP implies that some metabolites of Tes play a key role in this animal model of AD/HD.

P1783 Selective oestrogen receptor alpha stimulation prevents endothelial dysfunction in ovariectomized spontaneously hypertensive rats

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Estrogens exert protective vascular effects which are mediated by two different estrogen receptors, ER-alpha and ER-beta. To gain further insight into the role of ER-alpha in a functional setting and to identify novel compounds for clinical application, we investigated the influence of a novel and highly selective ER-alpha agonist on endothelial function in ovariectomized spontaneously hypertensive rats (SHR).
After ovariectomy or sham-operation, 12 week-old female (SHR) were treated by daily subcutaneous injections with a physiological dosage of 17-beta-estradiol (E2, 2μg/kg/d) or the selective ER-alpha agonist Cpd1471 (30μg/kg/d) or placebo. Acetylcholine-induced endothelium-dependent vasorelaxation was significantly blunted in aortae from ovariectomized rats compared with sham-operated animals (Rmax: 53%$\pm$3% vs. 79%$\pm$2%; $p<0.001$). Treatment with E2 or Cpd1471 significantly augmented acetylcholine-induced relaxation in ovariectomized rats (Rmax: 70%$\pm$2% resp. 73%$\pm$2%). Endothelium-independent relaxation induced by sodium nitroprusside was not different among the four groups. The contractile response induced by the nitric oxide (NO) synthase inhibitor N-nitro-L-arginine, an index of basal NO formation, was significantly lower in ovariectomized rats compared with sham-operated animals (53$\pm$2% vs. 77%$\pm$5%; $p<0.001$), and was normalized by either E2 (70%$\pm$2%) or Cpd1471 (70%$\pm$3%). Endothelial NO synthase expression (western blot) was reduced in aortae from ovariectomized SHR and normalized by E2 and Cpd1471.
In SHR after ovariectomy, endothelium-dependent NO-mediated vasorelaxation and endothelial NO synthase expression are attenuated. The novel and highly selective ER-alpha agonist Cpd1471 prevented these pathophysiological changes to a similar extent as E2. The pharmacological principle of ER-alpha subtype specific stimulation mediates positive vascular effects and may be a new treatment option for cardiovascular protection.

P1784 Thyroid hormone receptors in the heart: chamber specific patterns and T3 responsive cardiac fibroblasts

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Thyroid hormone (T3) responsive genes comprise essential cardiac functions: the contractile filament, calcium handling, adrenergic receptors and a variety of ion channels. Gene deletion studies indicate specific functions of the different T3 receptor isoforms. The present study analyses gene expression of thyroid hormone receptors (T3Rs) in heart compartments and in non-muscle cardiac cells.
Cardiac T3Rs profile was analysed at the mRNA level using real-time PCR. Both T3R genes alpha and beta were detected in all tissues examined. Cardiac tissue analysed displayed always the same pattern, T3Ralpha2 > T3Rbeta1 > T3Ralpha1. In contrast to the alpha gene, only one splice variant of the beta gene was found, T3Rbeta1. T3Rbeta2 positive pituitary gland served as controls. The T3Ralpha1, assumed to be responsible for the majority of cardiac T3 effects was higher in left atrium than in the ventricles. Left ventricle expressed more T3Ralpha2 and T3Rbeta1 than the right ventricle. Interestingly, both ventricles and atrium displayed a > 50 time higher expression of the non T3-binding splice variant T3Ralpha2 than the T3 binding receptor T3Ralpha1. The non T3-binding T3Ralpha2 isoform is presumed to have a protective role against T3 over stimulation.
Furthermore, we investigated T3Rs gene expression in cardiac non-muscle cells, the majority of which are cardiac fibroblasts. Cultures of proliferating cardiac fibroblasts expressed all three T3Rs as in vivo. Immunohistochemistry confirmed the protein expression of both T3 binding receptors. In contrast to the often observed loss of T3Rs in cultured cells, the early decrease of T3Ralpha2 and T3Rbeta1 but not T3Ralpha1 was followed by a stable expression of all T3Rs up to 15 passages. T3 treatment at a physiologic concentration of 10 nM decelerated proliferation of the cardiac fibroblasts. This is of interest concerning the observed cardiac fibrosis accompanying hypothyroidism. Our results demonstrate a compartment specific pattern of T3Rs and the T3 responsiveness of also the non-muscle cells in the heart.

P1785 Interaction of gender and large artery elasticity: a non-invasive study in male to female transsexuals

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Purpose: To assess the effect of gender on large artery elasticity in age-matched male, female and male to female transsexuals.
Methods: Towards this end, we evaluated aortic elastic properties in 13 male to female transsexuals (age 44$\pm$9 years, 18$\pm$11 years after surgery) and we compared these findings with those observed in 10 premenopausal women (age 42$\pm$5 years) and in 10 men (age 43$\pm$5 years). Aortic compliance was evaluated non-invasively on the basis of Doppler ultrasound measurements of pulse wave velocity (PWV) from the carotid to femoral artery by the foot-to-foot method. All included subjects had a negative glucose intolerance test.
Results: The three groups of men, women and male to female transsexuals were matched for age (44 vs 42 vs 43 years, respectively) body mass index (25 vs 23 vs 24 kg/m^2, respectively), smoking status (current smokers 45% vs 42% vs 48%, respectively), total cholesterol plasma levels (232 vs 229 vs 218 mg/dl, respectively) and office blood pressure (115/75 vs 110/75 vs 115/73 mmHg, respectively) (p=NS for all the above cases). Also, these three groups did not differ regarding the left ventricular echocardiographic data of left ventricular mass (171 vs 142 vs 158 gr, respectively), and relative wall thickness (0.41 vs 0.42 vs 0.41, respectively) (p=NS for all measurements). In contrast, the aortic PWV was significantly higher in men compared to transsexuals and women (817$\pm$30 vs 804$\pm$21 vs 801$\pm$20 cm/sec, respectively) while the PWV did not differ between transsexuals and women (p=NS). In the entire population aortic PWV had a positive correlation with age ($r=0.30$, $p<0.05$), systolic BP ($r=0.44$, $p<0.005$).
Conclusion: These results suggest that vascular adaptations in male to female transsexuals are more closely related to those observed in premenopausal women than those in age-matched men.

P1786 Insulin receptor number is decreased in healthy offspring of hypertensives

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Background: Epidemiological studies have shown that healthy offspring (HOF) of hypertensives (HTS) have already some features of metabolic syndrome, such as hyperleptinemia, hyperinsulinemia and haemostasis balance disturbances too. It is also known that human insulin receptor number (hINR) is decreased in HTS. Aim of our study was to determine hINR in HOF of HTS and to compare the findings to those of HOF of normotensives (NTS) matched for age, sex and BMI.
Methods: Twenty-five HOF of HTS (Group A), 12 M and 13 F, mean age 15,5±2,5 yrs and BMI 21,4±2,5 kg*/m^2 and 28 HOF of NTS (Group B), 13 M and 15 F, mean age 15,8±3,1 yrs and BMI 21,7±2,4 kg*/m^2 were studied. Mean systolic and diastolic blood pressure (SBP, DBP) levels and heart rate (HR) were recorded in both groups (resting position) at baseline. Human insulin receptor number and plasma immunoreactive insulin (IN) (RIA method) were also determined. The differences between the two groups are shown in the table.

Parameters	Group A	Group B	p
SBP (mmHg)	121±13	113±10	<.01
DBP (mmHg)	78±6	73±8	<.05
HR (b/min)	76±4	72±6	<.01
hINR (receptors x103/red cell)	5,6±1,4	6,8±1,3	<.001
IN (μIU/ml)	21±7	15±6	<.01

Conclusions: Our findings suggest that healthy offspring of hypertensives have significantly lower hINR number compared to normotensives. There are also significantly higher levels of resting SBP, DBP, HR and IN in the group of hypertensives' offspring (but within normal range). The above data indicate that HOF of HTS is a group who needs further investigation and close follow-up.

P1787 Interleukin-6 and flow mediated dilatation as markers of increased vascular inflammation in patients receiving hormone replacement therapy

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Ovarian hormone deficiency is associated with the development of cardiovascular disease in postmenopausal women (PMW). However, recent studies failed to show a beneficial effect of hormone replacement therapy on cardiovascular prognosis and have suggested that HRT may even increase cardiovascular events. It has been suggested that the lack of an effect of HRT and the early adverse effects may be related to an inflammatory effect of HRT.
To this end we have evaluated the effect of different estrogens, and estrogen-progestin combinations [conjugated equine estrogens + medroxyprogesterone acetate (CEE-MPA), estradiol + cyproterone acetate (E-Cyp), estradiol + dydrogesterone (E-Dyd), estradiol + norethisterone acetate (E-NETA)] and Tissue Selective Hormones (Tibolone, Raloxifene) on markers of vascular inflammation and on endothelial function assessed by flow mediated dilatation of brachial artery (FMD) in 205 PMW before and after replacement therapy. In all PMW estrogens alone increased plasma levels of C-Reactive protein but decreased all other markers of inflammation including IL-6 that is the primer of inflammatory production of CRP in the liver (CRP +75%, I-CAM -20%, V-CAM -14%, E-Selectin -18%, s-Thrombomodulin –10%, IL-6 –15%, percent changes compared to baseline). Overall estrogen-progestin associations did not reverse these effects but in selected patients the association of CEE-MPA 5% and, E-NETA 6% and, Tibolone 11% induced an increase in IL-6 and unfavorable changes on vascular inflammation markers (CRP +93%, I-CAM -3%, V-CAM -5%, E-Selectin +6%, s-Thrombomodulin +5%, IL-6 +12%, percent changes compared to baseline).
In all patients but in those increased IL-6 levels HRT improved FMD, Tissue Selective Hormones did not changed FMD compared to baseline. A significant correlation was found between changes in IL-6 and FMD. In conclusion ERT and HRT are associated with a decreased vascular inflammation, however, in selected patients some HRT formulations and Tibolone may increase vascular inflammation. These patients may be identified by an elevation in IL-6 levels or by the lack of an increase of FMD.

PLEIOTROPIC EFFECTS OF STATINS IN PATIENTS

P1788 Long-term treatment with rosuvastatin protects against nitrate-induced oxidative stress in the rat aorta

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Statins induce an upregulation of the endothelial NO synthase pathway and may, therefore, enhance NO availability and/or inhibit oxidative enzymes.
Methods: To assess whether the oxidative stress produced by an in vivo exposure to nitroglycerin (NTG) is attenuated by rosuvastatin, 3 groups of normocholesterolemic rats were treated; group 1 received rosuvastatin (10 mg/kg/d p.o) for 5 weeks and the last 3 days, a cotreatment with the statin plus NTG (50 mg/kg/d, sub-cutaneous injections b i d); group 2 (NTG) received only NTG (50 mg/kg/d, b i d for 3 days) and group 3 served as control.
Results: Rings of thoracic aortas from these groups were studied in organ baths. Relaxations to NTG (0.1 nM to 0.1 mM) were determined on phenylephrine-preconstricted rings and superoxide production (counts/10s/mg) was assessed by lucigenin chemiluminescence technique. In group 2 (NTG), the concentration-response curves to NTG were significantly shifted to the right: the pD2 (-log NTG concentration evoking a half maximal relaxation) was 6.76±0.06 (n=7) vs 7.77±0.08 (n=7) in group 3 (not exposed to NTG, $P<0.01$) and superoxide production was enhanced (289±23 (n=6) vs 183±34 (n=5, $P<.05$). In contrast, in group 1, the rightward shift was attenuated (pD2 values was 7.19±0.11 (n=8), $P<.05$ vs group 2); superoxide production was decreased: 208±19 (n=6), $P<.05$ vs group 2). The protective effect on nitrate tolerance disappeared when L-NAME (an eNOS inhibitor, 100 mg/kg/d) was co-administered with NTG in group 1. Moreover, rosuvastatin treatment decreased p22phox (the essential NAD(P)H subunit) abundance in aortic wall and NAD(P)H oxidase activity.
Conclusion: Long-term rosuvastatin treatment protects against nitrate tolerance by counteracting NTG-induced increase in superoxide production. This protection seems to involve a downregulation of NAD(P)H oxidase probably by an upregulation of the eNOS pathway.

P1789 Atorvastatin and simvastatin inhibit human Toll-like receptor expression on circulating monocytes in-vivo and ex-vivo: possible mechanism for plaque stabilization

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Introduction: It is widely accepted that HMG-CoA reductase inhibitors (statins) do not only lower LDL cholesterol but may also have a specific beneficial effect against plaque instability. Research over the last years has provided convincing evidence that atherosclerosis is an inflammatory disease. Recently, human Toll-like receptors (hTLR), key receptors of the innate immune system, could be detected on infiltrating macrophages in atherosclerotic lesions. We postulated that the clinical efficiency of statins could be partly due to a protective effect against activation of the innate immune response.
Methods: In 12 healthy test persons (LDL-cholesterol 120±29 mg/dl) mononuclear cells were isolated and ex-vivo coincubated with atorvastatin (ATOR) (0;0.5;1;2;10;20 μM) or simvastatin (SIM) (0;2.5;5;10;25;50 μg). After 24 hours hTLR2 and hTLR4 expression on circulating CD14+ monocytes was characterized using 2-color-flow cytometry.
Next the persons took 20 mg ATOR for 1 month. HTLR2 and hTLR4 expression on circulating CD14+ monocytes was characterized before and after ATOR treatment.
Results: Ex-vivo incubation with ATOR from 0.5 μM and SIM from 2.5 μg induced a dose dependent decreased hTLR2 (maximum decline to 47.2% as compared to untreated monocytes with ATOR ($p<0.05$), 38.3% with SIM ($p<0.05$)) and hTLR4 expression (41.3% with ATOR ($p<0.05$), 42.8% with SIM ($p<0.05$)) on circulating CD14+ monocytes. In vivo ATOR treatment for one month reduced hTLR2 by 48.4% ($p<0.05$) and hTLR4 expression by 36.2% ($p<0.05$) as compared to baseline levels. LDL was reduced by 36% (LDL-cholesterol 77±18 mg/dl).
Conclusion: The statin-induced effects on hTLR-expression on circulating monocytes could explain, at least in part, their beneficial effect on plaque stability. These findings provide first evidence that expression of hTLRs on circulating CD14+ monocytes might be influenced by drugs.

P1790 Vascular effects of simvastatin and ramipril in hypercholesterolemic patients

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Purpose: Because the mechanisms of the biological effects of statin and antiotensin converting enzyme inhibitor therapies differ, we studied the vascular responses to these therapies in hypercholesterolemic patients.
Methods: We administered simvastatin 20 mg and placebo or ramipril 10 mg daily during 2 months with washout 2 months to 32 hypercholesterolemic patients. This study was randomized, double-blind, placebo-controlled, crossover in design.
Results: Simvastatin alone or combined with ramipril significantly changed lipoproteins, and improved the percent flow-mediated dilator response to hyperemia relative to baseline measurements by 46±48% and by 59±66%, respectively (both $P<0.001$) and reduced plasma levels of nitrate relative to baseline measurements by 0±52% and by 13±30%, respectively (P=0.183 and P=0.012, respectively), the plasma malondialdehyde(MDA) levels relative to baseline measurements by 6±57% (P=0.045) and by 13±47% (P=0.045 and $P<0.001$, respectively) and MCP-1 relative to baseline measurements by 3±27% and by 9±16%, respectively (P=0.113 and P=0.001, respectively), and C-reactive protein relative to baseline measurements by 17±75% and by 17±37%, respectively (P=0.003 and P=0.001, respectively), and PAI-1 antigen relative to baseline measurements by 1±51% and by 14±32%, respectively (P=0.175 and P=0.009, respectively). However, simvastatin combined with ramipril changed to greater extent the percent flow-mediated dilator response to hyperemia and plasma levels of nitrate, MDA, MCP-1, and PAI-1 antigen than simvastatin alone.
Conclusions; Compared with simvastatin alone, added ramipril to simvastatin showed additive effects on flow-mediated dilation and the plasma levels of nitrate, oxidant stress, inflammation markers and fibrinolysis potential markers in hypercholesterolemic patients.

P1791 Comparative efficacy of fibrate and statin on endothelial function and novel inflammatory markers in patients with combined hyperlipidaemia: relations with baseline lipid profiles

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Background: Given that combination therapy with statin plus fibrate confers a risk of myopathy, it is worthwhile to determine whether first-line lipid-lowering therapy for individuals with combined hyperlipidemia should consist of statin or fibrate monotherapy. Methods and Results: In this study, we compared the efficacy of simvastatin and fenofibrate on indexes of endothelial function (flow-mediated dilation [FMD] of the brachial artery) and inflammatory markers (plasma high-sensitivity C-reactive protein [CRP], interleukin-1b [IL-1b], soluble CD40, and soluble CD40 ligand [sCD40L] levels), as surrogate indicators of future coronary heart disease, in patients with combined hyperlipidemia. A total of 70 patients with plasma triglyceride levels between 200 and 500 mg/dL and total cholesterol levels of ≥200 mg/dL were randomized to receive either simvastatin (20 mg/d)(n = 35) or micronized fenofibrate (200 mg/d)(n = 35) for 8 weeks. Treatment with simvastatin was associated with significantly greater reduction of total cholesterol and low-density lipoprotein cholesterol (LDL-C), while the decrease in triglycerides was significantly greater in patients receiving fenofibrate. Both fenofibrate and simvastatin markedly reduced plasma levels of high-sensitivity CRP, IL-1b, and sCD40L, and improved endothelium-dependent FMD without mutual differences. However, the changes in plasma inflammatory markers did not correlate with baseline clinical characteristics in both groups. Nevertheless, the improvement in FMD with fenofibrate treatment correlated inversely with baseline high-density lipoprotein cholesterol (HDL-C) levels, whereas the improvement in FMD with simvastatin treatment was positively related to HDL-C levels. Accordingly, in the subgroup with a baseline HDL-C of ≤40 mg/dL, only fenofibrate significantly improved the endothelium-dependent FMD. On the other hand, in the subgroup with HDL-C >40 mg/dL, only treatment with simvastatin achieved significant improvement in FMD. Conclusions: Our data indicate that both fenofibrate and simvastatin have comparative beneficial effects on various inflammatory markers and endothelial function in patients with combined hyperlipidemia. Furthermore, our findings suggest that clinicians might be able to use baseline HDL-C levels to determine whether to prescribe statin or fibrate monotherapy as the initial lipid-lowering agent in this clinical setting.

P1792 Atorvastatin decreases vascular superoxide production by reducing NAD(P)H oxidase activity without modification in gp91phox mRNA levels

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Introduction: Vascular superoxide anion (O2.-) originates from metabolic or enzymatic sources such as NAD(P)H oxidase which could be involved in cardiovascular diseases. Only few data are available concerning the effects of statin on O2.- sources. The aim of our study was to assess the effects of atorvastatin on vascular O2.- production level.
Methods: 14 New Zealand White normocholesterolemic rabbits were randomised in CONTROL group (CTRL, n=7) and ATOR group (n=7, 10 mg.kg-1.d-1, p.o). At 30 days, infra-renal aortas were tested to assess global vascular O2.- by Electron Spin Resonance (ESR) using Carboxy-Hydroxy-Pyrrolidine (CPH, 1 mM) as a O2.- label, and Dihydroethidium (DHE, 5 μM) as a O2.- fluorescent probe. NAD(P)H oxidase activation was evaluated by lucigenin (0.5 μM) assay using NAD(P)H (30 μM). RT-PCR experiments were also performed to estimate mRNA levels of NAD(P)H oxidase key sub-unit gp91phox.
Results: Global vascular O2.- levels were similar in CTRL and ATOR group, either with ESR (5.0 ± 0.8 vs 4.4 ± 0.5 Arbitrary Unit.mg-1, ns) or with DHE study (12.5 ± 1.0 vs 13.6 ± 1.7% relative fluorescence, ns). In contrast, there was a marked decrease in NAD(P)H activity by approximatively 40% in ATOR treated aorta (911 ± 49 vs 1429 ± 48 Arbitrary Units.mg-1, $p<0.001$). The transcription level of gp91phox, was similar in CTRL and ATOR group (0.07 ± 0.03 vs 0.09 ± 0.06 Arbitrary units, ns).
Conclusion: These results show that ATOR did not modulate global vascular rates of O2.-, but specifically decreased O2.- production by blunting NAD(P)H oxidase activation, without any effect on the transcriptional rate of gp91phox. The present data suggest that ATOR, by reducing NAD(P)H oxidase activity, could prevent the deleterious effects of O2.-.

P1793 Effect of atorvastatin on serum matrix metalloproteinase activity in hypercholesterolemic adults

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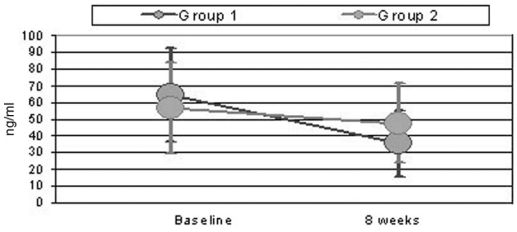
Objectives: Effect of atorvastatin on matrix metalloproteinase-9(MMP-9), C-reactive protein(CRP), tumor necrosis factor-alfa (TNF-alfa), and interleukin-1 (IL-1beta) as marker of the inflammatory and proteinolytic activity were investigated.
Methods: 44 patients with hypercholestrolemia and negative exercise stress test,were randomly assigned into 2 groups; Group 1(n=22), treated with atorvastatin and diet for 2 months and Group 2(n=22), diet alone. MMP-9, CRP, TNF-alfa,and IL-1beta were measured at baseline and two months later.
Results: Baseline lipid values decreased 32% (LDL from 153.9±26.6 to 94.5±20.8, $p<0.005$) in atorvastatin group and 9% in diet alone group (table). Compared to the diet alone, atorvastatin lowered serum CRP ($p<0.001$) and MMP-9 activity ($p<0.0001$). On the other hand, no significant change was observed in MMP-9 (p:0.2) and CRP (p:0.8) levels in Group 2.

	Group 1		Group 2	
	baseline	after atorvastatin	baseline	after diet
LDL-C(mg/dl)	153.9±26.6	94.5±20.8	151.2±27.9	133.0±25.8
CRP(mg/L)	5.16±1.9	2.88±1.06	4.78±1.4	4.05±1.3
TNF-alfa(pg/ml)	6.98±11.6	3.49±8.8	3.5±8.9	1.16±5.45
IL-1beta(pg/ml)	2.32±4.39	0.97±3.08	1.86±4.04	1.39±3.59
MMP-9(ng/ml)	64.3±28.1	35.4±20.0	56.7±27.6	47.4±23.8



MMP-9 activity after 8 weeks.

Conclusion: The beneficial effect of statin therapy in primary prevention may be due to plaque stabilization. Atorvastatin treatment decreases inflammatory and proteolytic activity in patients with hypercholestrolemia.

P1794 Reduction in ultra-sensitive C-reactive levels is preceeded by improvement in endothelial function in patients with non-familial hypercholesterolaemia treated with low dose atorvastatin

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Inflammation is involved in the pathogenesis of intimal injury in atherosclerosis but its relationship with endothelial dysfunction remains unclear. **Aim:** To examine the effects of low dose atorvastatin on serum levels of soluble intercellular adhesion molecule-1 (sICAM-1), interleukin-6 (IL6), and ultra-sensitive C-reactive protein (us-CRP) and brachial artery endothelial-dependent flow mediated dilatation (FMD) in patients with non-familial hypercholesterolaemia (NFH). **Methods:** A total of 47 NFH patients (26 males, 21 females, age 48.1 + 1.2 years) were recruited. Fasting serum lipid profiles, sICAM-1, IL6, us-CRP and FMD were measured at baseline, 2 weeks, 3 and 9 months after atorvastatin treatment [10mg/day]. sICAM-1 and IL6 were measured by elisa methods (BMS, Biopool, Vienna) while us-CRP by an immunoturbidimetric method (Tina-quant, Roche Diagnostics, Switzerland). FMD was measured by a non-invasive method using a 7.5mHz linear transducer and 2D Echocardiography sonos 5500. **Results:** The FMD at 2 weeks was higher than baseline with progressive improvement up to 9months (mean+SEM: 2.1+0.9 vs 6.7+1.0 vs 11.4+1.3 vs 16.9+1.0%, $p<0.0001$). The sICAM-1 levels were significantly reduced at 2weeks, with further reduction at 3months and maintained at 9months (1592+73 vs 974+75 vs 443+33 vs 471+20 ng/ml, $p<0.0001$). The IL-6 levels were significantly reduced at 3months and 9months compared to baseline (median[50%CI]: 3.6 [1.9-5.5] vs 3.1[2.2-5.0] vs 1.9[1.9-2.4] vs 1.9 [1.9-2.5] pg/ml, $p<0.0001$). The us-CRP levels were significantly reduced at 3months and 9months compared to baseline (median[95%CI]: 1.7 [0.2-9.3] vs 1.4[0.1-7.6] vs 1.3[0.1-7.6] vs 1.1[0.1-7.8] mg/L, $p<0.02$). **Conclusion:** Low dose atorvastatin treatment leads to reduced inflammation which is preceeded by improvement in endothelial function in patients with non-familial hypercholesterolaemia.

P1795 Effect of atorvastatin on soluble inflammatory markers and the circulating T cell repertoire in stable coronary artery disease

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Background: Coronary artery disease (CAD) is characterised by both inflammatory plaque infiltration and perturbation of the circulating T cell repertoire. Statins have anti-inflammatory effects beyond lipid lowering. Whether these properties are restricted to the vessel wall or affect the global immune system is unclear. The aim of this study was to investigate the influence of atorvastatin (atv) on circulating cytokine (IL-2, IFN-gamma)-producing T lymphocytes as well as on soluble inflammatory markers (soluble CD40-Ligand (sCD40L), soluble intercellular adhesion molecule-1 (sICAM-1) and high-sensitive CRP (hs-CRP)) known to be associated with CAD. **Materials and Methods:** 30 hypercholesterolemic patients with angiographically documented stable CAD were randomised in a double-blind study to placebo or atv (20mg/d) for 3 months. Eight healthy volunteers served as controls. Serum sCD40L and plasma sICAM-1 and hs-CRP levels were measured with ELISA. IL-2 and IFN-gamma producing T helper (CD4+) and T suppressor (CD8+) lymphocytes from whole blood samples were determined by FACS analysis. **Results:** sCD40L, sICAM-1 and hs-CRP levels as well as CD4+/IL-2+ and CD8+/IL-2+ lymphocytes were increased in CAD patients ($p<0.01$). LDL cholesterol was reduced by 37.3±16.5% in the atv-treated ($p<0.001$) and by 8.2±15.7% ($p=0.041$) in the placebo group. sCD40L, sICAM-1 and hs-CRP were attenuated by statin treatment ($p<0.02$) but remained unaltered in the placebo group. CD4+/IL-2+ and CD8+/IL-2+ cells did not change in both groups. IFN-gamma-producing T cells were similar in control and CAD patients and were unaffected by statin therapy. **Conclusion:** sCD40L, sICAM-1, hs-CRP and IL-2 producing T lymphocytes are increased in stable CAD. The reduction of sCD40L and sICAM-1 after atv therapy may reflect another atheroprotective effect of statins. The global T cell repertoire perturbation in stable CAD is not affected by statin treatment, which perhaps contributes to the safety profile of these drugs.

P1796 Pretreatment with statins, C-reactive protein and multifocal activation of coronary artery disease in patients with non-ST-elevation acute coronary syndromes

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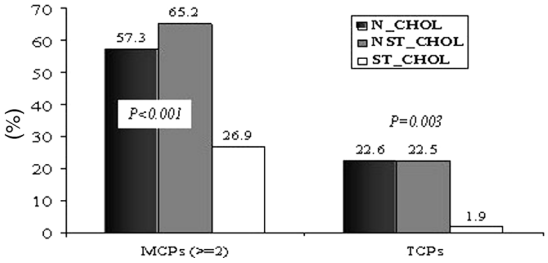
Background: The activation or rupture of multiple coronary lesions in the setting of acute coronary syndromes has been previously described, and a generalized inflammatory response may have a role. Additionally, the anti-inflammatory effect of statins has been considered as a fundamental mechanism in the process of coronary lesions stabilization. We hypothesize that pretreatment with statins may restrain the generalized activation of coronary lesions in the setting of non-ST elevation acute coronary syndromes (NSTACS) **Methods:** Out of 314 consecutive patients with NSTACS who underwent in-hospital coronary angiography were evaluated. Plasma C-reactive protein (CRP) levels were measured upon admission by high sensitivity method. All coronary lesions were classified as complex (CL) or non-CL according to Ambrose's criteria. There were 139 (44.3%) patients with no or one CL (≤1) and 175 (55.7%) with multiple CLs (≥2). Additionally, 60 (19.1%) patients had angiographically apparent thrombus-containing CLs (TCL). There was a significant relation of high plasma CRP levels with either the number of CLs ($P<0.001$), or angiographically apparent TCLs($P<0.001$). Hypercholesterolaemic pts pretreated with statins (ST_CHOL) during the last 6 months had significantly lower baseline plasma CRP levels than non- pretreated with statin hypercholesterolaemic (NST_CHOL) or non-hypercholesterolaemic (N_CHOL) ($P<0.001$)pts. Additionally, the former had less frequently multiple (≥2) ($P<0.001$) or angiographically apparent TCPs ($P=0.003$) than the other two groups (figure).



Conclusions: Inflammation seems to be implicated in the activation of multiple coronary lesions in the setting of NSTACS, and pretreatment with statins may restrain this generalized reaction.

P1797 Effect of statin therapy before percutaneous coronary intervention on peri-procedural creatine kinase-MB release and mortality at long-term follow-up

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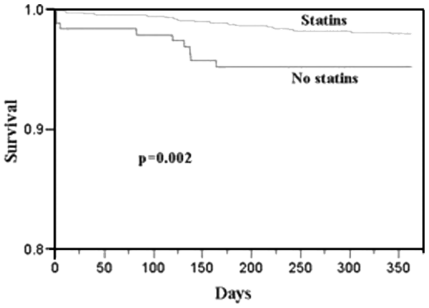
Purpose: Statin therapy has been shown to reduce mortality in patients with coronary artery disease as well as after PCI. However, the effect of statin therapy before percutaneous coronary intervention (PCI) on peri-procedural CK-MB elevation and long-term outcome after PCI has not been well established. **Methods:** We analyzed 4660 PCI patients for in-hospital events and 1-year mortality and compared the results between patients receiving statin therapy (PS) and no-statin therapy (NS) prior to PCI. All patients had CK-MB and troponin-I measured at baseline and 12-24 hrs after PCI. All PS patients continued statins after PCI.
Results: Any CK-MB elevation was 15.4% versus 14.4% ($p=0.37$) in NS versus PS group. Troponin-I release, procedural complications, and clinical success rate were similar in the 2 groups. At follow-up, pre-statin therapy was an independent predictor (HR=0.65, 95% CI 0.45-0.93; $p<0.0007$) of survival (Figure). Other important predictors of mortality were LVEF (HR=1.20), age (HR=1.03), peripheral vascular disease (HR=1.35), symptomatic heart failure (HR=1.42), and renal failure (HR=2.01). There was no difference in follow-up MI or revascularization.



Survival at 1 year.

Conclusions: Statin therapy at the time of intervention has a beneficial effect on survival in PCI patients. This survival benefit is mediated by other pleiotropic effects of statins and not by reduction of peri-procedural enzyme release or follow-up MI or revascularization.

GENE-ENVIRONMENT INTERACTION AND THE RISK OF CARDIOVASCULAR DISEASE

1821 Gene-environment interaction and the risk of fatal and non-fatal cardiovascular diseases: a prospective population-based study

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Conflicting results have been reported for the association between the Apo AI-CIII-AIV gene cluster and cardiovascular diseases (CVD) and for the modulating effects of lifestyle-related factors on this association. We evaluated the contribution of two known polymorphisms in this gene cluster (Apo AI G-75A and Apo CIII SstI) to the risk of CVD mortality and morbidity, as well as their interaction with smoking, overweight, alcohol consumption and physical activity. From 1987 to 1991, more than 35,000 Dutch men and women, aged 20-59 were examined for cardiovascular risk factors. At the end of 1999, a mortality follow-up was completed for all subjects. After 9.3 $\pm$ 2.8 years of follow-up 322 subjects had died of CVD. For the morbidity follow-up 50% of the participants received a follow-up questionnaire 6-11 years after baseline examinations. A first myocardial infarction, coronary bypass operation or PTCA was reported by 375 subjects.

The Apo AI G-75A polymorphism was not significantly associated with any of the lipid parameters studied in the total sample. However, women with the GA or AA genotype (35% of the population) had higher Apo AI levels than women with the GG genotype (1.73 versus 1.80 g/l, p=0.017). No association of the Apo AI G-75A genotype with fatal or non-fatal CVD was found. However, the risk for non-fatal myocardial infarction was decreased in –75A carriers (RR: 0.60, 95%-CI: 0.40-0.91).

The Apo CIII S2 allele was present in 19.5% of the subjects. Carriers of the S2 allele presented with a more unfavourable lipid profile as compared to non-carriers. They had higher levels of triglycerides (1.63 versus 1.36 mmol/l, $p<0.0001$), total cholesterol (5.74 versus 5.48 mmol/l, $p<0.01$) and apoB (1.13 versus 1.05 g/l, $p<0.001$), and lower HDL-c levels (1.21 versus 1.28 mmol/l, $p<0.01$) than subjects with the S1S1 genotype. The increase in triglyceride levels was more pronounced in subjects with a BMI above the median, but the interaction term did not reach statistical significance (p=0.16). No significant association between the Apo CIII SstI polymorphism and CVD risk was found. Smoking, alcohol consumption and physical activity did not modulate the association between the Apo AI-CIII-AIV gene-cluster and lipid levels or CVD risk.

In conclusion, this population-based prospective study shows that polymorphisms in the Apo AI-CIII-AIV gene cluster are associated with plasma lipid levels, but hardly with CVD risk.

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1822 Smoking and overweight modulate the effect of LPL gene polymorphisms on the risk of cardiovascular diseases

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Conflicting results have been reported for the cardiovascular (CVD) risk associated with polymorphisms in the lipoprotein lipase (LPL) gene. Additionally, it remains unclear whether lifestyle-related factors modulate this risk. Therefore we evaluated the contribution of polymorphisms in the LPL gene to the risk of fatal and non-fatal CVD, and their interaction with smoking and overweight.

From 1987 to 1991, more than 35,000 Dutch men and women (20-59 years) were examined for cardiovascular risk factors. After 9.3 $\pm$ 2.8 years of follow-up 322 subjects had died of CVD. For the morbidity follow-up 50% of the participants received a follow-up questionnaire 6-11 years after baseline examinations. A first myocardial infarction, coronary bypass or PTCA was reported by 375 subjects.

The LPL Asp9Asn mutation was not associated with plasma lipid levels or CVD risk. Carriers of the LPL 447Ter allele (17% of the population) presented with higher HDL-c and apoAI levels and lower triglyceride (TG) and apoB levels than subjects with the Ser/Ser genotype. Overall a trend towards lower CVD risk was found for 447Ter carriers. Smoking abolished this favourable effect, since carriers had a significantly decreased risk for non-fatal CHD in non-smokers only (RR: 0.37, 95%-CI: 0.17-0.80).

The rare allele of the Asn291Ser polymorphism was present in 4.3% of the subjects. Men with the Asn/Ser genotype had 10% lower HDL-c (p=0.06) and apoAI ($p<0.05$) levels than men with the Asn/Asn genotype. In smoking carriers, lipid profiles were even more unfavourable, as they also had increased total cholesterol, TG and apoB levels (p-interaction <0.05). The risk of fatal CVD was increased in male 291Ser carriers (RR: 3.14, 1.44-6.84). The risk in smoking 291Ser carriers was higher (RR: 14.1, 4.6-43) than expected (RR: 5.4) from the additive effects of genotype and smoking.

Overweight did not modulate the association between the Asn291Ser polymorphism and lipid levels, but the risk of fatal and non-fatal CVD was higher (RR: 7.51, 3.16-18, and RR: 5.17, 1.63-16, respectively) than expected from the additive effects (2.08 and 2.82, respectively). This finding suggests that overweight enhances the unfavourable effect of this polymorphism.

In conclusion, this population-based prospective study showed that smoking may interact with the LPL Ser447Ter polymorphism and the Asn291Ser polymorphism on CVD risk. Additionally, overweight seems to aggravate the risk associated with the LPL Asn291Ser polymorphism.

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1823 Association of genetic polymorphisms of serotonin, stromelisin-1, plasminogen activator inhibitor-1 and factor VII with premature acute myocardial infarction

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Background: There are evidences that genetic polymorphisms of the Serotonin (5-HT), Stromelisin-1 (MMP-3), Plasminogen activator inhibitor-1 (PAI-1) and Factor VII are involved in the pathogenesis of the Acute Myocardial Infarction (AMI).

Methods and Results: To investigate the association between polymorphisms in Serotonin (T102C 5-HT2A receptor), Stromelisin-1 (5A/6A promoter), PAI-1 (4G/5G promoter) and Factor VII (R353Q) genes with AMI, we conducted a case-control study of 296 patients with premature AMI and 77 control subjects. The difference between the groups was analyzed by the chi-square test. A multiple logistic regression model was carried out by using the SPSS statistical package.

The frequencies of T allele of the serotonin polymorphism in patient and control subjects were 0.43 and 0.32, respectively ($p<0.02$) and the prevalences of TT + TC genotypes were 67% and 57% in cases and control subjects, respectively (p=0.17).

The frequency of the 5A allele of stromelisin-1 polymorphism in the patient group was 0.62 and 0.37 in the control group ($p<0.001$). The distribution of the 5A/5A + 5A/6A genotypes was significantly more frequent in AMI patients (72%) than in control group (56%) (p=0.03), but this difference was not independent of known coronary risk factors in a multiple regression model.

The frequency of the 4G allele of PAI-1 polymorphism was 0.43 among patients and 0.48 among control subjects ($p>0.20$). The prevalence of 4G/4G + 4G/5G genotypes in the patient group was 69%, and 75% in control group, there was no significant difference (p=0.32). The carriers of 4G allele had increased incidence of late clinical events (re-AMI, stable and unstable angina, arrhythmias, left ventricular failure) (81%) when compared with 5G homozygotes (19%) (p=0.01).

The frequencies of Q allele of FVII polymorphism of case and control subjects were 0.14 and 0.09, respectively ($p>0.10$). The prevalence of Q/Q + Q/R genotypes was 24% in cases and controls subjects (p=0.99).

Conclusions: The 5A allele in the polymorphism stromelisin-1 promoter was significantly more frequent in AMI patients than in control subjects, which suggests that this polymorphism is a genetic risk factor for AMI. The 4G allele in the PAI-1 gene is not associated with the risk of AMI, but was associated with higher incidence of late clinical events.

1824 Impact of APOA5/A4/C3 cluster genetic polymorphisms on lipid variables and cardiovascular disease risk

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Purpose: Apolipoprotein A5, the latest discovered apolipoprotein, forms a cluster with APOA1/C3/A4. Genetic variability at APOA5 locus is associated with high triglycerides levels. The goal of the present study was to assess the impact of APOC3/A4/A5 single nucleotide polymorphisms (SNPs) on lipid levels and coronary heart disease (CHD.
Methods: To this end, 761 CHD patients were compared to 1195 CHD free controls from the Urban community of Lille. Four SNPs, APOA5 (-12,238T>C, S19W), APOA4 T347S and APOC3 -482C>T, were examined.
Results: In multivariate logistic regression including the 4 SNPs, the odds ratio (OR [95% CI]) of hypertriglyceridemia was 1.85 [1.07-3.19] and 1.55 [1.08-2.21] in subjects bearing the APOA5 19W and APOC3 -482T alleles respectively, suggesting an independent and additive effects of these SNPs on plasma triglyceride levels. In contrast, APOA5 -12462T>C and APOA4 T347S SNPs were not associated with lipid levels. In patients with CHD, both APOA5 19W ($p<0.01$) alleles was associated with increased triglycerides levels. The distribution of APOA5 (-12,238T>C, S19W), APOA4 T347S and APOC3 -482C>T was similar in CHD patients and controls. Similarly, there was no evidence for an increased frequency of any haplotype in CHD patients as compared to controls.
Conclusion: The APOA5 S19W and APOC3 -482C>T SNPs are associated with increased triglycerides levels in CHD patients and controls, but not with increased risk of CHD.

1825 Genotypes and haplotypes predisposing to premature myocardial infarction

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Purpose: The genetic influence on risk of coronary disease is strongest for premature disease. The purpose of this study was to identify genetic factors predisposing to early myocardial infarction (MI).
Methods: We studied 205 cases (mean age at MI 42.3 (5.7) yrs, mean age at recruitment 46.8 (6.2) yrs) and 200 controls (mean age 49 (6.0) yrs). A novel multilocus assay was used to genotype 63 polymorphisms within 35 cardiovascular candidate genes. In addition to standard analysis by genotype, we imputed haplotype frequencies from the genotype data using a log-linear model embedded within an Expectation-Maximization (EM) algorithm and tested the relationship between haplotypes and disease status by maximum likelihood estimation of the log-linear model using the iterative proportional fitting algorithm.
Results: Of the 58 non-rare polymorphisms, after adjusting for age and sex, under an additive genetic model, five polymorphisms showed a significant effect on MI risk. The APOE E4 allele (Odds Ratio (OR) 1.69 (95% CI 1.15-2.50) P=0.008) and the NOS3 -948G allele (OR 1.42 (1.06-1.90) P=0.018) increased the risk of MI. LPL 447ter (OR 0.61 (0.38-0.98) P=0.042), CETP 405val (OR 0.73 (0.53-0.99) P=0.048), and ELAM 554phe (OR 0.37 (0.15-0.89) P=0.026) showed protective effects on MI risk. After adjusting for smoking the effects of APOE E4, NOS3 -948G and CETP 405val were no longer significant, suggesting that smoking may be an important determinant on the aetiological pathway. Haplotype analyses were consistent with the above results, and identified two additional haplotypes with a significant effect on risk: APOCIII (ATCCCC at loci -641*-482*-455*1100*3175*3206, OR 0.59 (0.44-0.89) and PAI1 (T 4G at loci 11053*5G/4G, OR 1.69 (95% CI 1.27-2.96).
Conclusions: Studies of extreme phenotype can help to elucidate genetic influences on complex traits. Polymorphisms in APOE, NOS3, LPL, CETP, ELAM, PAI1 and APOCIII exert significant effects on the risk of premature MI, with evidence of haplotype effects within genes. Further studies are necessary to identify the mechanisms underlying these genetic effects.

1826 Genotyping of multilocus risk markers in patients with myocardial infarction

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Myocardial infarction (MI) is a phenotypically complex disease due to interaction of numerous genetic and enviromental factors. Advances in molecular genetics have led to identification of some potential genetic risk factors for MI, such as variants of genes involved in vascular homeostasis, hypertension, lipid metabolisam and body iron status. The purpose of this study was to investigate possible genetic markers for cardiovascular disease in pts with a history of MI in comparison with normal subjects.
Patients and methods: 179 pts with acute MI consecutively admitted to our Coronary Care Unit were studied for: 1) e4 allele of apolipoprotein E (apo E 4/4); 2) polymorphism in intron 6 of lipoprotein lipase gene (LPL Pvul+/+); 3) deletion allele of angiotensin converting enzyme (ACE I/D); 4) 807T/873A polymorphisms of glycoprotein (GP) Ia receptor and 5) hemochromatosis gene (HFE) C282Y, H63D, H65C mutations. The control group consisted of 200 healthy individuals without a family history of coronary heart disease. The apoE genotypes, HFE mutations and GP Ia polymorphisms were analysed by LightCycler technology, ACE genotypes and LPL polymorphisms by polymerase chain reaction (PCR) and restriction isotyping as conventional methods.
Results: In the group with the history of MI there were 34.1% of the pts to be ACE DD homozygote, 2% apoE4/4, 31.8% LPL Pvul+/+, 14% GP 807T/873A, 1.2% HFE 63D, 1.2% HFE 282Y. In control subjects the following genotypes were found: 26% ACE DD; 0% apoE 4/4; 12% LPL Pvul+/+, 0% GP 807T/873A; 0% HFE 63D and 0% HFE 282Y. Furthermore, 40% of MI pts had 4 positive genetic markers, and 15% only one. Among pts with 4 positive genetic markers, there were 37% pts with previous history of MI.
Conclusion: Presented results suggest that apo E4, ACE D, LPL +, GP 807T/873G and HFE 282Y/63D may be important genetic risk factors of coronary artery disease. The finding of an increased frequency of these genetic alleles in MI might prove useful to the detection of those pts with an increased risk of reinfarction.

ESC LECTURE ON BASIC SCIENCE

1832 Endothelial nitric oxide synthase gene polymorphism (G894T) and levels of inflammation and oxidation markers; the ATTICA study

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Background: Recently a point mutation of guanine to thymine at nucleotide position 894 (G894T) in the endothelial nitric oxide synthase (eNOS) gene has been reported to be associated with endothelial dysfunction and cardiovascular disease. However, the effect of this polymorphism on inflammatory and oxidative stress markers (C-reactive protein, white blood cell counts (WBC), amyloid – A, fibrinogen, homocysteine and oxidized LDL-cholesterol) remains to be established.
Methods: During 2001–2002, we conducted a population-based study of 2282 participants. In this work we studied 267 men (18-87 years old) and 327 women (18-89 years old), without any evidence of CHD. Participants were randomly selected from the general population according to age-gender distribution of Athens grater area (census 2001). DNA was extracted from peripheral leukocytes. For detection of G894T polymorphism of the eNOS gene, we used primer pairs to amplify a part of the eNOS gene containing exon 7 by polymerase chain reaction (PCR). ANCOVA was used to examine the associations between the genotypes and the investigated markers, after adjusting for several potential confounders.
Results: 10.6% of the participants were homozygotes (HOM), 40% heterozygotes (HET) and 49.4% normal (NOR). No association between the distribution of the polymorphism and sex of the participants was observed ($p = 0.564$). Compared to heterozygotes and normal, homozygotes had higher levels (mean±SD) of fibrinogen (HOM: 332±46 or HET: 329±33 vs. NOR: 319±29 mg/dl, $p = 0.009$), higher levels of WBC counts (6,9±0.6 or 6,5±0.3 vs. 6,1±0.9, $p = 0.023$), higher levels of homocysteine (13.7±2.3 or 12.8±3.9 vs. 12.1±2.5 mg/dl, $p = 0.041$) and higher levels of oxidized LDL-cholesterol (68±21 or 61±22 vs. 59±20 mg/dl, $p = 0.008$), after controlling for age, blood pressure levels, body mass index, smoking habits and physical activity status. No association was found between C-reactive protein and the distribution of G894T polymorphism of eNOS ($p = 0.982$).
Conclusion: Our results imply that the G894T polymorphism of eNOS gene is associated with elevated inflammatory process and oxidative stress. This may partially explain the increased prevalence of G894T polymorphism among patients with cardiovascular disease.

1833 Relationship between endothelial nitric oxide synthase gene polymorphisms and coronary heart disease: importance of case definition

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Background: Nitric oxide has an important role in vascular function and integrity. Basic research suggests that polymorphisms of the endothelial nitric oxide synthase (eNOS) gene are functional. Results regarding an association with CAD are contradictory. However, case definition widely varies among studies. We, therefore, tested whether the association of eNOS gene polymorphisms with CAD depends on the selection of the outcome variable.
Methods: We included 241 controls without evidence for CAD and 261 cases with angiographically established CAD. Of the latter, 122 had a history of myocardial infarction (MI), and 139 had significant CAD without history of MI. The polymorphisms T-786C, G894T (Glu298Asp) and the 4ab polymorphism in intron 4 were determined by PCR.
Results: When CAD patients with and without MI were chosen as case group, there was only a weak and non-significant trend toward an increased risk among carriers of the rare alleles (T-786C, p=0.20; G894T, p=0.22; and 4ab, p=.015). However, in patients with prior MI, the rare alleles of the T-786C and the 4ab polymorphisms were associated with a markedly increased risk for this endpoint. In contrast, there was no evidence for a genotype-associated increase in risk for CAD in absence of a history of MI (Table).

Table: Odds ratios for eNOS genotypes

Polymorphism	Case selection	OR w/w	OR w/m	OR m/m	P-value
T-786C	MI	1	1.3	2.0	0.04
T-786C	CAD, no MI	1	1.3	1.0	0.71
ab Intron 4	MI	1	1.5	3.2	0.02
ab Intron 4	CAD, no MI	1	1.0	1.1	0.90
G894T	MI	1	1.3	1.4	0.23
G894T	CAD, no MI	1	1.5	1.2	0.24

OR=Odds ratio. w=frequent allele. m=rare allele

Conclusions: This study suggests that the rare alleles of the promoter polymorphisms T-786C and the 4ab in intron 4 are associated with an increased risk for MI, but not for CAD in absence of MI. Possible mechanisms for MI precipitation in carriers of the rare alleles are reduced endothelial NO production with increased propensity to vasoconstriction as well as with increased platelet adhesion. Precise case definition may be crucial to understand the role of these polymorphisms in the pathophysiology of vascular diseases.

1834 The promoter T-786C gene polymorphism of endothelial nitric oxide synthase: impact on exercise-induced correction of endothelial dysfunction in patients with coronary artery disease

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Polymorphisms of the human endothelial nitric oxide synthase (eNOS) gene have been identified as risk factors of cardiovascular diseases. In particular the eNOS promoter T-786C polymorphism has been characterized to alter eNOS activity. Aim of the present study was to evaluate the impact of this polymorphism on the extent of endothelial dysfunction in patients (pts) with coronary artery disease (CAD) and on endothelial response to physical exercise training.
Methods: Thirty three pts with CAD were randomly assigned to an exercise training group (6 times daily for 4 weeks) or an inactive control group (sedentary lifestyle). Endothelial function of a coronary or mammary artery was invasively assessed. At begin and after 4 weeks, the response in average peak flow velocity (APV) to acetylcholine (Ach, 7.2 μg/min) was measured by Doppler velocimetry. Promoter polymorphism was determined by PCR restriction length polymorphism using Nae I as restriction enzyme.
Results: Eighteen pts (54%) were heterozygous for the promoter polymorphism, and none was homozygous. At begin Ach-induced increase in APV was significantly blunted in polymorphism positive pts (47$\pm$10% vs. 78$\pm$9% in wild type allele carriers, $p<0.05$). After 4 weeks of exercise training agonist-mediated increase in APV was +28$\pm$11% in polymorphism positive pts (from 48$\pm$9% to 76$\pm$8%, $p<0.05$ vs. begin) compared to +69$\pm$14% in wild type pts (from 79$\pm$8% to 148$\pm$20%, $p<0.05$ vs. begin and polymorphism positive pts).
Conclusion: The presence of the eNOS promoter T-786C polymorphism in pts with CAD is associated with a blunted agonist-mediated endothelial response of coronary and mammary arteries. The effect of 4 weeks of exercise training on endothelial function was significantly impaired in pts positive for the eNOS promoter polymorphism compared to wild type allele carriers presumably due to a decreased eNOS activity.

DIVISION, MOVEMENT AND DEATH OF VASCULAR SMOOTH MUSCLE CELLS

1835 Mechanotransduction in vascular smooth muscle cells: Src-kinases activate PI(3)-kinsase/Akt within caveolae

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Background: Vascular adaption to chronic changes of pulsatile stretch represents an integral part of vessel homeostasis. An increase in mechanic force causes proliferation of vascular smooth muscle cells (VSMC), a key component of vascular remodelling and lesion formation. Previously, we had demonstrated that cyclic stretch rapidly activates phosphoinositide 3-kinase (PI(3)k)/proteinkinase B (Akt) resulting in cell cycle entry and progression of VSMC in vitro. Mechanosensitive PI(3)k/Akt activation is integrin dependent but growth factor-independent. In this study we further elucidated the signalling molecules involved in VSMC mechanotransduction.
Methods and Results: Quiescent, mitogen-free rat VSMC were subjected to cyclic stretch (0,5 Hz at 125% resting length). Lysates were used for immunoblot of activated (phospho-) Akt, PI(3)k and Src-kinase family (Src and Fyn) acitivity assays, and co-immunoprecipitation studies. PI(3)k as well as Akt were phosphorylated and activated within 10 min of stretch. Co-immunoprecipitation studies demonstrated that cyclic stretch caused PI(3)k to associate with caveolin 1. After cyclic stretch Src and Fyn located to caveolae, resulting in their enzymatic activation. Inhibition of Src-kinase activity with the pharmacologic inhibitor PP1 prevented stretch-induced PI(3)k activation and Akt phosphorylation as did transfection of VSMC using caveolin 1 antisense (but not control) oligonucleotides (AS-ODN) or disrupting caveolae structure with cyclodextrin. AS-ODN were also able to prevent stretch-induced cellular proliferation as measured by propidium iodide staining and FACS analysis of cells in S/G2 phase (quiescent cells: 8$\pm$2%; stretch: 22$\pm$3%; stretch+control-ODN: 24$\pm$3%; stretch+cav1AS-ODN:8$\pm$3%; each n=6, $p<0.05$).
Conclusion: Targeting PI(3)k to caveolin 1 and its activation by Src-kinases is essential for mechanosensitive Akt activation and subsequent entry of VSMC into cell cycle. Caveolae and Src-kinases represent important components of the pulsatile force-regulated homeostasis and remodeling of the vascular wall.

1836 Glycoxidation of low-density lipoprotein activates MAPK-ERK/JNK pathways and AP-1 complex

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The Maillard's reaction (glycoxidation) represents a combination of both glycosylation and oxidation damage to proteins. There is now evidence for the presence of glycoxidized LDL (glc-oxLDL) in human atherosclerotic plaques. When cells are exposed to oxygen radicals, a plethora of oxidation-sensitive mechanisms can activate mitogen-activated protein kinase-extracellular regulated kinase (MAPK-ERK) and Jun kinase (JNK). These events could be amplified by co-existing glycosylation. The goal of the study was to explore the mechanisms by which glc-oxLDL modulate MAPK-ERK and JNK activities, and AP-1 complex in human coronary smooth muscle cells (SMC). The percentage of MAPK activity induced by glc-oxLDL was about 30%, while glcLDL alone induced about 5%. In the presence of PD98059, the MAPK activity for glc-oxLDL was reduced to 48%. Western blot analysis also revealed a marked increase in phosphorylated form of c-Jun protein in SMCs after incubation with glcLDL and glc-oxLDL, compared to the native LDL and oxLDL. Direct measurements of JNK activity confirmed that glcLDL and glc-oxLDL significantly increased JNK activity (2.54$\pm$2 and 93.1$\pm$5 arbitrary units, respectively; mean of n=4 experiments), compared to native and oxLDL (2.0$\pm$0.8 and 83$\pm$0.5 arbitrary units, respectively; $p< 0.01$ for both comparisons). We have also investigated the effect of these stimuli on the JNK-dependent AP-1 complex. We found a marked AP-1 activation in the nucleus of cells exposed to glc-oxLDL, when compared to oxLDL. The AP-1 complex was subjected to dissociation analysis (off rate), to determine its in vitro DNA stability at the site of AP-1 binding. The AP-1 complex in cells exposed to glc-oxLDL exhibited a slower dissociation with a significant amount of complex still bound after 10 min, while was almost completely dissociated within 2 min in oxLDL-treated cells. Thus, the AP-1 complex in glc-oxLDL-treated cells binds the DNA in a more stable fashion than that achieved with oxLDL. In oxLDL-treated cells, a supershifted band was observed in the presence of antibodies against c-Jun, JunB and Fra-1 proteins. In contrast, glc-oxLDL-treated cells mainly supershifted with c-Jun and Fra-1 antibodies. Thus, the composition of the AP-1 complex is different in oxLDL and glc-oxLDL. We demonstrate, for the first time, that glc-oxLDL stimulates MAPK-ERK and JNK, coupled to activation of the c-Jun and Fra-1 of the AP-1 complex. These data suggest that glycoxidation may promote atherogenesis and vascular complications in diabetes mellitus through MAPK-ERK/JNK pathways.

1837 Lack of insulin receptor substrate (IRS)-2 causes more progressive neointima formation in response to vessel injury than lack of IRS-1

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Although insulin resistance is thought to be associated with atherosclerosis in humans, the mechanism is unknown. Recent reports in mice have shown that the lack of insulin receptor substrate-1 (IRS-1) results in insulin resistance without developing diabetes, and the lack of the IRS-2 also results in insulin resistance, which is subsequently followed by diabetes mellitus. We investigated vascular intima formation in response to injury in insulin-resistant mice lacking the genes of insulin receptor substrate (IRS) -1 or IRS-2. Methods: Vascular intima formation was induced by the external vascular cuff model in IRS-1 deficient (IRS-1-/-) and IRS-2 deficient (IRS-2-/-) mice at both 8 and 20 weeks: a polyethylene tube (ID=0.56mm) placed around a 2-mm segment of the left femoral artery ensheaths the adventitia but avoids direct intraluminal injury. Two weeks after cuff placement, cuff-sheathed arteries from wild-type (WT), IRS-1-/- and IRS-2-/- mice were compared with the volume ratios of intima to media (I/M). Result: At 8 weeks, the IRS-2-/- mice (I/M=60%) showed much greater neointima formation before developing diabetes than the IRS-1-/- (I/M=32%, P=0.004) or wild-type mice(I/M=40%, P=0.02). At 20 weeks, the IRS-1-/- (I/M=68%) and IRS-2-/- mice (I/M=96%) showed much greater neointima formation than the wild-type mice(I/M=41%, P=0.04 vs. IRS-1-/-, $P<0.001$ vs. IRS-2-/-) and 20 week models showed much greater neointima formation than the 8 week models. The IRS-2 protein was detected in wild-type mouse vessels, but not the IRS-1 protein. The IRS-1-/- and IRS-2-/- mice also exhibited hyperinsulinemia, hypertriglyceridemia, and hypertension.
Conculusions: These findings collectively suggest that the increased neointima formation in IRS-2-/- mice at 8 weeks may be a direct consequence of lack of IRS-2 in the vessels rather than that of multiple risk factors for atherosclerosis. However, the increased neointima formation in IRS-1-/- and IRS-2-/- mice at 20 weeks can be due to additional effects of multiple risk factors. We therefore conclude that IRS-2 is more protective against the development of neointima formation compared with IRS-1 in mouse models of insulin resistance.

1838 Cell-cell contact by cadherins provides an essential survival signal to migrating smooth muscle cells

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Inhibition of vascular smooth muscle cell (VSMC) migration is a potential strategy for reducing intimal thickening during restenosis and vein graft failure. Migrating VSMCs establish cell-cell contacts mediated by cadherins and these could influence migration. In this study, we examined the effect of disrupting cadherins contacts on VSMC migration. Human saphenous vein VSMCs were grown to confluence on coverslips in the presence or absence of collagen type I and then the cell layer was subjected to wounding. Proliferation was inhibited by addition of 2mM hydroxyurea to the culture media. The distance of the migrating edge into the wound and the percentage of apoptotic VSMCs by in situ end labeling in the outermost 100μm were assessed 24 hours after wounding. Cell-cell contacts were disrupted by addition of 2mM EGTA, which chelates extracellular calcium required for integrins and cadherins, 200μg/ml cadherin binding site inhibitory peptide (HAV), 80μg/ml N-cadherin neutralizing antibody and adenoviral expression of dominant negative N-cadherin. Addition of EGTA significantly reduced VSMC migration by 90$\pm$9% and 86$\pm$11% on collagen and glass respectively (n=4, Student t-test, $p<0.05$). Migration was restored by addition of 2mM calcium but not magnesium. Selective inhibition of cadherin function using the HAV peptide significantly reduced migration by 56$\pm$5% and 53$\pm$8% on collagen and glass compared to the control peptide (n=3, Student t-test, $p<0.05$). Furthermore, inhibition of only N-cadherin function using neutralizing antibodies and adenoviral expression of dominant negative N-cadherin significantly reduced migration on glass by 33$\pm$1% and 40$\pm$12% compared to non-immune immunoglobulin and reporter gene controls, respectively (n=3, Student t-test, $p<0.05$). Death of VSMC was significantly increased by inhibition of cadherin function (EGTA 25$\pm$7-fold, HAV peptide 3$\pm$1-fold, N-cadherin antibody 3$\pm$1-fold, dominant negative N-cadherin 4$\pm$1-fold, n=4, Student t test, $p<0.05$). Death was abolished by addition of a caspases inhibitor, illustrating that caspases-mediated apoptosis is induced by disruption of cadherin cell-cell contacts. This increase in cell death clearly contributes to reduced migration of VSMCs. This study indicates that cell-cell adhesion mediated by cadherins, particularly N-cadherin, is a survival signal for migrating VSMCs. We suggest disruption of cadherin-mediated cell-cell contacts is a potential strategy for reducing VSMC migration and intimal thickening.

1839 Protein kinase C-δ regulates smooth muscle cell apoptosis and migration

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Purpose: We demonstrated previously that neointima formation in vein grafts is markedly accelerated in protein kinase C (PKC) delta-knockout mice (Leitges et al, J Clin Invest, 2001, 108:1505-1512). The aim of the present study is to elucidate the mechanisms of PKCdelta-enhanced arteriosclerosis.
Methods and Results: We undertook proteomic analysis of vascular smooth muscle cells (SMCs) from PKCdelta-/- mice. Profound changes in protein profiles were observed for mitochondrial enzymes related to energy metabolism and free radical generation. Functional assays confirmed a decreased production of reactive oxygen species in PKCdelta-/- SMCs, which was associated with resistance to apoptosis induced by cytokine treatment. In contrast, PKCdelta-/- SMCs rapidly underwent cell death after exposure to sodium nitroprusside (SNP), but not to other nitric oxide donors. SNP spontaneously releases nitric oxide and cyanide, a potent inhibitor of mitochondrial respiratory chain reactions. Moreover, PKCdelta deficiency was associated with changes in small heat shock proteins and the cytosolic chaperonin containing the T-complex polypeptide 1, which assist in the assembly and protection of cytoskeletal proteins. Immunofluorescence staining confirmed an abnormal cytoskeletal structure in PKCdelta-/- SMCs. Interestingly, platelet-derived growth factor BB (PDGF-BB)-induced cell migration was significantly diminished in PKCdelta -/- SMCs. Inhibition of PKCdelta by Rottlerin resulted in altered actin fiber rearrangement and decreased SMC migration after stimulation by PDGF-BB.
Conclusion: Taken together, our findings demonstrate that PKCdelta plays an essential role in SMC apoptosis and migration.

ASSESSING LEFT-VENTRICULAR FUNCTION: NEW ULTRASOUND METHODS

1841 Agreement among current clinical methods in ejection fraction quantification: gated single-photon emission computed tomography, contrast echocardiography and angiography

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Ejection fraction (EF) is a fundamental parameter in management and prognosis of heart diseases. The agreement among new methods currently used in clinical practice for EF quantification has not been fully established. To this end we compared EF determined by echocardiography, radionuclide study and contrsat angiography at an interval $<$ 4 hours in 37 consecutive patients (62$\pm$11 y) with good image quality in echo; 29 patients had ischaemic heart disease, 3 dilated cardiomyopathy, 3 aortic valve disease and 2 no heart disease.
Harmonic imaging (HAR) and contrast echocardiography (CON) with performed by Gated-SPECT (G-S). Both techniques were compared with angiographic ventriculography (ANG). EF values by ANG ranged from 19-80%.
Results: Correlations among non-invasive methods and ANG were good: HAR (r=0.75), CON (r=0.86)and G-S (0.74). HAR and CON sightly underestimated ANG (-5.2$\pm$10.9% and -4.4$\pm$8.4%, respectively); G-S significantly underestimated ANG (-15.8$\pm$11.4%). Taking into account EF ranges: $<$35%, 35-50% and $>$50%, the Kappa indices obtained with ANG were: HAR=0.55, CON=0.64 and G-S=0.12. The percentage of cases in wich differences $<$10% were: HAR=62%, CON=73%, G-S=23%.
Conclusions: Ejection fraction quantification by contrast echocardiography presents better agreement with angiography than harmonic imaging or Gated-SPECT. Gated -SPECT underestimates significantly the ejection fraction.

1842 Ventricular-arterial interaction in diastolic heart failure: relationship of arterial compliance with cardiac function, haemodynamics and workload

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Background: Arterial stiffness is thought to contribute to left ventricular (LV) dysfunction in diastolic heart failure (DHF). Using sensitive quantitative echocardiographic techniques, we examined the significance of ventricular-arterial interaction in hypertensive heart disease.
Methods: Ninety-six subjects (57 women, age 57±8y) were prospectively recruited in 3 groups: 39 hypertensive pts with DHF (symptoms of HF, no angina, LV ejection fraction>50%, diastolic dysfunction); 42 hypertensive pts with normal diastolic function (HT-NF); 15 normotensive controls. All underwent echocardiography for transmitral and pulmonary venous Doppler, tissue Doppler for systolic (Sa) and early (Ea) and late (Aa) diastolic velocities at septal and lateral mitral annulus, flow propagation velocity (Vp), and measurement of systemic arterial compliance (SAC). A subgroup (59pts) underwent maximal exercise treadmill testing (Bruce protocol).
Results: Of 39 pts with DHF, 30 had impaired relaxation, 9 pseudonormal filling. SAC was highest in controls (1.318±0.576 ml/mmHg), and became progressively lower in pts with HT-NF (1.045±0.347), impaired relaxation (0.911±0.408), and pseudonormal filling (0.797±0.447, p=0.008 by ANOVA). In DHF pts, SAC correlated negatively with age, systolic BP and filling pressures approximated by lateral E/Ea ratio, and positively with myocardial systolic and diastolic function (Table). Analysis of all pts with HT revealed similar results; in addition there were significant positive associations of SAC with Vp and exercise capacity, and negative associations with LV systolic wall stress, pulmonary venous atrial reversal velocity, E/Vp ratio and BNP in these pts.

	r	p
Age	-0.40	0.01
Systolic BP	-0.70	<0.01
Septal Sa	0.41	0.01
Lateral Ea	0.46	0.004
E/Ea ratio	-0.44	0.005

Conclusions: Progression to hypertensive heart disease is associated with increased arterial stiffness. Arterial compliance is a determinant of myocardial function and filling pressures in DHF.

1843 Exercise capacity and cardiac function assessed by tissue Doppler imaging in chronic heart failure

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Introduction-Chronic heart failure (CHF) causes reduced exercise tolerance. The reasons underlying impaired exercise capacity remain unclear. Conventional echocardiographic measures of resting ventricular function correlate poorly with exercise capacity. We examined the relation between longitudinal left ventricular function assessed by Tissue Doppler imaging (TDi) and exercise capacity in heart failure patients and controls.
Methods-We investigated 153 patients with chronic heart failure and 87 age and sex matched controls using echocardiography to measure conventional indices of left ventricular (LV) systolic function. We also used tissue Doppler imaging (TDi) to assess LV and right ventricular (RV) longitudinal function by measuring mitral during the cardiac cycle in six mitral annular positions, which were then averaged and lateral tricuspid annular velocities. Velocities measured at each point were the systolic peak (Sm) and the diastolic troughs of Am and Em corresponding to passive LV filling and LV filling due to atrial contraction respectively. Each patient also underwent treadmill exercise testing with metabolic gas exchange to derive peak oxygen consumption (pVO2) and the slope of the relationship between ventilation and carbon dioxide production (VE/VCO2 slope).
Results- LV and RV TDi velocities were significantly greater in controls than patients. LV ejection fraction (LVEF) correlated with Sm (r=0.30, p=0.0005), but not with Em, Am or the Em/Am ratio. There were no significant differences between NYHA classes for any of the TDi variables. RV indices were not related to exercise capacity. Systolic and diastolic TDi values correlated more closely with pVO2 than LVEF (r=0.21, p<0.02); S2 (r=0.35, p<0.0001), Em (0.20, p<0.05), Am (r=0.23, p<0.02). The Em/Am ratio did not correlate with pVO2. In multiple regression with Sm, Em, Am and Em/Am ratio, Sm was the only LV TDi variable to predict exercise capacity independently (p<0.05).
Conclusions- Exercise capacity and symptoms are poorly related to conventional measures of central cardiac function but more closely related to indexes of longitudinal left ventricular function as assessed by TDi.

1844 Echocardiographic screening for heart failure must analyse left-ventricular longitudinal function. Comparison versus brain natriuretic peptide

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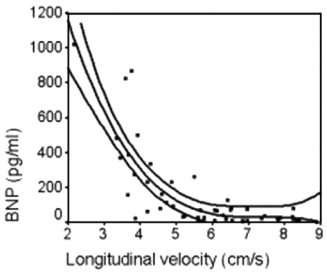
Echocardiographic screening for LV dysfunction is still based on the assessment of ejection fraction (EF). Compared against biochemical markers such as brain natriuretic peptide (BNP), however, EF performs suboptimally. Assessment of longitudinal (subendocardial) LV function is a more sensitive marker of early changes in systolic function caused by ageing or subclinical disease, and therefore we investigated its diagnostic potential in suspected heart failure, in a comparison against BNP.
Methods: 50 subjects (65±12 yrs) were examined by echocardiography; plasma BNP was measured by fluorescence immunoassay. Global systolic function was assessed from EF (Simpson's rule), and global diastolic function from the transmitral flow propagation velocity (colour M-mode). Digital image loops of tissue Doppler were analysed off-line. Radial function was assessed from the velocities of the posterior wall (parasternal view), and longitudinal function as the mean velocity of 4 basal segments (apical views).
Results: Global EF correlated with BNP (r=-0.47), as did global diastolic function (r=-0.55), and radial systolic function (r=-0.61) (all Spearman's, and p<0.01). The echo parameter that correlated best with BNP, however, was LV longitudinal function (r=-0.77, p<0.001) (graph). By stepwise multiple regression analysis, BNP was also predicted by longitudinal systolic velocity, in association with LV mass index (r=0.78, r^2=0.60, p<0.001). Sensitivity and specificity of LV longitudinal function to diagnose subclinical heart failure (BNP>100 pg/ml) were 88% and 91%, respectively.



BNP vs longitudinal velocities.

Conclusion: Echo diagnosis of subclinical LV dysfunction or suspected heart failure, especially in patients with normal radial systolic function, must include assessment of longitudinal systolic function.

1845 Cardiac function by strain imaging: key to the increased performance capacities of endurance trained athletes

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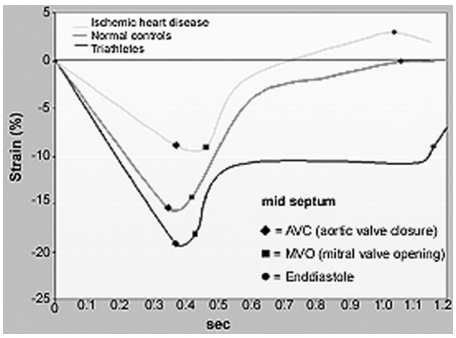
Background: To increase the performance capacity of a triathlete (Tri), a variety adaptations are necessary. The heart is the central and the most important limiting factor. The structural heart adaptations in Tri have important repercussion on cardiac function. The left ventricular diastole shows specific characteristics that determine the performance capacity.
Methods: 40 male Tri were compared with 31 active male controls and with 112 patients with ischemic heart disease. All subjects underwent tissue doppler and strain imaging.
Results: The late diastolic filling period in Tri has specific characteristics. Tissue imaging demonstrated in Tri specific characteristics of both the late passive diastolic filling period and the early active diastolic relaxation period. Extremely striking were the significant differences between the three groups concerning the strain values at the basal and the mid septum in the longitudinal axis by aortic valve closure and by mitral valve opening. Fascinating were the values of the enddiastolic strain by the end of the a-wave: negative in Tri, near zero in normal controls and marked positive in coronary patients (figure).



Conclusions: The marked negative enddiastolic strain in Tri can be explained by an increased muscular tone after a rapid and almost complete early diastolic filling of the left ventricle. This increased muscular tone is caused by an increase in the sarcomere length and by an increase in the number of actin-myosin crossbridge interactions. These specific systolic and especially supernormal diastolic properties of the left ventricle with an increased diastolic reserve, enhance the aerobic capacities, resulting in an increased performance capacity.

1846 Assessment of left-ventricular volumes and function using high-resolution transthoracic real-time three-dimensional echocardiography: comparison of semi-automatic border detection with manual contour tracing

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A new real-time (rt) three-dimensional echocardiography (3DE) system has been introduced allowing acquisition of rt-3DE data sets with improved image quality and high spatial resolution. Additionally, a novel semi-automatic contour detection algorithm has been developed allowing for quantitation of left ventricular (LV) volumes with only minimal interaction by the investigator. The aim of the present study was to compare end-diastolic (EDV) and end-systolic volumes (ESV) and ejection fraction (EF) determined by the semi-automatic border tracking algorithm with results obtained by manual tracing in data sets acquired with high-resolution rt-3DE.
Methods: In twenty patients with and without heart disease rt-3DE (Sonos 5500, Philips Medical Syst., Andover, MA) was performed from an apical window using a novel matrix transducer (Live 3D, Philips). The system allows acquiring of a pyramidal volume (sector width ~90°x90°) in a short breath-hold of 6-8 seconds duration with ECG triggering. Data sets were transferred to a workstation for off-line data analysis. The semi-automatic border detection algorithm (4D analysis 1.1, TomTec Imaging Syst., Unterschleißheim, Germany) obviates the need for manual border tracing. After initiation of the model with placement of an ellipse within the cavity of the left ventricle at end-systole and end-diastole, contours are detected automatically using Finit Impulse Response and Thin-Plate-Splines. Two observers independently analyzed the data, one observer using the semiautomatic method and the other using manual contour tracing (LV analysis, TomTec).
Results are given in the table.

	Semi-automatic	Manual	r	Mean difference
EDV (ml)	155±119 ml	159±120 ml	0.99	-4±5 ml
ESV (ml)	88±114 ml	89±111 ml	0.99	-1±8 ml
EF (%)	54±16%	54±16%	0.98	0±3%

Results for volumes and function determined by the semi-automatic method and by manual contour tracing.

Conclusion: The semi-automatic border detection method allows accurate assessment of LV volumes and function compared with manual border tracing performed by an independent observer in data sets acquired with rt-3DE. Further validation of the method using an independent reference standard is warranted.

EPIDEMIOLOGIC ASPECTS OF HYPERTENSION

1847 The incidence rate and the determinants of subsequent development of hypertension in normotensive screened subjects in Okinawa, Japan

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Hypertension is an important risk factor of cardiovascular disease and a prevention of development of hypertension is an essential public issue. The aim of the present study is to evaluate the incidence rate and the determinants of subsequent development of hypertension in normotensive screened subjects in Okinawa, Japan. Subjects were the participants of one-day clinic both 1997 and 2000 held by Okinawa General Health Maintenance Association. Those who were treated as hypertension or receiving medications for heart disease were excluded. In total, 4407 normotensive subjects (2916 men, 1554 women, from 18 to 89 years of age) were studied. These subjects were classified as optimum (systolic <120 mmHg and diastolic <80 mm Hg, n=2402), normal (systolic 120-129 mm Hg and diastolic 80-84 mmHg, n=1268), high normal (systolic 130-139 mmHg or diastolic 85-89 mmHg, n=800) according WHO-ISH BP classification of blood pressure. The incidence rate of subsequent development of hypertension was 1.6% subjects with optimum BP, 6.9% with normal BP, and 19.1% with high normal BP. The relative risk of subsequent development of hypertension was elevated in relation to their initial BP levels. The relative risk (95% CI) of subsequent development of hypertension was 4.28 (2.89-6.33) subjects with normal BP, and 12.69 (8.70-18.50) subjects with high normal BP compared with optimum BP as the reference. The odds ratios (OR) and 95% confidence intervals (95% CI) of the determinants of subsequent development of hypertension were age (OR: 1.02, 95% CI: 1.00-1.03), obesity (OR: 1.35, 95% CI: 1.04-1.74), proteinuria (OR: 1.52, 95% CI: 1.09-2.12) and weight gain (OR: 1.08, 95% CI 1.01-1.15). However, sex, hyperlipidemia, diabetes mellitus and current smoking were not statistically significant. In conclusion, the incidence rate of subsequent development of hypertension subjects with normal BP or high normal BP was significantly higher than those with optimal BP. Our data also suggest that intervention may be needed even if the subjects were normotensive. Weight control, especially the correction of obesity may be the most important factor for prevention of hypertension. Moreover, subjects with proteinuria should be carefully followed.

1848 Prevalence of clinically recognized hypertension and dyslipidaemia in the United Kingdom

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Aim: To estimate the prevalence of recognised, clinically relevant hypertension (HT) and dyslipidaemia (DL) in a UK primary care setting. Method: Using the General Practice Research Database (GPRD) for the years 1997 to 2001, we identified patients with recognized HT (with a clinical diagnosis of HT or blood pressure above 140/90 mmHg averaged over 3 successive occasions, or who were treated for HT,recognized DL (with a clinical diagnosis, a total cholesterol above 6.2mmol/L or who were treated for DL), or were medically monitored (ie blood pressure or lipid tests) for either condition. We compared the observed rates with rates reported by the 1998 Health Survey of England(HSE). Results were examined for time trends.
Results: Table 1 shows the prevalence of recognised HT and DL in the population aged 40+ years in 1998 (HSE rates in parentheses). About half of the HT+ men and one quarter of the HT+ women in this age group were undiagnosed, and 84% of DL+ women and 65% of DL+ men were undiagnosed. The prevalence of recognised HT/DL comorbidity was 5% in men and 4% in women. The prevalence of recognised DL in patients with recognised HT was 16% in men and 12% in women. Monitoring rates for HT changed little over the period 1997-2001, so the rates of undiagnosed HT in 2001 probably remained similar to those in 1998. Monitoring rates for DL increased in patients with recognized HT, but not in other patients. In 2001, the prevalence of recognized DL in patients aged 40+ was 9% in women and 10% in men, and for patients with recognised HT it was 25% in men and 19% in women.

Table 1

	Men (N=529,565)			Women (N=600,115)		
	HT-	HT+	Total	HT-	HT+	Total
DL-	69.4	23.3	92.7 (77)	63.7	30.4	94.1 (69)
DL+	2.7	4.6	7.3 (23)	1.8	4.1	5.9 (31)
Total	72.1	27.9	100	65.4	34.6	100
	(50)	(50)		(56)	(44)	

Prevalence of recognised HT and DL in the population aged 40 years or older in 1998

Conclusions: If the true prevalence of DL has not increased since 1998, these results suggest that 71% of women and 54% of men with DL were undiagnosed in 2001, and that a substantial proportion of patients with comorbid HT/DL remain undiagnosed.

1849 Left-ventricular hypertrophy increases the risk for microalbuminuria exclusively in hypertensive subjects

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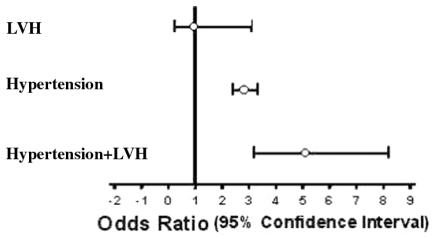
Objective: In recent data hypertensives with left ventricular hypertrophy (LVH) on ECG, were independently associated with microalbuminuria (MA), suggesting cardiac and microvascular damage. Whether LVH is associated with MA in normotensive subjects is unknown. Therefore, the present study was undertaken to evaluate the interrelationship between LVH and MA in normotensive subjects. Furthermore, we investigated whether LVH adds to the risk on MA in hypertensive subjects.
Methods: In a large population based survey (8040 subjects), standard 12-lead electrocardiograms (ECG) were recorded, and classified according to the Minnesota code. LVH on ECG was present in 154 (1.9%) subjects. Mean age was 49 $\pm$ 12.6 years and 51.5% was male. Microalbuminuria was defined as 30-300 mg/24h.
Results: In a multivariate regression analysis, adjusted for gender, age and atherosclerotic risk markers (obesity, smoking, hypercholesterolemia and C-reactive protein), hypertension was significantly associated with MA. Interestingly, hypertension in combination with LVH increased the risk for MA. On the other hand, LVH in normotensive subjects showed no association with MA (see figure).



Conclusion: No association was observed between LVH and MA in normotensive subject. However, hypertension was related to MA, and in the presence of LVH this association was even stronger.

1850 Insulin levels, sleep apnea and sympathetic activity in obesity

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Studies on sympathetic nervous system activity in obesity have provided conflicting results, and both decreased and increased sympathetic activity has been reported. Furthermore, obese patients have a high prevalence of insulin resistance and sleep apnea, both having been proposed to influence sympathetic activity. We analyzed the relationships between insulin levels, sleep apnea and sympathetic activity in an obese population.
Data from 4000 obesity patients included in the Swedish Obese Subjects (SOS) study were analyzed. BMI and sagittal diameter were used as measures of general and central obesity, respectively. Patients were asked if a family member or other person had observed frequent pauses in breathing during sleep and those who reported a positive history were considered to have sleep apnea. Twenty-four-hour urinary norepinephrine excretion was used as an estimate of sympathetic activity.
BMI, sagittal diameter and insulin levels all correlated with 24-hour norepinephrine excretion (r ranging from 0.18 to 0.28, $p<0.001$). The mean level of 24-hour norepinephrine excretion was 77 nmol/24 hr (22%) higher in patients with sleep apnea as compared to those without (95% CI 63-92). In multiple regression analysis, controlling for age and sex, BMI, sagittal diameter, insulin levels and the presence of sleep apnea were all independently and positively associated with 24-hour norepinephrine excretion ($p<0.001$).
It is concluded that general and central obesity is associated with increased sympathetic nervous system activity. Furthermore, both the degree of insulin resistance and the presence or absence of sleep apnea in such patients with are of importance for the level of sympathetic activity.

1851 Air pollution are related to increase in blood pressure

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Purpose: Investigating the effects of urban air pollutants on blood pressure (BP).
Subjects and Methods: 46 male traffic controllers, mean age of 39.2 years ($\pm$ 6.4), non-smokers and healthy, with at least complete high school education, working in high traffic avenues in São Paulo City, Brazil. We performed 24-hour ambulatory blood pressure monitoring, in working days, in three different periods: August 2000 (winter), January/February 2001 (summer), and August 2001, corresponding to different mean levels of air pollutants exposure. Linear regression models with generalized estimating equations (GEE) were used to assess the effect of particulate matter with aerodynamic diameter less than 10 μm (PM10), CO, SO2, NO2, and O3 on 24-hour mean pressure and systolic and diastolic blood pressures when the workers were awake, controlling for temperature, humidity, age, and body mass index.
Results: Excepting O3, all pollutants were high in winter and were positively associated with changes in blood pressure. An interquartile range increase of PM10 (33.6 mg/m^3) was associated with increases of 6.0 mm Hg (95% CI: 4.1 - 8.0), 3.4 mm Hg (95% CI: 2.0 - 4.7), and 3.7 mm Hg (95% CI: 2.4 - 5.0) on systolic, diastolic, and 24-hour mean blood pressures, respectively.
Discussion: This result is similar to those observed by other authors. However, in the present study, estimates were done using a 24-hour blood pressure monitoring, device that gave more accuracy to the results.
Conclusions: The results showed that blood pressure levels are direct related to air pollution levels, even after controlling for temperature, age, humidity, and body mass index, in a healthy group of workers.

1852 Increased dietary sodium intake correlates to left-ventricular hypertrophy and geometry and microalbuminuria in arterial hypertension

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Introduction: Left ventricular hypertrophy (LVH) and geometry reflecting myocardial involvement and microalbuminuria (MARB) reflecting microvascular damage are strong, independent risk factors for cardiovascular disease in arterial hypertension. Their relationship with dietary sodium intake has not been adequatly examined.
Methods: The study comprised 3710 consecutive, non diabetic patients, with uncomplicated, untreated, mild - moderate essential hypertension. Sodium was measured in 24hour urine collection (Na24). The patients were classified in Na24 quartiles. a) Left ventricular mass index (LVMI) and geometry were calculated after echo evaluation. b)Microalbumin, a-1 microglobulin, sodium (Na24) and the microalbumin/creatinine ratio (ACR) were measured in 24hour urine collection.
Results: a) Gradual increase of LVMI (F=51.4, $p<0.00001$) was found in the quartiles, while the incidence of LVH also increased in parallel to the quartiles (42 to 56%, $p<0.00001$). Moreover, normal geometry and concentric remodeling incidence was inversely related to Na24 quartiles while the incidence of eccentic hypertrophy increased in parallel to the quartiles. Gradual Na24 increase was demonstrated for LVMI quartiles. (F=42.1 $p<0.00001$). b) Gradual increase of microalbumin (F=23 $p<0.00001$), a-1 microglobulin(F=8.7 p=0.0003) and ACR(F=258 $p<0.00001$) was found in the quartiles, while the incidence of microalbuminuria, a-1 microglobulinuria, and ACR>30 also increased in parallel to the quartiles/(from 40 to 50%, from 25 to 38% and from 29 to 43%, respectively). Gradual Na24 increase was demonstrated for ACR quartiles. (F=27.3, $p<0.00001$).
Conclusions: Increased dietary sodium intake, as indicated by elevated urine Na24 correlates with LVH/or concentric remodeling and microalbuminuria in non diabetic hypertensive patients.

IS THERE A HEART BEHIND A STROKE?

1853 Fixed low dose warfarin reduces the risk of stroke after myocardial infarction

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Background: After an acute myocardial infarction patients are at increased risk of various cardiovascular complications, of which stroke is one of the most serious and costly. The value of low dose warfarin in reducing such complications has been under debate. Furthermore, risk factors for stroke during long term follow-up after myocardial infarction are less well documented in the literature.
Aim: To evaluate the efficacy of a fixed low dose of warfarin in combination with aspirin after myocardial infarction and, in addition, to identify risk factors for stroke after myocardial infarction during long term follow-up.
Methods: Patients hospitalized for myocardial infarction were randomized to fixed dose warfarin 1.25 mg od without INR controls and aspirin 75 mg od or to aspirin 75 mg od alone.
Events were registered during a mean follow-up of 4.7 years (range 1.7 – 6.7 years). Endpoints were adjudicated blindly using the PROBE design (Prospective Randomized Open-label Blinded Endpoint Evaluation).
Results: A total of 3.300 patients were randomized in 31 Swedish hospitals, 1.659 to warfarin and aspirin in combination and 1.641 to aspirin alone. Of these patients 159 (6.0%) suffered a stroke. Addition of fixed low dose warfarin to aspirin was associated with a lower risk of stroke (RR; 95% CI 0.39; 0.22-0.71) compared to aspirin alone. Factors associated with an increased risk of stroke in the total population were high age (> median 68 years) (3.7; 2.0-6.8), diabetes mellitus (3.1; 1.7-5.6), previous stroke (3.0; 1.4-6.5) and hypertension (2.0; 1.2-3.6).
Conclusion: Treatment with fixed low dose warfarin in combination with aspirin reduced the risk of stroke after myocardial infarction compared to treatment with aspirin alone. Risk factors associated with an increased risk of stroke were high age, diabetes mellitus, previous stroke and hypertension.

1854 Magnitude of, and risk factors for, stroke in patients with acute coronary syndromes. The global registry of acute coronary events

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Background: Risk of stroke may be affected by modern treatment regimens. The aim of this study was to determine the incidence, risk factors for, and clinical consequences of stroke in a large unselected population of patients with the full spectrum of acute coronary syndromes (ACS). **Methods:** GRACE is a prospective registry enrolling ACS patients from 94 hospitals in 14 countries. Patients were stratified according to the occurrence of stroke in-hospital. **Results:** Data from 20,140 ACS patients were analysed. A total of 218 strokes occurred: 1.6% in ST-elevation myocardial infarction (STEMI), 1.1% in non-STEMI, and 0.6% in unstable angina. Particular types of strokes were recorded: embolic 58.2%, haemorrhagic 23.8%, other 17.9%. Adverse outcomes including myocardial infarction, heart failure, cardiogenic shock, cardiac arrest, atrial fibrillation/flutter, acute renal failure, atrioventricular block, major bleeding and death were more frequent in patients with stroke. In-hospital mortality in the stroke vs non-stroke groups was: 28.1% vs 5.2% (OR 7.2, 95% CI 5.5-9.7). Multivariate logistic regression analysis identified the following risk factors for stroke (table).

Variable	OR	95% CI	P-value
CABG	3.1	2.1-4.5	<0.0001
Thrombolytics (t-PA or r-PA)	3.0	2.1-4.2	<0.0001
Prior stroke	1.8	1.2-2.7	<0.004
Chronic use of aspirin	1.5	1.1-2.0	<0.007
Female gender	1.4	1.01-1.7	<0.05
Age (per 10-year increase)	1.03	1.02-1.05	<0.0001

Conclusions: The incidence of stroke varies according to ACS type, being the highest in STEMI. Embolic stroke occurs most frequently. Stroke in ACS patients is uncommon but this devastating event is associated with high mortality. Identification of risk factors for stroke, including iatrogenic, warrants particular care.

1855 Risk factors for stroke and thromboprophylaxis in atrial fibrillation. What happens in daily clinical practice? (The GEFAUR-1 study)

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Background: The indications for stroke prophylaxis in atrial fibrillation (AF) are detailed in widely available guidelines based on the results of several clinical trials. However, there is contradictory data concerning the applicability of these recommendations in daily practice due to differences on patients' risk profiles (embolic and haemorragic). **Objectives:** to determine patients risk profile, the real prescription of stroke prophylaxis and the applicability of the guidelines (ACCP, 1998) in a scenario of daily clinical practice. **Methods:** Prospective observational study carried out in 12 emergency departments (ED). Data was collected on clinical-epidemiological variables, risk factors (RF) for stroke, the prophylaxis prescribed and the reasons for no anticoagulation. Therapeutical reccomendations were not made. **Results:** We included 1,178 patients, age 74±12 years, 55.6% older than 75 (28% of them disabled). Hemorrhagic complications of current antithrombotic treatment (ATT) were responsible for the ED attendance in only 0.8% of the cases and 1.8% of hospital admissions while embolism was responsible of 3.7% and 10.5% of them. Of patients without current ATT, 86% had RF for stroke (2 RF 28%, >2 RF 30%), but anticoagulation was only prescribed to 31.8%.In the multivariate analysis its indication was only associated to paroxysmal AF (OR=3.61; $p<0.001$) and a heart rate > 100 bpm (OR=1.69; p=0.03),while a negative correlation was obtained with disability (OR=0.28; p=0.012), current antiplatelet treatment (OR=0.04; $p<0.001$) and cardioversion attempt in the ED (OR=0.24; p=0.039). Anticoagulants were formerly contraindicated in 23%. Reasons argued for not to prescribe anticoagulants in spite of the presence of RF for stroke were advanced age (12%), high risk of haemorrhage (28%) or it was not considered indicated by the physician (24%). **Conclusions:** Patients with AF attended in the ED have a higher embolic risk than those included in clinical trials and a similar risk of haemorrhage. It suggest that the benefits from acting in accordance with the guidelines recommendations in ED daily practice would be even greater. In spite of this, the prescription of anticoagulants is insufficient, fundamentally due to the lack of knowledge about the indications for prophylaxis and the inappropriate impact of the advanced age of the patients in medical decisions. Given the high effectiveness of antithrombotic treatment, application of clinical practice guidelines in routine practice should be emphasized with the aim of improving the prognosis and quality of life of these patients.

1856 Leptin predicts stroke in males, but not in females

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The adipocyte-derived hormone leptin may be an important link between obesity and cardiovascular disease. In this prospective nested case-referent study, we tested whether leptin is a risk marker for a first-ever stroke.
Two hundred seventy six cases with first-ever stroke (234 cases with ischemic and 42 with haemorrhagic stroke) were identified who, prior to the stroke, had participated in population based health surveys in northern Sweden. Referents were matched for sex, age, date and type of health survey and geographic region. Blood pressure (BP), body mass index (BMI), presence of smoking, diabetes and hypertension were recorded and cholesterol was analysed. Leptin was analysed in stored samples. Risk markers for first-ever stroke were analysed by conditional logistic regression analysis.
The stroke event occurred on average 4.9 years after the initial survey. Subjects with a future stroke were more obese and had higher levels of cholesterol and fasting glucose and had a higher frequency of diabetes mellitus and hypertension. Leptin levels were higher in male subjects with a future stroke (p=0.004). Leptin correlated independently to diastolic blood pressure (p=0.003) and cholesterol (p=0.01) in men, and to postload glucose (p=0.01). A high leptin level predicted stroke independently in men (ORQ4=3.16; 95%CI: 1.32-7.61) but not in women. The increased risk was similar for both ischemic and hemorrhagic stroke. Males with high leptin developed their stroke faster than males with low levels (p=0.0009) and the time-related effect of leptin was independent of traditional risk factors. An interaction analysis indicated a positive interaction between high blood pressure and high leptin in men.
A high leptin level is independently associated with both risk for and time to a first-ever stroke in men but not in women. Leptin may be a key link in the development of cardiovascular disease in obesity.

1857 Is anticoagulation required in patients with unexplained cerebrovascular accident and paroxysmal junctional tachycardia?

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The purpose of the study was to assess the significance of paroxysmal junctional tachycardia (PJT) in patients studied for unexplained embolic cerebrovascular accidents (CVA). Some of them are related to atrial tachycardia or fibrillation (AT/AF), but the significance of other arrhythmias remains unknown.
Methods: the population of study consisted of 128 patients, aged 32 to 82 years, who had presented an unexplained CVA unrelated to an overt AT/AF or a vascular disease; 24 Hour Holter monitoring, 2D and/or transesophageal echocardiogram and transesophageal or intracardiac electrophysiologic study were indicated: at baseline, atrial pacing up to 2 nd d AV block and programmed atrial stimulation using 1 and 2 extrastimuli delivered on 2 CL's (600, 400 ms) were performed and if necessary were repeated after infusion of 20- 30 μg of Isoproterenol.
Results: 1) salvos of atrial premature beats (APB) were noted in 38 patients; 2) there was no thrombi in left atrium, but underlying heart disease was present in 18 patients (hypertrophic cardiomyopathy 3, moderate aortic valvular disease 2, aneurysm of atrial septum 2, ischemic heart diseas 6, dilated cardiomyopathy 5); 3) electrophysiologic study remained negative in 74 patients (58%); sustained (>1 min) AF/AT was induced in 27 patients (21%); 12 of them had an underlying heart disease and 7 had salvos of APB's on Holter monitoring; PJT was induced in 17 patients (13%) (atrioventricular nodal reentrant tachycardia 15, reentrant tachycardia in a concealed accessory pathway 2; in 2 patients with inducible PJT, PJT degenerated into AF; all, but two were older than 65 years; none of the patients had an underlying heart disease, but 5 of them had salvos of APB's on Holter monitoring. During the follow-up, 4 patients with inducible AT/AF developed later spontaneous AF; 1 patient without inducible SVT had repeated strokes, but remained sinusal; 4 patients with inducible AVNRT had frequent tachycardias, requiring RF ablation of the reentrant circuit. 1 of them dead from a new CVA after anticoagulation was stopped; 3 patients developed documented AF.
Conclusion: in 13% of patients with unexplained stroke, paroxysmal junctional tachycardia was the only possible cause for the embolic event; the relationships between PJT and AF were previously reported; therefore these patients required anticoagulation even after the curative treatment of PJT by catheter ablation of the reentrant circuit.

1858 Realtime three-dimensional contrast echocardiography improves interatrial shunt localisation

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Purpose: The aim of the study was to assess the differences in diagnostic quality of transthoracic echocardiography in postinterventional interatrial occluder control using contrast in realtime three-dimensional echocardiography versus standard 2D views.
Methods: In a total patient population of 152 patients after percutaneous interventional closure of patent foramen ovale (PFO) with or without atrial septal aneurysm (ASA) was performed with Amplatzer and STARFlex devices. All patients had a history of ischemic stroke or transient ischemic attack (TIA) and a documented right-to-left shunt (RLS) in transesophageal echocardiography(TEE), which was also used during the interventional closure procedure. Follow-up consisted of contrast transthoracic echocardiography after one day, one, three and twelve months after the intervention with one TEE procedure. Starting in 2002 realtime 3D contrast studies were used to control both localisation of the device in the fossa ovalis and of potential residual shunts. Image aquisition and analysis were performed realtime within only 5 to 7 seconds including valsalva pressure tests on a Sonos 7500 3D echo scanner and on a 3D workstation (TomTec Imaging Systems).
Results: The devices were placed correctly in all patients. Residual shunts could be demonstrated during the first three months after PFO closure affecting more STARFlex than Amplatzer devices. Sensitivity of very small residual shunt detection with few bubbles was higher in 2 D echocardiography but exact shunt localisation was possible in realtime 3D echo demonstrating a main localisation at the valvular and anterior rim of the occluder. Most of the residual shunts could only be detected on valsalva tests which were possible in the new realtime 3D procedure but excluding conventional 3D recontructional approaches.
Conclusions: Realtime 3D contrast echocardiography is able to control size, localisation and function of interatrial closure devices giving instantaneous additional shunt information.

NUCLEAR IMAGING: EVOLVING ROLE IN DIAGNOSIS AND PROGNOSIS

1859 Life-threatening arrhythmias during the follow-up of patients with idiopathic ventricular fibrillation: impact of presynaptic sympathetic innervation

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Background: Idiopathic ventricular fibrillation (IVF) is a rare cardiac rhythm disorder characterised by episodes of ventricular fibrillation (VF) in the absence of other underlying structural cardiac or known rhythm disease. The only therapeutic option appears to be the implantation of an ICD. So far, little is known about pathogenetic mechanisms and the relevance of methods for individual risk stratification in IVF patients. Therefore, we evaluated the impact of 123I-Meta-Iodo-benzylguanidin scintigraphy (123I-MIBG-SPECT) in 20 patients with IVF.
Methods: In 20 IVF patients, 13 male and 7 female (mean age 37±13years), 123I-MIBG-SPECT was performed off antiarrhythmic drugs. Images were acquired four hours post injection and analysed for regional 123I-MIBG uptake in a 33-segment bull's eye scheme.
Results: An abnormal 123I-MIBG uptake was observed in 13 patients (65%). During a mean follow-up of 7.2±1.5 years (range 4.9 to 10.5 years), 4 patients (31%) with an abnormal tracer uptake experienced recurrent episodes of VF/fast polymorphic ventricular tachycardias after a mean time interval of 2.5±1.6 years. No patient with normal sympathetic innervation succumbed a second episode of ventricular tachyarrhythmias.
Conclusions: An impairment of adrenergic innervation seems to account for a higher risk of a recurrent episode of ventricular fibrillation in patients with IVF. Studies in larger cohorts are required to validate the significance of 123I-MIBG-SPECT during the long-term follow-up of these patients.

1860 ^{123}I-MIBG dynamic single-photon emission computed tomography in patients with congestive heart failure

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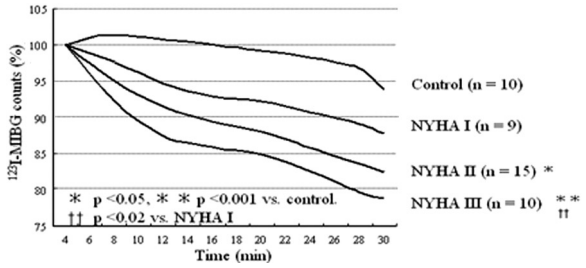
Previously studies have reported that ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) is useful for the assessment of severity and prognosis in patients with congestive heart failure. Purpose: To examine ^{123}I-MIBG kinetics in the early phase soon after tracer injection, we performed dynamic single photon emission computed tomography (SPECT) in 34 patients with congestive heart failure and 10 control subjects. The consecutive 15 images of 2 min-dynamic SPECT were acquired for 30 min after injection. From 0 to 4 min, a significant amount of radioactivity existed in the blood pool, thus we calculated washout rate of ^{123}I-MIBG from 4 to 30 min (WR-E).
Results: As the New York Heart Association (NYHA) functional class advanced, WR-E increased (control, NYHA I, II, and III; -20±7, -45±6, -64±9*, -93±21**# counts/min, respectively, *p <0.05 vs. control, **p <0.001 vs. control, and #p <0.02 vs. NYHA I). WR-E was compared with hemodynamic parameters. WR-E was correlated with conventional WR from 30 min to 4 hr (R = 0.46, p <0.05), and was inversely correlated with mean pulmonary artery pressure (R = 0.49, p <0.02) and pulmonary capillary wedge pressure (R = 0.39, p <0.05).



^{123}I-MIBG washout from dynamic SPECT.

These data suggest that washout rate of ^{123}I-MIBG in the early phase (4-30 min) reflects cardiac sympathetic nervous disintegrity and is useful to evaluate the severity of congestive heart failure.

1861 Prognostic value of exercise ^{99m}Tc-tetrofosmin myocardial perfusion single-photon emission computed tomography for the prediction of cardiac events

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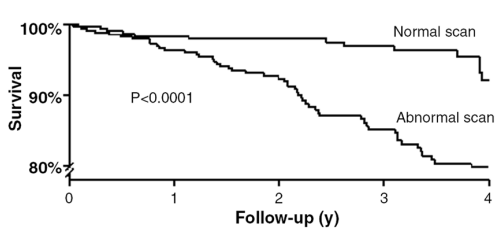
Background: This study assessed the incremental value of exercise 99mTc-tetrofosmin SPECT for the prediction of cardiac events in patients with known or suspected coronary artery disease.
Methods: Exercise 99mTc-tetrofosmin SPECT imaging was performed in 655 consecutive patients. Follow-up was successful in 648 (98.9%) patients. Ten patients underwent early coronary revascularization and were excluded. End points were cardiac death, nonfatal infarction, and late (>60 days) coronary revascularization. An abnormal study was defined as the presence of fixed and/or reversible perfusion defects. A summed stress score (SSS) was derived to estimate the extent and severity of perfusion defects.
Results: An abnormal scan was detected in 344 (54%) patients. During a mean follow-up period of 4 ± 1.3 years, 56 (9%) patients died (22 cardiac deaths). Nonfatal myocardial infarction occurred in 19 (3%) patients, and 89 (14%) patients underwent late coronary revascularization. An abnormal scan was an independent predictor of cardiac death (hazard ratio 3.5, CI 1.1-12.2), and provided incremental information over clinical and exercise test data (Loglikelihood -133 to -125, P<0.05). The SSS provided incremental prognostic information over clinical data as well (Loglikelihood -133 to -127, P<0.05) (hazard ratio 1.23 (CI 1.10-1.38). An abnormal scan (hazard ratio 3.3 (CI 1.1-12.2)) and the SSS (hazard ratio 1.25 (CI 1.07-1.45)) were powerful independent predictors of the combined end point of any cardiac event.
Conclusion: Exercise 99mTc-tetrofosmin myocardial perfusion SPECT provides information incremental to clinical data, for the prediction of cardiac events in patients with known or suspected coronary artery disease.



Cardiac events.

1862 Influence of infarct-zone viability detected by rest ^{99m}Tc-sestamibi-gated single-photon emission computed tomography on left-ventricular end systolic enlargement after acute myocardial infarction treated by percutaneous transluminal coronary angioplasty in the acute phase

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Background: The left ventricular (LV) end systolic volume (ESV) is the most important predictive factor on the long term prognosis in patients (pts) surviving acute myocardial infarction (MI). Tc-99m-Mibi SPECT is a useful method for the analysis of the myocardial perfusion and function and can be used for the detection of myocardial viability.
Aim of the study: To analyse the importance of myocardial viability detected by rest Tc-99m-Mibi SPECT on the LV volumes evolution in pts treated by PTCA in the acute phase of MI.
Material and Methods: A series of 29 pts treated successfully by emergency PTCA were included in this study. All pts had two contrast LV angiography, performed immediately after PTCA and at the 6-month control coronarography. The global LV ejection fraction (EF), end diastolic and end systolic volumes were analysed using area-length method. The rest Tc-99m-Mibi was performed 30±15 days after PTCA. The severity of perfusion defect in the territory of MI was calculated using a quantitative method and expressed in standard deviation (SD). The systolic thickening and wall motion in the corresponding sectors were analysed with a semi-quantitative method using a 3-point scoring system.
Results: Two groups (Gr) of pts were individualised, based on the individual evolution of the ESV; Gr I (n=21, 72%) without ESV enlargement (from 25.4±9.7 ml/m^2 to 25.1 ±8.9 ml/m^2, p=ns), and Gr II (n=8, 28%) with ESV dilatation (from 32±16.7 ml/m^2 to 48.5±16 ml/m^2, p<0.01). The perfusion defect in the territory of MI was -2.3±2.9 SD in Gr I and -6.4±2.8 SD in Gr II (p<0.01). The scores of wall motion were 1.2±0.6 in Gr I and 0.5±0.5 in Gr II (p<0.01) and the scores of systolic thickening were 6.4±3.7 and 2.2±2.4 (p<0.05), respectively. With the cut off value of -2.5 SD for tracer uptake in the infarct zone, the sensibility and specificity of Tc-99m-Mibi SPECT for the prediction of ESV enlargement are 100% and 62%. When the functional data from gating are added the sensibility and sensitivity are 87.5% and 85.7%, respectively.
Conclusions: 1) Despite a successful PTCA in the acute phase of MI, the ESV enlargement at 6 months is observed in 28% of pts. 2) Tc-99m-Mibi Gated SPECT performed four weeks after the acute phase can predict this enlargement with a high accuracy.

1863 Impact of viability, ischaemia, scar tissue and revascularization on outcome after aborted sudden death

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Background: Survivors of aborted sudden death due to ventricular arrhythmias in the presence of coronary artery disease are at risk for recurrences. The substrate underlying these arrhythmias is not clear and therefore the relation between ischemia, viability, scar tissue (and revascularization), and the incidence of ventricular arrhythmias (and sudden death) was studied over a 3-year follow-up period.
Methods and Results: 156 survivors of sudden death underwent stress-rest perfusion imaging. Patients with ischemic/viable myocardium (n=73) were revascularized if possible. Final antiarrhythmic therapy was based on the outcome of electrophysiological testing and/or left ventricular ejection fraction (LVEF). Implantation of a defibrillator was performed in 112 (72%) patients. During 3-year follow-up, 15 (10%, 1 arrhythmic) patients died and 42 (29%) patients had recurrent ventricular arrhythmias. Patients with events (death and/or recurrence) exhibited more often a severely depressed LVEF (=<30%), more extensive scar tissue and less ischemic/viable myocardium on perfusion imaging and underwent less frequently revascularization. Multivariate analysis identified extensive scar tissue and LVEF =<30% as the only predictors of death/recurrent ventricular arrhythmias.
Conclusion: In patients with aborted sudden death, extensive scar tissue and severely depressed LVEF are the only predictors of death and/or recurrent ventricular arrhythmias. These patients should be considered for implantation of a defibrillator.

1864 Assessment of myocardial perfusion after coronary stenting and implications of incomplete revascularization in multivessel coronary disease: role of gated single-photon emission computed tomography imaging

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Purpose: The aim of the study was to evaluate myocardial perfusion scintigraphy (MPS) findings in patients (pts) with multivessel coronary disease (MVD) who undergo percutaneous revascularization with coronary stenting, with special attention to perfusion and function in the regions of stented vessels vs. areas of nonrevascularizated myocardium.
Methods: We examined 56 pts (age 56 ± 7) with MVD, who underwent myocardial revascularization with coronary stenting. 34 pts received complete revascularization, (LAD+ RCA 23 pts; LAD+LCx 8 pts; PDA+OM1 3 pts). Tc-99m sestamibi Gated SPECT was performed using one day rest/stress protocol 6 to 9 months after revascularization. Both rest and stress studies were gated. We have evaluated left ventricular (LV) volumes, wall thickening (WT), wall motion (WM) and left ventricular ejection fraction (LVEF) at rest and stress. MPI images were read using 17-segment analysis with 5 point scoring system (0=normal; 4=no uptake) for estimation of defect severity. Semiquantitative analysis was done using summed stress score (SSS), summed rest score (SRS) and summed differential or reversibility score (SDS), to evaluate the extend of jeopardized myocardium.
Results: After stent implantation MPS was normal in 19 pts with LAD+ RCA stent, in 7 pts with LAD+ LCx stenting and in 3 pts with PDA+OM1 stenting in the follow up period. In pts with incomplete revasularization we found inducible ischemia in 11 pts in anterior and antero-septal wall-LAD; in 7 pts in inferior wall - RCA region and 4 pts has infero-lateral and lateral wall ischemia. Pts with incomplete revascularization had average SSS>10 comparing to the group with complete revascularization (SSS<5), higher prevalence of transit ischemic LV dilatation (TID), higher lung/heart ratio and lower post stress LVEF ($p<0.05$). Eight pts with incomplete revascularization had silent ischemia. Clinical deterioration in form of acute coronary syndromes and heart failure was higher in the latest group as well ($p<0.001$).
Conclusions: Myocardial scintigraphy provides significant independent prognostic value in patients with both complete and incomplete revascularization irespectable of clinical and angiographic findings. It better predict the risk of cardiac events and it should be used for evaluation of revascularization and guidance for further management decision.

HEART FUNCTION IN CONGENITAL HEART DISEASE

1865 Closure or conservative management of atrial septal defects in adults: experiences from 25 years of follow-up of 325 patients

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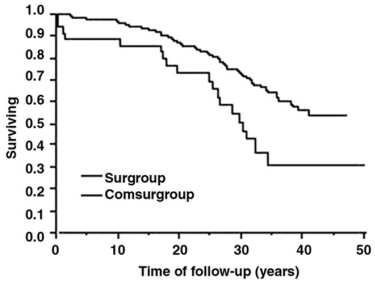
Background: The management strategy for adults with atrial septal defects (ASD) is still a subject of debate. One available approach is the conservative, leaving the defect at least until symptoms or to close it even in the asymptomatic patient. The decision to close is often based on the magnitude of the shunt with the level pulmonary vs systemic blood flow (Qp:Qs) >1,5-2:1 as a guideline. A remaining issue is whether closure already at a lower level would have prognostic benefits in particular when the ASD is detected in adults. This study reports on mortality in patients (pat) followed up to 50 years.



Material and Methods: 325 consecutive pat (age: 38±14) referred between 1953-1994 for isolated atrial septal defects were followed until 2000. Shunt flow was graded with cardiac catheterisation. Mortality and major morbidity was collected via case records, interviews and from the Swedish death registry. ASD related deaths were defined as arrhythmia, heart failure, pulmonary hypertension and thromboembolic, The ASD was surgically closed in 288 (Surg group) and conservatively managed in 37 pat (Cons group).
Results: The mean follow-up period was 26±12 years (range: 0-50). The two groups had a similar age distribution. Average Qp:Qs was 3.3±1.2 for the Surg group and 2.2±0.7 for the Cons group ($p<0.001$). Nineteen (51%) pat in the Cons group died compared to 83 (29%) in the Surg group ($p<0.01$). Survival curves are presented in the figure. Reasons for mortality were ASD-related in 32% in the Cons group and 14% in the Surg group.
Conclusion: The conservative ASD-management was related to higher long-term mortality than the surgical although the latter was chosen in pat with the largest shunts. This support the closure even of small ASD's in the adult pat.

1866 Evaluation of regional longitudinal and radial function in patients with congenital aortic regurgitation: an IBS, strain and strain rate imaging study

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Background: To recognise the exact timing for cardiac surgery in asymptomatic patients with congenital aortic regurgitation (CAR) represents still a challenge. Indeed, if the operation is deferred until patients become symptomatic there is a very high risk of irreversible left ventricular (LV) dysfunction. A more sensitive, non-invasive, quantitative approach could be crucial in the management of those patients. The conventional echocardiographic assessment of LV function, a non-quantitative, subjective and experience dependent evaluation, showed a very low predictive value in defining the time to surgery in CAR patients. Integrated Backscatter (IBS) as well as ultrasonic Strain (S) (%) and Strain Rate (SR) (1/s) imaging, are new echocardiographic technique which allow us to asses textural properties and regional deformation properties, respectively.
Aim: To define the ability of these non-invasive techniques to unmask subtle functional abnormalities in asymthomatic patients with CAR.
Methods: We studied 13 patients (age 18±6 yrs) with moderate to severe isolated CAR by standard grey-scale echocardiographic indices, IBS and S/SR imaging, comparing data to those of age and BSA matched healthy subjects.
Results: Compared to normals CAR patients showed increased LV end diastolic diameter (5.6±0.5 vs 4.2±0.6 cm, $p<0.01$) and a comparable shortening fraction (36±5 vs 37±3%, p=NS). Cyclic variation at IBS analysis was reduced at both septal (9±1.7 vs 10.1±1.6, $p<0.05$) and posterior wall (7.6±1.4 vs 10.8±1.3, $p<0.0001$). In addition, S/SR imaging were reduced for both longitudinal (SR: -1.5±0.7 vs –1.9±0.5; S: -21±6 vs -25±5, $p<0.05$) and radial (SR: 3.1±1.1 vs 3.7±0.9, $p<0.05$; S: 42±14 vs 55±12, p=0.003) deformation properties. Radial S was significantly correlated with Jet/LVOT (p=0.04; R=-0.77), while longitudinal SR was significantly correlated with age (p=0.0031; R=0.77).
Conclusions: In asympthomatic patients with CAR, the use of IBS and S/SR indices is able to early detect functional abnormalities. Significantly, S/SR indices are related to both duration and degree of aortic regurgitation.

1867 Pulmonary blood flow pattern in patients with fontan circulation depicted by cine magnetic resonance imaging

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Background: After palliation of univentricular heart with a Fontan modification there is no subpulmonary ventricle modifying pulmonary blood flow. The aim of the study was to test the influence of cardiac cycle on pulmonary blood flow pattern in those patients and to compare it with that in normal subjects.
Patients and Methods: Blood flow pattern was investigated with cine MRI in the left pulmonary artery of 18 patients (20.6 ± 7.4 years old, 7 females) with Fontan circulation (4 RA-RV connections, 9 RA-PA connections, 5 TCPC) and compared with that in the superior caval vein and main pulmonary artery of 12 healthy volunteers (26.3 ± 6.0 years old, 10 females). Measurements were sampled over a period of about 2 minutes to distinguish respiratory effects. Blood flow pattern was depicted by interpolating the variable number of measured phases to 100 phases and normalizing flow to mean blood flow in that vessel. Then, average flow pattern could be calculated and compared between the studied groups.
Results: Fontan patients had an almost constant flow pattern in their left pulmonary artery. There was only a slight flow acceleration at the end of diastole and, depending on the type of Fontan modification, an even minor one in systole. This blood flow pattern did not resemble that in the caval vein of healthy volunteers, where a clear systolic flow peak and an only small flow acceleration in the beginning of the diastole was depicted. Nor it resembled that in the normal pulmonary artery, where blood flow is almost confined to a single systolic peak.
Conclusion: Pulmonary blood flow pattern in patients with Fontan circulation is almost independent from cardiac cycle. Further studies should focus on the influence of respiration on pulmonary blood flow.

1868 B-type natriuretic peptide: a strong predictor of outcome in adult patients with congential heart disease and pulmonary vascular disease

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Background: Elevated neurohormones, in particular B-type natriuretic peptide (BNP) have been shown to predict outcome in pts with heart failure and in pts with primary pulmonary hypertension. However, their prognostic value in congenital heart disease (CHD) pts with pulmonary hypertension (PHT) remains insufficiently determined.
Methods: 52 pts (age 37.1±15.8, 30 female) with congenital heart disease and significant PHT (syst. pressure > 50mmHg; mean±SD 64±23mmHg) were followed for 14.4±10.7 months (ventricular septal defect, 22; other shunt lesions, 10; double inlet ventricle, 8; pulmonary atresia 4; tricuspid atresia 2, others 6). BNP at study entry was 147±199 pg/ml, 26 pts were in NYHA class III/IV, and 14/52 (27%) had abnormal ventricular function (VF). Event-free survival with events defined as death, transplantation or congestive heart failure (CHF) requiring hospital admission was analyzed with the Kaplan-Meier method for pts. with BNP < 150pg/ml (group I, N=36) and those with BNP * 150pg/ml (group II, N=16).
Results: BNP levels were significantly higher in pts with NYHA class III/IV as compared to I/II (216±245 vs 79 ±104 p<.05) and in pts with abnormal VF as compared to pts with normal VF (300±244 vs 59±87, p<.0001). During FU 14 events occurred (Sudden Cardiac Death [SCD], 2, transplantation, 2, CHF 10 of whom 8 eventually died). Pts with events had significantly higher BNP levels (364±248 vs 67±92, p<.0001) but also higher NYHA class (2.9±.5 vs 2.1±.6, p<.0001) and more frequently abnormal VF (71% vs 24%, p<.005). BNP was a strong predictor of outcome: event-free survival in group I was 94±4% at 1yr, 94±4% at 2yrs, 94±4% at 3 yrs (1 SCD, 1 transplantation). In contrast event-free survival was 59±13% at 1yr, 30±14% at 2yrs, 10±10% at 3 yrs in group II (SCD, 1, tranplant, 1; CHF, 10). Group I and II did not only significantly differ in BNP (40±41 vs 386±205, p<.0001) but also in NYHA class (2.1±.7 vs 2.8 ±.6 p<.005) and presence of abnormal VF (81% vs 17%, p<.0001).
Conclusion: BNP is a strong predictor of outcome in pts with CHD and PHT providing prognostic information beyond NYHA class and VF. Considering the difficulties of assessing VF and functional status in pts with complex CHD, BNP may have major impact on treatment decisions, particularly the optimal timing of transplantation.

1869 Univentricular heart in adults. Late outcome in patients with natural survival compared to fontan or aortopulmonary shunt palliation

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Background: Comparison of late outcome in univentricular heart patients with natural survival up to adulthood and patients previously treated by atrio-or-cavo-pulmonary shunt (CVS) or aorto-pulmonary fistula (APF) has not been reported.
Methods: Long-term evolution of 69 adults (mean age 27+7 years) with univentricular heart was analized. CVS repair or definitive APF palliation had been undergone during childhood in 23 and 19 patients respectively, but 27 patients had not surgical intervention before adulthood. Primary end point was actuarial survival free from surgical intervention during adulthood and secondary end points were functional class, clinical atrial arrhythmias, cyanosis, need for medication, and systolic ventricular function.
Results: During adult follow-up, 4 patients died and 15 underwent surgical intervention. Prevalence of primary end point events was 15% in natural survival patients compared to 26% and 47% in CVS and APF respectively. Actuarial survival free of surgical intervention at age of 20, 25 and 30 years old was 100%, 95% and 83% in patients with natural survival, 91%, 80% and 70% in patients with CVS (Log Rank = 4.4; p = 0.034) and 94%, 65% and 54% in patients with APF (Log Rank = 8.8; p = 0.003). Functional class was worst in APF patients (p = 0.01) but there was no significant difference between CVS and natural survival groups. Patients with natural survival had more cyanosis than CVS rapaired patients (p = 0.01), but they had less clinical arrhythmias (15% vs 30% and 26%) thrombotic complications (4% vs 17% and 11%), systolic ventricular dysfunction (31% vs 52% and 63%) and need for diuretics, anticoagulants, or antiarryhtmics (26% vs 50% and 53%) than patients with CVS repair or APF palliation respectively.
Conclusion: Long-term outcome of univentricular heart patients with natural survival into adulthood compares favorably with that of previous CVS repair or APF palliation. Surgical intervention during infancy and childhood should be recommended only to high degree symptomatic patients.

1870 Prognostic value of aortic elasticity on aortic complications in patients with Marfan syndrome

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Background: In patients with Marfan syndrome prognosis is mainly determined by progressive dilation of the aortic root, potentially leading to aortic dissection and rupture. Although the risk of aortic dissection increases with aortic diameters, dissections may occur in non-dilated aortas. The objective of this study was to investigate the prognostic value of aortic elasticity on aortic complications.
Methods: 78 Marfan patients (aged 31±8 years, 46 men and 32 women) underwent MR flow mapping at 4 aortic levels (1: ascending aorta, 2: thoracic descending aorta, 3: descending aorta at the level of the diaphragm and 4: abdominal descending aorta). Distensibility at each level and flow wave velocity between levels were calculated. Aortic complications were defined as: mean aortic diameter increase > 1 mm/year, aortic dissection or death.
Results: After 6±0.5 years of follow-up, 20 of 78 (26%) patients had developed complications of the aortic root; 1 patient with a type A dissection, 19 patients with a mean aortic growth > 1mm/year, of which 17 underwent elective aortic root replacement because of an aortic root diameter > 50 mm. In these 20 patients ascending aortic distensibility was significantly lower compared to uncomplicated patients (2±1 vs. 3±1 10-3 mmHg-1, respectively, p<0.05). In 11 patients complications in the descending aorta had occurred; 1 patient with a type B dissection and 10 patients with a mean aortic growth > 1 mm/year, of which 2 patients underwent intervention. In these 11 patients thoracic descending aortic distensibility was significantly lower compared to patients without descending aortic complications (2±1 vs. 4±2 10-3 mmHg-1, respectively, p<0.05). No significant difference in diameters and flow wave velocity was observed between complicated and uncomplicated patients.
Conclusion: These results suggest that local decreased aortic elasticity has a strong prognostic value regarding the occurrence of aortic complications.

AORTIC STENOSIS: NEW INSIGHTS FROM CARDIAC IMAGING

1871 The amount of aortic valve calcification – quantified by electron beam tomography – impacts the clinical course of severe aortic valve stenosis

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In patients with aortic valve stenosis, the presence of severe calcification - assessed by echocardiography - has been identified as a predictor of rapid progression and poor outcome. The aim of this study was to determine the amount of aortic valve calcification by electron beam tomography (EBT) in patients with a symptomatic aortic valve stenosis (SAS) as compared to patients with asymptomatic aortic valve stenosis (AAS).
Methods: In 61 patients (mean age 73.1±10 years, 62% male, 38 SAS and 23 AAS) with severe aortic valve stenosis (valve area < 1,0 cm^2 calculated by echocardiography), EBT was performed. In all data sets the amount of calcification in the aortic valve and in coronary vessels was quantified using a volumetric score.
Results: The average amount of aortic valve calcification in all patients was 1942±2419 mm^3. The calculated aortic valve area was 0.7±0.2 cm^2. There was no significant relation between the ammount of aortic valve calcium and the aortic valve orifice (r=0.14, p=0.2). Age (68.3±8 vs. 73.1±10 years, p=0.2), sex (63% vs. 60%male, p=0.2), coronary calcium score (453±533 vs. 433±501 mm^3, p=0.1), and aortic valve orifice (0.7±0.3 vs. 0.8±0.3, p=0.1) were not significantly different between patients with symptomatic and asymptomatic aortic stenosis. However, the amount of aortic valve calcification was significantly higher in patients with SAS than in patients with AAS (2433±2823 vs. 1187±1648, p=0.008). In a multivariate analysis, only the degree of aortic valve calcification was found to be an indipendent predictor of SAS (p=0.01)
Conclusion: In patients with severe aortic valve stenosis, a statistically significant association between the amount of aortic valve calcification and the presence of symptoms was found. These data support the prognostic value of aortic valve calcification concerning the clinical course of aortic valve stenosis.

1872 Ultrasonic tissue characterization by means of cyclic variation of integrated backscatter in patients with aortic stenosis

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Introduction: Cyclic variation of integrated backscatter (CVIBS) has been shown as useful echocardiographic method able to quantitavly describe function and structure of myocardium. In many pathological states, including coronary heart disease and dilated cardiomyopathy magnitude of cyclic variation of integrated backscatter is reduced. There is no data on CVIBS measurement in patients with pressure overload in aortic stenosis.
Aim: The aim of our study was to determine values of CVIBS among patients with aortic stenosis and its association with other echocardiographic parameters.
Methods: We have studied 27 (mean age 61 $\pm$ 14 years;17 males and 10 females) patients with aortic stenosis admitted to our hospital for invasive diagnostic procedure preceding AVR. Two-dimensional integrated backscatter images of the left ventricle were obtained from standard long axis transthoracic echocardiographic views. SONOS 5500 (HP Co, Andover, Mass) ultrasonic imaging system operating in the commercially available Acoustic Densitometry acquisition mode was used. Integrated backscatter from digitally acquired images was measured by placing an elliptic region of interest at the center of myocardial wall. Values of CVIBS were calculated using Cyclic Variation Analysis Tool v.1.0 (Laboratory for Ultrasonics, Washington University).
Results: Mean transaortic gradient in study group was 51,9 $\pm$ 20,8 mmHg. Mean value of CVIBS was 3,6 $\pm$ 1,7 dB for septum and 3,6 $\pm$ 1,8 dB for posterior wall. We have found a significant negative correlation between left ventricle mass and mean CVIBS (r = -0,62; p< 0,05). We have also observed significant positive correlation between mean CVIBS and ejection fraction (r=0,41;p<0,05), and negative correlation between mean CVIBS with left ventricular diastolic diameter (r = -0,48; p<0,05). CVIBS correlated significantly with relative thickening for septum and posterior wall (r = 0,51 for septum p<0,05; r = 0,46 for posterior wall p<0,05).
Conclusion: Our results suggest that CVIBS is an addtional echocardiographic parameter which significantly correlates with other echocardiographic structural and functional measurements in advanced aortic stenosis.

1873 Valve compliance predicts symptoms during exercise in aortic stenosis

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Purpose Aortic valve compliance is the relation of effective orifice area to transaortic flow. Valve compliance might determine the onset of symptoms better than resting measures of aortic stenosis. This study compared valve compliance measured by dobutamine stress echocardiography with resting haemodynamic variables against the end-point of symptoms at low workload during exercise testing.
Method Doppler echocardiography was performed at rest and during each stage of a dobutamine stress test in 65 asymptomatic patients with moderate or severe aortic stenosis (resting continuity effective orifice area < 1.2cm^2) and normal left ventricular systolic function. Each patient also completed a modified Bruce treadmill exercise test. A positive test was defined by limiting symptoms at <70% age-predicted maximum workload.
Results At peak dobutamine stress, peak transaortic velocity increased by 1.0 $\pm$0.4 m/s and effective orifice area by 0.25 $\pm$0.22 cm^2. Valve compliance was 0.23 $\pm$0.10 cm^2/100 ml.s-1, and was independent of baseline effective orifice area. 19 exercise tests were positive and 46 were negative. In the 19 patients limited by symptoms on exercise testing, valve compliance was significantly lower (0.19 $\pm$0.09) cm^2/100mls-1) than in those who remained asymptomatic (0.25 $\pm$0.10) cm^2/100mls-1, p = 0.03). Effective orifice area at peak stress was also lower (1.0 $\pm$0.3 vs. 1.2 $\pm$0.4 cm^2, p = 0.03), but there were no significant differences in resting measures of effective orifice area (0.8 $\pm$0.2 vs. 0.9 $\pm$0.2 cm^2, p = 0.13), transaortic velocity (3.8 $\pm$0.5 vs. 3.7 $\pm$0.8 m/s, p = 0.7) or mean pressure drop (35.3 $\pm$19.4 vs. 34.9 $\pm$10.4 mmHg, p = 0.9).
Conclusions Effective orifice area is flow-dependent in patients with moderate and severe aortic stenosis with preserved left ventricular function. Exertional symptoms are better predicted by compliance than resting effective orifice area, mean pressure drop or peak transaortic velocity.

1874 Usefulness of aortic valve resistance in assessment of haemodynamic severity in aortic stenosis

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Background: This prospective study was designed to determine the usefulness of aortic valve resistance for the evaluation of aortic stenosis (AS) and separation of patients with severe aortic stenosis from those with milder disease.
Methods: In 193 patients (pts) aortic valve area (AVA), mean pressure gradient (delta pmean), valve resistance (VR), left ventricular function (LVF) and cardiac output (CO) were determined by transthoracic echocardiography at rest. A threshold value of valve resistance was identified to seperate patients with truly critical (AVA < 0.7 cm^2) from those with truly non critical aortic stenosis (AVA > 0.8cm^2 and delta pmean < 50 mm Hg). The usefulness of this threshold value for assessing the hemodynamic severity of aortic stenosis was investigated in the subgroup of pts with aortic valve area ranging from 0.7 to 0.8 cm^2.
Results: When severe AS was diagnosed in pts (AVA < 0,7 cm^2) valve resistance was determined > 250 dyn s cm-5 (n = 93, mean: 455.8 $\pm$ 169.1 dyn s cm-5) in all but one pt with severe LV dysfunction and low CO. In all pts with AS classified as mild to moderate (AVA > 0,8 cm^2 and delta pmean < 50 mm Hg) calculated VR was < 250 dyn s cm-5 (n = 43, mean: 158.5 $\pm$ 48.2 dyn s cm-5). Patients with marginal aortic valve area (0.70 - 0.80 cm^2) were separated by this threshold value (table).

	VR < 250 dyn s cm-5	VR > 250 dyn s cm-5	p
n	13	30	
delta pmean	36.0 $\pm$ 8.8 mmHg	53.1 $\pm$ 7.8mmHg	< 0.001
AVA	0.77 $\pm$ 0.04 cm^2	0.75 $\pm$ 0.04 cm^2	ns
CO	5.1 $\pm$ 0.8 l/min	5.2 $\pm$ 0.7 l/min	ns

Separation of pts with valve area between 0.70 cm^2 and 0.80 cm^2

Conclusion: The identified threshold value of VR = 250 dyn s cm-5 helps to separate patients with truly critical aortic stenosis from those with moderate disease even if aortic valve area is marginal und fails to make this separation.

1875 Diagnostic value of dobutamine stress echocardiography in patients with aortic stenosis with and without left ventricle hypertrophy and hypertension

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Background: Coronary artery disease (CAD) is a frequent finding in patients with aortic stenosis (AS), particularly in the elderly. Due to concomitant left ventricle hypertrophy (LVH) ECG exercise test has well known limitations in this population. Dobutamine stress echo (DE) is potentially more objective non-invasive test helping to decide about indications for coronary angiography. However little is known about accuracy of DE in patient with AS and LVH.
Aim: Assessment of accuracy of DE in patients with AS and analysis of influence of concomitant LVH and hypertension on DE results.
Material and Methods: Study group consisted of 162 patients in the age of 18-81 years (mean 59$\pm$13), with moderate AS, without other valvulopathies and without contraindications to DE. Clinical data and detailed echocardiographic examination at rest and during DE was performed. Standard DE protocol (max 40mcg/kg/min) as well as termination and interpretation criteria were used. Based on the value of left ventricle mass index, patients were divided into groups with and without LVH (LVH+ and LVH-). According to WHO criteria they were also divided to groups with and without hypertension (HT+ and HT-). Coronary angiography was considered positive if at lease one stenosis >50% was found.
Wyniki Comparison of LVH+ and LVH- groups revealed that: sensitivity (80,6% vs. 54,5%), specificity (82,9% vs 93,8%), accuracy (81,9% vs 77,8%), positive predictive value (78,1% vs 85,7%) and negative predictive value (85% vs. 75%) were not statistically different. Above mentioned parameters were not statistically different in HT+ and HT- groups. In LVH+ group lower dobutamine dose (30,0 vs 35,1mcg/kg/min, p<0.05) was required to reach DE termination criteria. Maximal systolic blood pressure during DE was higher in HT+ group comparing to HT- group (144 vs 139mmHg, p<0.05).
Conclusions 1. Accuracy of DE in patients with AS, LVH and NT is high. 2. In patients with AS, accuracy of DE remains high regardless of the presence of LVH.

1876 Assessment and monitoring recovery after aortic valve replacement using tissue Doppler echocardiography: a 6-month follow-up study in elderly

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Background: Tissue Doppler Echocardiography (TDE) is a reliable new modality that assists in the objective evaluation of regional right and left ventricular function. In this work we monitored left (LV) and right (RV) ventricular function as assessed by TDE, immediately before, and 15 days, 3 and 6 months after the aortic valve replacement (AVR) in patients with severe aortic stenosis (peak gradient 91 $\pm$ 21).
Methods: During 2002 we enrolled 43 consecutive patients (27 men, 65 $\pm$ 12 years old and 16 women, 69 $\pm$ 7 years old) who had undergone AVR. TDE images obtained from the apex, visualizing triscupter and mitral free wall annulus. RV and LV systolic and diastolic velocities were compared immediately before, as well 15 days, 3 and 6 months after AVR, based on the Analysis of covariance for repeated measurements. Mitral and triscupted diastolic velocities (E, A) were also measured.
Results: Systolic (S) velocity in LV showed a significant increased after AVR (15d: 11$\pm$1 v 3m: 12$\pm$2 v 6m: 13$\pm$1, p for trend $<$ 0.01), while RV S velocity showed no statistically significant changes (15d: 11$\pm$2 v 3m: 12$\pm$1 v 6m: 12$\pm$1, p for trend $<$ 0.1). Both diastolic E velocities in RV and LV increased significantly from 15 days to 6 months after AVR (15d: 52$\pm$3 v 3m: 58$\pm$3 v 6m: 58$\pm$3, p for trend $<$ 0.05 and 15d: 5$\pm$1 v 3m: 8$\pm$2 v 6m: 16$\pm$3, p for trend $<$ 0.01). The ratio E/E(TDI) in LV showed a significant decrease after the AVR (15d: 10$\pm$2 v 3m: 9$\pm$2 v 6m: 7$\pm$2, p for trend $<$ 0.001), while the ratio E/E(TDI) in RV decreased significantly between pre and post operation (pre: 6$\pm$2 v 15d: 0.97$\pm$1, p = 0.02), but remained constant thereafter AVR (3m: 0.86$\pm$1 v 6m: 0.92$\pm$1, p = 0.67).
Conclusion: Significant LV systolic improvement was observed after AVR, although no such improvement observed in RV systolic function. E diastolic velocity was also increased in both chambers. TDE can provide a simple non invasive quantitative method for monitoring RV and LV function.

NATRIURETIC PEPTIDES IN HEART FAILURE

1922 Effects of interval training on functional capacity and circulating brain natriuretic peptide in patients with chronic heart failure

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Background: exercise intolerance is an hallmark of heart failure and physical training improves exercise capacity, quality of life and survival. Brain natriuretic peptide (BNP) levels correlate with functional class and have a powerful diagnostic and prognostic value.
Aim of the study. To test the hypothesis that physical training can modify circulating BNP levels in stable congestive heart failure (CHF) patients.
Methods: 22 stable CHF patients (M 21, age 67$\pm$7 years, NYHA I/II: 8/13, ejection fraction 36 $\pm$5%, peak VO2 16.8$\pm$4.5 ml/kg/min), were randomized to a training program (12) or to control group. Before randomization they performed cardiopulmonary exercise test (CPX), six minute walking test (6MWT) and dosage of BNP blood level. Blood was sampled after 10 minutes of supine resting before starting CPX. Training group performed a supervised 8 weeks program of interval training with three session for week of 35 minutes each at 50% of maximal work rate for 30 seconds followed by an unloaded period of 60 seconds. Maximal work rate was determined previously by a steep effort test with 25 watts increase every 10 seconds. Controls were not included in any program of exercise and maintained their usual activities. At the end of training patients and controls repeated CPX, 6MWT and BNP dosage.
Results: Age, NYHA, ejection fraction and peak VO2 were not significantly different in patients and controls. All patients completed the program without need for therapy changes. Peak VO2 significantly increased from 17$\pm$3 to 18$\pm$3 ml/kg/min in patients after training (p=0.029) and 6MWT increased from 498$\pm$7 to 519$\pm$7 mt. No differences of functional capacity were observed in the control group (16$\pm$1 to 16$\pm$2 ml/kg/min and 517$\pm$8 to 516$\pm$6 mt respectively). BNP decreased from 172$\pm$1 pg/ml to 122$\pm$6 in patients (p=0.039) whereas in controls no differences were observed from the basal levels (163$\pm$9 vs 166$\pm$7)
Conclusions: Our data indicate that in CHF patients interval training increases functional capacity and induces a reduction of circulating levels of BNP, confirming the beneficial effects of physical activity in these patients. If our data will be confirmed, BNP could be proposed as an useful marker of the training effect.

1923 Eighteen-minute N terminal pro-brain natriuretic peptide versus 24-hour brain natriuretic peptide assay as diagnostic markers in congestive heart failure

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The raising relevance of cardiac natriuretic peptide assay for diagnosis and follow-up of patients with congestive heart failure (CHF) requires a fast and accurate method for BNP assay. The IRMA assay of BNP is, at the moment, the gold standard, but presents the disadvantage of a long (24 hours) and rather complex procedure. A new, fast (18 minutes), fully-automated electrochemiluminescence "sandwich" immunoassay (ECLIA) method for NT-proBNP (proBNP) assay has been recently proposed. This study was designed to evaluate the relation among proBNP, cardiac function and exercise capacity in patients with severe CHF and to compare the results with those obtained with BNP, measured with the IRMA technique.
Fifthy-six patients (mean age 62$\pm$1 yrs, mean$\pm$SEM), with either ischemic (31) or idiopathic (25) cardiomyopathy were enrolled in the study. Mean left ventricular ejection fraction (LVEF) was 29.4$\pm$0.9%. Tirthy-two patients were in NYHA class I-II, 24 in III-IV. All patients were on three/four drug regimen (frusemide, ACE-inhibitor, carvedilol, spironolactone). In the same day, blood was sampled at 8 a.m. for BNP and proBNP, and a maximal cardiopulmonary stress test (Vmax 229, Sensormedics) was performed in all patients.
Plasma BNP value was 270$\pm$33 pg/mL (range: 34-1074), while proBNP was 1954$\pm$236 pg/ml (range 55-7547). Mean peak oxygen consumption 12.4$\pm$0.5 ml/min/kg and VE/VCO2 slope was 46.2$\pm$1.5. BNP and proBNP showed a highly significant correlation (r= 0.92, p$<$0.001). A significant negative correlation were found among either BNP or proBNP and EF (r=0.37, p=0.005 and r=0.33, p=0.014, respectively) or peak VO2/kg (r=0.43, p$<$0.001 and r=0.48, p$<$0.001, respectively); conversely, the relation was positive with VE/VCO2 (r=0.46, p$<$0.001 and r=0.52, p$<$0.001, respectively). Finally a slight positive correlation was observed also with NYHA class (r=0.30, p=0.02 and r=0.27, p=0.04, respectively).
These results show that proBNP in CHF is more feasible than BNP assay, due to an easier and faster procedure, with an equivalent power as marker of clinical status and cardiac dysfunction in medical practice.

1924 Preserved venous natriuretic peptide responsiveness in congestive heart failure

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Background: The phenomenon of natriuretic peptide (NP) resistance (diminished responsiveness to endogenous and exogenous NP) has so far hindered successful practical application of a theoretically appealing therapeutic approach. Recent data suggest that ANP vascular effects may be in part endothelium dependent. Endothelial dysfunction may therefore, at least partly, be responsible for this phenomenon. However, we recently reported preserved endothelial function in the capacitance vasculature of CHF patients despite marked arterial endothelial dysfunction. We therefore hypothesised that a) venous ANP responsiveness may be preserved in patients with CHF and b) that this may be partly due to preserved venous endothelial function.
Methods: We studied forearm vascular function in response to incremental doses (0.05, 0.5, 1μg/min) of intra-arterial infusion of ANP in 14 stable CHF patients and 10 matched controls. Relative changes in vascular volume (VV), venous tone and compliance were assessed by combining equilibrium blood-pool-scintigraphy with a standard venous occlusion plethysmography (VOP) technique. Forearm blood flow (FBF) was assessed using conventional strain gauge VOP. The contribution of nitric oxide (NO) to ANP induced changes in vascular volume was assessed by ANP (1μg)-LNMMA (12mg/min) co-infusion.
Results: In healthy controls ANP increased FBF and VV in a dose dependent manner by 61% (P=0.06), 96% (P$<$0.01), 124% (P$<$0.0001) and 1% (P$<$0.6), 8% (P$<$0.13), 13% (P$<$0.05) respectively. In patients FBF increased markedly less, by 13%, 31%, and 49% (P=NS for all), whilst VV increased to a similar amount as in controls, by 2% (P=NS), 11% (P$<$0.05), and 15% (P$<$0.05). LNMMA/ANP co-infusion halved the increase in VV in both groups equally (P$<$0.01 for both controls and CHF).
Conclusion: This data indicate, that despite impaired resistance vessel responsiveness, venous ANP responsiveness is preserved in patients with CHF. The latter might be partly due to preserved venous endothelial function.

1925 Combined endurance/resistance training reduces serum N terminal pro-brain natriuretic peptide in patients with chronic heart failure

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Background: NT-proBNP (brain natriuretic peptide) and BNP levels have important diagnostic and prognostic properties in the setting of chronic heart failure (CHF). The implementation of combined endurance/resistance training for patients (pts) with CHF has been hampered by fear of detrimental effects. Hence, most training programs focus on aerobic exercise.
Methods: NT-proBNP (Elecsys®, Roche Diagnostics) was measured in fasting venous blood samples before and after 4 months combined endurance/resistance training in 36 pts (25 males) with CHF (ischemic: 22 pts/dilated cardiomyopathy: 14 pts). Training comprised 20 min cycling and walking/or stepping at a heart rate of 90% of ventilatory threshold and 30 min of resistive weight training at 50% of the 1 repeated maximum.
Results: NT-proBNP levels were higher in pts with moderate to severe CHF (NYHA III/IV: n=22) when compared to those with mild CHF (NYHA I/II: n=14, p=0.0002, see table). Both groups were comparable with regards to age and left ventricular ejection fraction, whereas VO2max and Wattmax were significantly higher in the latter patient group (p=0.01, p=0.04). For the group as a whole, NT-proBNP remained unchanged. However, pts with moderate to severe CHF showed a significant decrease in NT-proBNP concentrations after 4 months training (table). Changes in the mild CHF group were borderline significant. No changes in NT-proBNP occurred in a matched non-trained control CHF group (1148±243pg/ml vs 1010±209pg/ml after 4 months, p=NS).

NT-proBNP/exercise parameters: evolution

	NT-proBNP pre	p	NT-proBNP post
NYHA I-II	641±148 pg/ml	0.07	538±118 pg/ml
NYHA III-IV	2428±459 pg/ml	0.04	1900±358 pg/ml
	VO2max pre	p	VO2max post
NYHA I-II	20.3±0.9 ml/kg/min	0.1	22.8±1.4 ml/kg/min
NYHA III-IV	16.9±0.8 ml/kg/min	0.05	19.0±1.2 ml/kg/min
	Wattmax pre	p	Wattmax post
NYHA I-II	100±8	0.007	142±14
NYHA III-IV	85±5	<0.0001	120±8

Conclusion: In pts with moderate to severe CHF, 4 months combined endurance/resistance training significantly reduced NT-proBNP concentrations, thus underscoring the safety of this training modality.

1926 Brain natriuretic peptide and N terminal pro-brain natriuretic peptide for treatment monitoring in patients with left-ventricular systolic heart failure: a substudy of the CARMEN trial

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Background: The purpose of the study was to assess brain (BNP) and N-terminal pro brain (NT-proBNP) natriuretic peptides as markers for treatment monitoring in patients with chronic heart failure.
Methods: In a substudy of the Carvedilol ACE Inhibitor Remodelling Mild CHF EvaluatioN (CARMEN) trial, 295 patients with symptoms of heart failure and left ventricular (LV) ejection fraction (LVEF) of 0.39 or less underwent echocardiography and blood sampling at baseline and 12 months after randomization to 1 of 3 treatments: Carvedilol + enalapril (CE: n=91), carvedilol (C: n=99) or enalapril (E: n=105).
Results: LV dimensions decreased significantly in CE (mean LV end-diastolic (LVEDVI: 84-77, p=0.0005) and end-systolic volume indices (LVESVI: 60-52 ml/m^2, p=0.0002); LVEF increased from 0.29-0.34, p=0.0001). C: LVEDVI: 90-87, p=0.02; LVESVI: 65-60 ml/m^2, p=0.002; LVEF: 0.29-0.32, p=0.0005. E: LVEDVI: 87-87, NS; LVESVI: 62-62 ml/m^2, NS; LVEF: 0.30-0.31, NS. BNP decreased over time in CE (92-72, p=0.01) and E (114-65 pg/ml, p<0.0001), but was unchanged in C. NT-proBNP was unchanged in CE and C but decreased in E (155-129 pmol/l, p=0.03). Baseline levels of BNP and NT-proBNP were unrelated to changes in LV dimensions. Please see table for monitoring data.
Conclusions: Despite an independently increasing effect of β-blockade on BNP and NT-proBNP, our data indicate that both markers could be useful for monitoring LV dimensions and function during treatment with carvedilol and/or enalapril in chronic heart failure.

WHAT AFFECTS PROGNOSIS IN HEART FAILURE: NEW INSIGHTS

1928 The prognostic value of body mass index in patients with heart failure: data from the Val-HeFT trial

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Purpose: Obesity has been shown to be an independent risk factor for the development of heart failure (HF). However, obese patients with established HF may have more favorable outcomes. We assessed the prevalence and prognostic role of BMI in 5010 HF patients enrolled in Val-HeFT trial.
Methods: Patients randomized in Val-HeFT were divided in 4 BMI groups: Underweight ≤22; Normal 22-24.9; Overweight 25-29.9; and Obese ≥30. Univariate and multivariate analyses were performed to assess the prognostic significance of BMI on all cause mortality (mean follow-up period 23 months).
Results: Underweight patients were older, had more advanced NHYA class, lower systolic blood pressure (SBP), higher heart rate (HR), higher serum creatinine (Cr) and lower hemoglobin (Hg). All-cause mortality was inversely related to BMI. Multivariate analysis showed that low BMI was independently associated with a worse prognosis (RR 1.21, 95% CI 1.00-1.48 for BMI =<22 vs. normal BMI, p=0.049).

BMI	≤22	22-24.9	25-29.9	>=30	p-value
n. of pts	547	1192	2245	1026	
>70 yrs %	41.5	32.1	24.5	13.6	.0001
NYHA III-IV %	45.9	38.8	35.3	39.4	.0001
SBP=<100 mmHg %	17.7	14.9	12.2	12.4	.002
HR ≥100 bpm %	6.8	5.6	4.3	6.2	.02
EF <30%	66.0	61.9	60.3	61.0	.09
Serum Cr ≥1.5 mg/dL %	22.5	21.8	20.9	17.7	.08
Anemia %	13.9	10.7	7.4	7.2	.0001
% All cause mortality	27.2	21.7	17.9	16.5	<0.0001

Conclusions: Unlike population data, in patients with established HF, BMI has an inverse relationship to prognosis. Although the mechanisms are unclear, this relationship may represent a catabolic state of advanced HF.

Abstract 1926 – Table 1

	All patients	All patients	Carvedilol + enalapril group	Carvedilol + enalapril group	Carvedilol group	Carvedilol group	Enalapril group	Enalapril group
r/p Values	deltaBNP	deltaNT-proBNP	deltaBNP	deltaNT-proBNP	deltaBNP	deltaNT-proBNP	deltaBNP	deltaNT-proBNP
deltaLVEDVI	0.26/<0.0001	0.36/0.0004	0.31/0.0006	0.32/0.07	0.39/0.0006	0.47/0.02	0.12/0.27	0.54/0.0005
deltaLVESVI	0.30/<0.0001	0.40/<0.0001	0.36/0.002	0.34/0.04	0.42/0.0002	0.52/0.007	0.18/0.10	0.57/0.0002
deltaLVEF	-0.25/0.0002	-0.27/0.0009	-0.32/0.006	-0.21/0.24	-0.29/0.01	-0.41/0.04	-0.22/0.05	-0.36/0.03

Associations between changes in LV dimensions and ejection fraction and changes in BNP and NT-proBNP

1929 Insulin resistance predicts impaired survival in chronic heart failure

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Background: Impaired insulin sensitivity (Si) is a feature of chronic heart failure (CHF) independently of ischaemic aetiology. In CHF, impaired Si is related to abnormal energy metabolism, decreased exercise capacity and muscle fatigue. The relationship between presence of insulin resistance (i.e. low Si) and survival in patients with CHF has not been established.
Methods: We prospectively studied 105 patients with CHF due to an ischaemic aetiology (64%) or dilated cardiomyopathy (36%). All patients were in stable clinical condition and had full conventional medical therapy (mean age 62±1y, NYHA class 2.6±0.1, BMI 24.7±0.5 kg/m^2, LVEF 28±2%, peak VO2 17.9±0.7 mL/kg/min. Si was assessed from glucose and insulin dynamic profiles during an intravenous glucose tolerance test using the minimal model technique.
Results: During a mean follow-up period of 44±4 months, 53 (50%) patients died. Cumulative mortality was 28% at 24 months. In univariate Cox proportional hazard analysis, low Si predicted increased mortality (RR 1.21, p=0.015). Also age, NYHA class, and peak VO2 predicted mortality (all p<0.01), but LVEF and BMI did not. In multivariate analyses, low Si (p<0.01) predicted increased mortality independently of age (p<0.001), BMI and peak VO2 (both p<0.05) but not independently of NYHA class (p=0.10).
According to median Si (1.82 min-1.μU.mL-1.104), we divided the CHF patients in two groups. Patients with Si below median (n=52: mean Si 0.95±0.07 min-1.μU.mL-1.104) had worse survival than patients with Si above median (n=53: mean Si 4.08±0.40 min-1.μU.mL-1.104): hazard ratio 2.7 [95% CI 1.5-4.7], p<0.001). Both patient groups were similar for age and NYHA (both p>0.3), but patients with Si above median had higher LVEF (33±3 vs 24±2%) and peak VO2 (19.9±1.0 vs 16.8±1.0 mL/kg/min; both p<0.05). Patients with Si below median had 2-year survival of 61% [95% CI 46-74], but patients with Si above median had 2-year survival of 83% [73-93] (hazard ratio adjusted for age, NYHA, LVEF, and peak VO2: 3.0 [1.5-6.0]). In a 2 risk factor model (Si <median, peak VO2 <14mL/kg/min) the 2 year survival with the presence of none, 1, and 2 risk factors was 88% [78-98], 72% [59-85] and 38% [16-60], respectively.
Conclusion: In patients with CHF, impaired insulin sensitivity relates to poor survival, independently of established prognosticators. therapeutically targeting impaired insulin sensitivity may potentially improve prognosis in CHF patients.

1930 Anemia in chronic heart failure patients: clinical significance and prognostic value

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Background: The prognosis of chronic heart failure (CHF) remains poor despite advances in medical management. During the last few years anemia has emerged as another prognostic variable in the evaluation of CHF. It is important to analyze the prevalence and prognosis of anemia in CHF.
Objective: 1) to evaluate, in a large general population of CHF patients, the frequency of anemia and its correlation with clinical profile. 2) to determine the prognostic value of anemia and weighed its prognostic power in association with other consolidated prognostic variables.
Methods: Two-dimensional echocardiography, right heart catheterization, cardiopulmonary tests and laboratory examinations were performed in a population of 980 consecutive patients with CHF (53±9.4 years, 85% male, LVEF25±8%; 45% with NYHA class III-IV). A hemoglobin (Hb) concentration less than 12 g/dl was used to define anemic patients. The primary end point was cardiac death or urgent heart transplantation.
Results: Nineteen percent of patients were anemic. These patients had a lower body mass index (24±3 vs 25±4 kg/m^2 p<0.0004), a worse functional class (64% were in NYHA class III-IV vs 41% in the non-anemic group, p< 0.0001), poorer exercise capacity (12.4 vs14.8 ml/kg/min peak VO2, p<. 0001) and increased right (7±5 vs 5±4 mmHg, p<. 0004) and left (21±9 vs 19±10 p<. 007) ventricular filling pressures. After a 3-year follow-up there had been 288 (29%) hard cardiac events. Cardiac deaths occurred in 236 (24%) and 52 (5%) patients received a heart transplant in Status I. On univariate regression analysis anemia was significantly correlated with hard cardiac events (39% of anemic patients had hard cardiac events vs 27% of non-anemic patients). By multivariate logistic regression analysis different prognostic models were identified using non-invasive, with or without VO2 peak, or invasive parameters. The prognostic model including anemia (AUCROC:0.720) showed similar accuracy (area under curve Receiver operator curve- AUCROC -) in predicting cardiac events as other prognostic models with peak VO2 (AUCROC: 0.719) or invasive variables (AUCROC: 0.719).
Conclusions: The present study demonstrates that anemia in CHF patients is associated with prognosis, worse NYHA functional class, exercise capacity and hemodynamic profiles. The relationship between anemia and mortality is independent of other simple non-invasive prognostic factors. Prognostic models with more complex independent predictors did not increase the accuracy in predicting hard cardiac events.

1931 Statins and mortality in chronic heart failure: data from ELITE-II

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Background: There is no evidence that HMG-CoA reductase inhibitors (statins) are beneficial in patients with chronic heart failure (CHF). We hypothesized that statin therapy is related to lower mortality in CHF, independently of cholesterol (Chol) levels, CHF etiology and clinical status.
Methods: We included 3127 patients of the ELITE-II study (age 71±7y, LVEF 31±7%, NYHA II/II/IV: 1628/1358/141, female: 31%, ischemic etiology: 74%) in whom body mass index (BMI: 26.2±4.4kg/m^2), Chol (5.34±1.19 mmol/L, >5.18 mmol/L (i.e. >200 ng/mL): 1655, 53%), and presence of statin therapy at baseline (n=397, 12.7%) were assessed.
Results: Patients who received statin therapy at baseline showed different clinical characteristics compared to patients without statins: age 70±5 vs 72±7, NYHA 2.4±0.5 vs 2.5±0.6, beta-blocker (BB) therapy at baseline 36 vs 20%, ischemic etiology 89 vs 71% (all p<0.0001), BMI 26.9±4.2 vs 26.0±4.5, Chol 5.15±1.16 vs 5.37±1.19 (both p<0.001), and LVEF 32±6 vs 31±7% (p<0.05). Patients with and without statins were similar for gender, serum uric acid (UA) and creatinine levels (p>0.2). The following statins were used: simvastatin (n=272, dose 16±10 mg), pravastatin (n=125, 22±11 mg), atorvastatin (69), lovastatin (48), fluvastatin (37) and cerivastatin (11).
Follow-up was 9±6 months in 520 patients (16.6%) who died (in survivors 19±4 months). Patients on statins had lower mortality (RR 0.60, 95%CI 0.44-0.82, p=0.0006). In univariate Cox-proportional hazard analysis, also age, BMI (RR 0.94), NYHA, LVEF, UA, creatinine, Chol (RR 0.85, 0.78-0.91), BB therapy at BL (RR 0.61) (all p<0.0001), and ischemic etiology (RR 1.40, p<0.002) predicted mortality. In multivariate analysis, statin therapy related to lower mortality independently of all these parameters (RR 0.66, 0.47-0.93, p=0.017). Also low Chol (RR 0.90) and BB therapy (RR 0.70, both p<0.006) independently predicted lower mortality. Other independent prognosticators were: NYHA, BMI, UA (all p<0.0001), etiology and age (p<0.01).
Conclusion: In chronic heart failure, treatment with statins is related to lower mortality, independently of cholesterol levels, CHF etiology and clinical status. Prospective trial data are required.

1932 Idiopathic dilated cardiomyopathy, an important predisposing factor for early onset and higher grade rejection: relevance to outcome

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We have previously identified idiopathic dilated cardiomyopathy (DCM [in a study cohort of 117 pts]) a predisposing factor for a higher frequency and incidence of highgrade (ISHLT 3A/3B) rejection and its early onset compared to pts with ischemic heart disease (IHD). However, little is known of the relative and comulative effect of these events on the clinical outcome in a larger clinical setting. We revieved 1074 consecutive adult heart transplant recipients (pts with complete histological profiles only) transplanted (Tx) for DCM or IHD at Harefield Hospital. Eighty five point five percent (n=918) had rejection within 1 year post-Tx. Fourteen point five percent (n=156) had either no rejection or an episode 1 year post-Tx. Of the 918 pts, 356 were candidates Tx for DCM and 562 for IHD. The mean frequency of ISHLT histological rejection was higher in pts Tx for DCM compared to IHD: 3m; 2.25 (0.06) vs 1.81 (0.042, $p<0.00001$) and 6m; 2.72 (0.085) vs 2.07 (0.05, $p<0.00001$) respectively. Percentage incidence of ISHLT grade 3A/3B rejection was comparatively higher in pts Tx for DCM; 3m; 33% vs 21% (p=0.0001) respectively. Hence, these observations further support the underlying indication for Tx a predisposing factor in cardiac allograft rejection. With Cox proportional hazards multivariate analysis, an episode of rejection significantly altered the rate to death. Incidence and frequency of ISHLT rejection grade 3A/3B compared to 1A/1B significantly reduced survival (p=0.0076). Incidence or frequency of ISHLT 1A/1B had no discernible effect on survival. The probability of time (days) to rejection in pts with DCM was significantly earlier compared with IHD (p=0.000001). Onset of early rejection (independent of Tx-associated CAD) correlated with early mortality. Days to rejection in pts with survival time of up to 1 year vs >1 year was significantly lower ($p<0.00001$). This difference was less prominent when discriminated by a 2 year survival interval (p=0.0023) and not significantly different by an interval of 3 year survival (p=0.168). Whereas early rejection marked early mortality, the single most significant and independent predictor of long term outcome (>15 years) was ISHLT grade 3A/3B rejection. We conclude that onset of early rejection and the incidence of 3A/3B rejection are mutually exclusive contributors of Tx-associated mortality in which the long term outcome is best predicted by grade (3A/3B) rejection. This rejection profile analysis may provide an algorithm to determine the relative impact and significance of markers associated with Tx-related morbidity and mortality.

1933 Decreasing 1-year mortality and hospitalization rates for heart failure in Sweden. Data from the Swedish hospital discharge registry 1988 to 2000

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Background: In the last 10-15 years several treatment modalities have demonstrated improved prognosis in heart failure in selected study populations. Little is known whether this has translated into improved prognosis for the patient population at large. We conducted a survey of trends in 1-year prognosis of patients treated for heart failure in Sweden over the years 1988 to 2000.
Methods: Data from the Swedish Hospital Discharge and the Swedish Cause of Death registers were used. The study population consisted of all patients aged 55 to 84 (n=140,087) discharged with a principal diagnosis of heart failure from any Swedish hospital in 19 Swedish counties (80 per cent of the Swedish population) with complete coverage over the period 1988 to 2000.
Results: One-year mortality for patients hospitalised for heart failure was reduced by about 50% from 1988 to 2000 (see table). The decrease in mortality was more marked after 1994. Hospitalisation rates for heart failure decreased from 1993 to 2000 in all age groups among both sexes. The decrease in hospitalisations was particularly evident in the younger age groups (55-64 years: men 32%, women 38%).

One-year mortality

Age	1988	2000	% change
Men			
55-64	31	15	-60
65-74	38	22	-54
75-84	49	35	-43
Women			
55-64	30	16	-56
65-74	33	22	-44
75-84	43	30	-44

One-year mortality (per cent) among men and women hospitalised with heart failure

Conclusion: One-year survival after hospital discharge for heart failure has improved markedly during the last decade. The reduction in mortality was probably not due to milder cases being admitted since admissions for heart failure also decreased during the period. The improvement coincides with the establishment of ACE-inhibitors and beta-blockers as beneficial pharmacological therapies. These benefits may now also translate into non-study populations.

RESYNCHRONIZATION IN HEART FAILURE – CLINICAL RESULTS

1962 Long-term follow-up after cardiac resynchronization therapy: poor clinical outcome in patients enrolled in NYHA Class IV

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Heart failure (HF) pts with prolonged QRS, low EF, in NYHA Class III-IV, are considered the best candidates to CRT.
Aim of our study was to compare long term effect of CRT according to NYHA class at enrollement.
Methods and Results: From Oct'99 to November'02, 201 pts (age 66±9 yrs, mean ejection fraction-LVEF-29,7±7%) underwent successful CRT. Follow-up data at 3,6, 12, 24 months have been collected (mean follow- up 19 ± 8 mos). At baseline, 15% of pts were in NYHA II, 71% in NYHA III, and 14% in NYHA IV. A significant reduction of ESV was observed in NYHA II and III only, while EF and 6 min WT significantly increased in survivors of all groups. The hospitalization rate after CRT was significantly higher in NHYA class IV vs III (IRR 3 p=0.02) and vs II (IRR 5.5 p=0.001). Survival analysis showed a significantly higher mortality rate in NYHA class IV (21%/yr) than in class III (5.5%/yr) and class II (0%/yr) (Log-rank test: II vs III: ns; III vs IV: p=. 004; II vs IV: p=.0007).

NYHA class

	NYHA II				NYHAIII				NYHA IV			
	Basal	3mos	12mos	p	Basal	3mos	12 mos	p	Basal	3mos	12mos	
FE	30	35	41	.000	30	36	40	.000	25	29	34	
	±7	±8	±10		±7	±9	±12		±5	±9	±11	
ESV	149	134	103	.007	142	115	109	.000	168	159	131	
	±66	±78	±59		±59	±57	±55		±72	±94	±84	
6minWT	401	455	485	.000	335	404	453	.000	224	359	377	
	±118	±100	±91		±113	±102	±82		±108	±88	±101	

Conclusions: NYHA class IV pts maintain a poor prognosis even after CRT (higher hospitalization rate, significant mortality rate). On the other hand, NYHA class IV "survivors" exhibit satisfying echocardiographic and functional parameter improvement during long term follow-up.
These data claim for reconsideration for this expensive therapy in NYHA IV pts.

1963 Clinical efficacy of one year cardiac resynchronization therapy in heart failure patients stratified by QRS duration: results of the PATH-CHF II trial

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The objective of the Pacing Therapies in Chronic Heart Failure II (PATH-CHF II) multi-center trial was to assess efficacy of cardiac resynchronization therapy (CRT) in mild to severe HF patients (pts), with or without ICD indication, who were prospectively stratified by severity of ventricular conduction delay, as assessed by QRS duration. We have previously reported that pts with a QRS between 120 and 150 did not demonstrate CRT benefit after 3 months therapy. This abstract present the one year results.
Method: The design was a randomized controlled six months crossover trial (three months therapy on and off) followed by a six months chronic CRT, with equal distribution of patients having QRS duration greater than 150 ms (Group I) or QRS between 120 and 150 ms (Group II). 89 pts were implanted with hemodynamically optimized VDD pacing (LV pacing: 86, RV pacing: 3). 68 pts have complete datasets at baseline and one year. Mean age 59 ± 9 years, 44 males, mean LVEF 24 ± 7%, mean QRS interval 156 ± 20 ms, NYHA class II/III: 25, 43.
Results: The underneath table summarizes treatment effects at one year for the whole population and both pt groups.
Conclusions: While patients with QRS between 120 and 150 ms did not demonstrate CRT benefit after 3 months therapy, the PATH-CHF II study demonstrates long term significant clinical improvement in mild to severe heart failure patients, for both the group with QRS greater than 150 ms and also the group with QRS between 120 and 150 ms.

1964 Long-term prognostic value of criteria of cardiac resynchronization therapy for cardiac death and heart transplantation in idiopathic dilated cardiomyopathy

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Background: Cardiac resynchronization therapy (CRT) is effective to improve cardiac symptoms in heart failure patients with dilated cardiomyopathy. There are still controversies about patients who will benefit from CRT. We tried to determine the best criteria in idiopathic dilated cardiomyopathy (IDC) according to the several completed trials of CRT.
Methods: In 201 patients with IDC in sinus rhythm (WHO criteria; normal coronary angiography in all patients; age 51±12 years; range 18-70; 162 men; left ventricular ejection fraction 32±12%), the relative risk of cardiac death or heart transplantation was calculated according to the inclusion criteria in the MUSTIC, InSync, MIRACLE and CONTAK-CD studies.
Results: The percentage of patients meeting the inclusion criteria was respectively 6% for MUSTIC, 7.5% for InSync, 10% for MIRACLE and 23% for CONTAK-CD. With a follow-up of 51±42 months, 28 patients suffered cardiac death (15 progressive CHF, 13 sudden deaths) and 20 underwent heart transplantation. Relative risks of cardiac events are in table. The sensitivity, specificity and accuracy of inclusion criteria for the occurrence of cardiac events were respectively 13%, 96% and 75% for MUSTIC, 17%, 95% and 75% for InSync, 21%, 93% and 75% for MIRACLE and 47%, 81% and 72% for CONTAK.

Relative risk for cadiac events

	NYHA	LVEDD	LVEF	QRS d	RR (95% CI)	p
MUSTIC	III	> 60 mm	< 35%	>= 150 ms	4.00 (1.67-9.62)	0.0018
In Sync	III-IV	>= 60 mm	< 35%	>= 150 ms	3.37 (1.56-7.24)	0.0019
MIRACLE	III-IV	>= 55 mm	≤ 35%	>= 130 ms	2.59 (1.29-5.21)	0.0077
CONTAK CD	II-IV		< 35%	>= 120 ms	3.41 (1.92-6.06)	0.0001

Conclusion: In the long term follow-up of this series of patients with well characterized IDC, patients with MUSTIC criteria of CRT had the highest relative risk of cardiac death or heart transplantation. Moreover, less restrictive inclusion criteria did not have a better accuracy to determine the occurrence of cardiac events.

1965 Upgrading from right-ventricular pacing to biventricular pacing in previously paced patients with advanced heart failure: a randomized controlled study

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Biventricular pacing (Biv) improves symptoms and exercise tolerance in non-paced patients with advanced heart failure (HF), intraventricular conduction delay and LV systolic dysfunction. Only few small and non controlled studies have evaluated the effect of biventricular pacing in HF patients previously paced in the right ventricle for a conventional indication. The RD-CHF study is a randomized single-blinded cross-over trial aimed to assess the clinical effect of upgrading from RV pacing to biventricular pacing in HF patients (NYHA class III or IV) with LV systolic dysfunction and electricomechanical dyssynchrony (aortic pre-ejection delay > 180 ms or interventricular delay > 40 ms). Pts were randomized in two groups for two 3-months cross-over periods: RV followed by Biv in one arm, or Biv followed by RV in the other arm. Arrhythmia assessment was performed at the end of the 2 cross-over phases using the Automatic Interpretation for Diagnostic Assistance (AIDA) algorithm included in the biventricular pacemaker.
44 pts were randomized (73 ± 8 years; LVEF = 25±9%). 21 pts were in sinus rhythm and 23 in permanent atrial fibrillation.
Baseline characteristics and results in the two pacing modes are shown in the table below. During the follow-up, 6 patients died,including 2 from HF (1RV, 1Biv), and 2 from sudden cardiac deaths (Biv). No significant difference in ventricular arrhythmias were observed between the 2 groups. During the 1-st cross-over phase, 21 pts were rehospitalized, 81% were in RV and 19% in Biv. Rehospitalization was related to HF in 8 pts, 7 in RV and 1 in Biv (p=0.01).

Results

	Baseline	RV pacing	Biv pacing	Delta Biv/RV (%)	P
QRS (ms)	206 ± 26	200 ± 20	154 ± 26	- 23%	< 0.001
NYHA	3.2 ± 0.4	2.6 ± 0.7	2.1 ± 0.5		0.002
6 WT (m)	276 ± 127	324 ± 149	386 ± 99	+ 19%	0.002
QOL	49 ± 20	40 ± 28	29 ± 23	- 29%	0.0001

Conclusion: The RD-CHF study shows that in previously paced CHF pts with poor LV function, upgrading from RV to biventricular pacing significantly improves symptoms and exercise tolerance and decreases the hospitalization rate.

1966 Long-term results of cardiac resynchronization therapy in patients with permanent atrial fibrillation

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Heart failure (HF) pts with prolonged QRS, low ejection fraction, NYHA III-IV, in sinus rythm (SR) are considered to be the best candidates to cardiac resynchronisation therapy (CRT). Only few data have been collected concerning long term results of CRT in pts with permanent atrial fibrillation AF.
Aim of our study was to compare long term effect of CRT in SR pts compared to pts with permanent AF in our cohort of pts.
Methods and Results: From Oct'99 to November'02, 201 pts (age 66±9 yrs, mean ejection fraction-LVEF-29,7±7%) underwent successful CRT. Follow-up data at 3,6, 12, 24 months have been collected. Mean follow-up was 19 + 8 mos). At enrollement, permanent AF was present in 41/201 pts (20%), after CRT all 41 pts received AV node ablation to obtain constant biventricular pacing. The table shows the main results of CRT in the 2 groups: A significant improvement of LVEF, ESV (end-systolic LV volume), NHYA class and 6 minute walking test (6WT) was observed both in SR and in AF groups of pts. The percentage of non responders was similar in the two groups (19% in SR pts and 16% in AF pts respectively at 3 mos, 12% vs 6% at 6 mos, 13% vs 16% at 12 mos)
Survival analysis (Log-rank test) did not show statistical significance in mortality on the 2 groups (7.0%/yr in SR vs 3.5%/yr in AF)

SR versus AF pts

	SR					AF				
	Basal	3mos	6mos	12 mos	p	Basal	3 mos	6 mos	12 mos	p
LVEF%	29 ±7	35 ±9	38 ±10	39 ±10	.0001	31 ±7	35 ±9	39 ±13	40 ±15	.0001
ESVml	150 ±63	127 ±71	116 ±65	108 ±57	.0001	134 ±60	120 ±61	109 ±65	118 ±73	.006
NYHAIII-IV	83%	23%	11%	14%	.0001	93%	26%	19%	19%	.0001
6minWT mt	349 ±119	413 ±98	445 ±96	458 ±88	.0001	291 ±131	388 ±121	415 ±139	427 ±114	.0001

Conclusions: At long term follow up 1-CRT is beneficial in pts with HF regardless the presence of SR or AF; 2-AF is not a predictor for non responsiveness to CRT. For these reasons, pts in permanent atrial fibrillation should not be excluded "a priori" from CRT.

1967 Is left-ventricular lead positioning useful to predict clinical improvement in heart failure patients treated with cardiac resynchronization therapy? The InSync/InSyncIII/InSyncICD Italian Registry

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Purpose: to investigate in a wide heart failure (HF) population treated with cardiac resynchronisation therapy (CRT) weather the improvement in clinical condition could be correlated to the final positioning of left ventricular lead. To date, target coronary sinus (CS) veins are the lateral, posterior-lateral and posterior veins since these veins generally allow the maximun interventricular conduction time between ventricles.
Methods: 804 pts (81% male, age 69.9±9.6) with advanced HF (NYHA class 2.9±0.8), low ejection fraction (EF 26.6±15.6%) and ventricular conduction delay (QRS width 140.1±64.8 ms) received CRT and were followed in the InSync/InSyncIII/InSyncICD Italian registries. Heart failure etiology was non ischemic in 57%. LV lead was positioned in the lateral vein in 273 pts (34%), in posterior-lateral vein in 282 (35%), in posterior vein in 72 (9%), so 78% of pts received the lead in a target veins (TV group). LV lead was positioned in median and anterior veins (no target veins) in 177 pts (22%) (NTV group).
Pts who had a persistent improvement of at least 1 NYHA class without hospital admission for HF during a follow-up of at least 6 months were classified responder (R).
Results: Over a median period of 14±7 months, pts with at least 6 months FU and compliant for FU data were 317. 263 pts (83%) were in the TV group and 54 (17%) pts were in the NTV group. TV group significantly improved EF% (from 26.2±8.1 to 36.5±11.5, P=0.002), significantly decreased NYHA class (from 3.0±0.6 to 2.0±0.7, P<0.001) and QRS width (from 167.5±25.7 to 136.9±24.9, P<0.001). Similarly, NTV group slightly improved EF% (from 26.8±6.8 to 31.8±5.4, P=0.06), significantly decreased NYHA class (from 3.0±0.5 to 1.9±0.7, P<0.001) and QRS width (from 170.5±24.1 to 150.0±37.7, P<0.05). 218/263 TV pts (83%) were classified as R and 43/54 NTV pts (81%) were R. No statistical differences were observed in term of clinical improvement and percentage of R between two groups.
Conclusions: Our data showed no correlation between clinical improvement and left ventricular lead positioning in a wide CRT population as confirmed by the same increase in EF, same reduction in NYHA class and QRS width in the two groups. Moreover there was no statistical difference in the percentage of R and NR between groups.
These findings confirm the recent observation that pts paced at a site concordant with the most delayed wall showed a greater improvement in LV performance, despite of the positioning of the LV lead.

PRESENCE AND THERAPEUTIC POTENTIAL OF STEM CELLS IN CORONARY ARTERY DISEASE

1978 Role of SDF-1 in endothelial differentiation of hematopoietic stem cells

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Background: Endothelial progenitor cells (EPCs) are recruited in peripheral blood (PB) following ischemic injury or treatment with mobilizing cytokines. Prior studies have shown that circulating CD34+/AC133+ EPCs from PB give rise to endothelial cells in culture. However, little is known on the mechanisms driving their endothelial commitment. SDF-1 is a chemokine implicated in trafficking of stem cells from/to the bone marrow through its selective receptor CXCR4 and is an angiogenic factor. The aim of our study was to test whether SDF-1 promotes endothelial differentiation of c-kit+ cells in culture onto ECM components.
Methods and Results: c-kit+ cells (>90%pure) were obtained from mouse bone marrow by magnetic cell sorting purification. These cells were first tested for expression of EPC markers (c-kit, CD34, Sca-1) and CXCR4 by FACS analysis. They were then cultured onto glass chamber slides coated with Fibronectin (FN), Collagen I and IV (Co I/IV) and Vitronectin (VN) for one week in low serum-containing medium (5% FCS) or serum-free medium, in the presence or the absence of 100 ng/ml SDF-1. Endothelial differentiation of c-kit+ cells was measured by DiI-Ac-LDL uptake and by the expression of endothelial markers (KDR, vW factor). Our study showed that c-kit+ cells differentiated into endothelial cells onto Co I, FN and VN but not Co IV after 7 days of culture. Interestingly, the addition of SDF-1 markedly enhanced the number of endothelial cells onto FN and Co I (1460±446 vs 416±133 cells, mean±S.E. for Fn and 3752±695 vs 1441±219 for CoI, n=5, P<0.05, respectively), but not on VN. To assess whether SDF-1 affects proliferation/survival of c-kit+ cells, we performed BrdU uptake and FACS analysis of PI-stained cells. The results showed that SDF-1 did not affect the proliferation or apoptosis of stem cell-derived endothelial cells at either 1 day and 7 days of culture. To unravel whether increase in cell adhesion to specific substrates is responsible for endothelial differentiation of c-kit+ cells, we analyzed the expression of VLA-2 and VLA-4 integrins in the presence or the absence of SDF-1, by FACS analysis. Although at day 1 and day 7 of culture the expression of VLA-4 was downregulated, the addition of SDF-1 partially prevented such downregulation. By contrast, VLA-2 was not affected by SDF-1.
Conclusions: our observations suggest that SDF-1 has a role in endothelial differentiation of EPCs possibly via the regulation of VLA-4 expression.

1979 Gene expression profile of bone marrow derived macrophages after rm-vascular endothelial growth factor stimulation: arteriogenic properties versus endothelial phenotype

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Introduction: Invasion of circulating monocytes as well as macrophage maturation play an important role in arteriogenesis. VEGF is known to induce chemoattraction of monocytes, however the effect of rmVEGF on the expression profile of pluripotent mononuclear stem cells is largely unknown. Purpose: The aim of the work is to study the gene- and protein expression profile of BMDM of 6-8 weeks old Balb/c mice under rmVEGF stimulation.
Methods: Cells were cultured for 8 days in L-conditioned medium and incubated with 0.2, 2, and 20 ng/ml rmVEGF for 10 and 20h. Gene-expression was studied by microarray technology and verified via realtime PCR. Protein expression was assessed via flow-cytometry and immunofluorescence. The cytokine expression in cells and supernatants was analysed via ELISA.
Results: There was no significant effect of VEGF on proliferation (BrdU-test and cell vitality). Flt-1 and Flk-1 receptors in BMDM were constitutively expressed, although no significant changes in their gene expression were detected. Interestingly, we found significant high levels of mRNA expression of cadherin-5 and of the cytokine inducible SH protein, (CISH) which showed a 24x up-regulation after VEGF treatment. On the contrary, RANTES, MCP-1, IL-1β and mac-1 mRNA were significantly down regulated. In summary our data are the first comprehensive analysis of gene and protein expression in BMDM after VEGF incubation.
Conclusion: The stimulation of BMDM with rmVEGF leads to a specific gene expression profile, with "silencer" function on arteriogenic cytokines and "enhancer" function towards an endothelial-like phenotype of BMDM.

1980 Identification and characterization of potential stem cells in the vascular wall of normal adult mouse aorta

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Background: Cell phenotype changes participate to vascular remodeling. It has recently been suggested that hematopoietic stem cells could contribute to vascular remodeling. Resident stem cells have been identified in several human and murine organs. These cells are termed side population [SP] cells. The aim of this study was to determine the existence of SP vascular stem cells in normal adult mouse aorta.
Methods and Results: Stem cells show the ability to efflux Hoechst 33342 (a DNA-binding dye) via a specific membrane transporter. Vascular cells from 5 to 8 week-aged C57Bl/6 mice aortas were isolated and stained with Hoechst. Separate sets of mice (at least 4 mice per experiment) were used for SP isolation and characterization by flow cytometry. We identified SP vascular potential stem cells which represented 0.5%±0.05 of total aortic cells. These SP vascular cells were further evaluated for standard stem cell markers: 91.2%±1.2 were sca-1+, 64.9%±2.2 were lin-, 9.8%±1.1 were CD34+, 48.8%±2 were c-kit+, 54.9%±1.1 were Flk-1+, confirming the stem cell phenotype of this newly identified side population. Interestingly, 44.4%±1.7 of these cells did not express CD45 (a bone marrow-derived cell marker) indicating that these potential stem cells do not systematically originate from bone marrow.
Conclusion: These data suggest the existence of potential stem cells residing in the normal adult mouse arterial wall. An important proportion of these cells do not derive from the bone marrow. These resident stem cells could play a role in tissue homeostasis as well as in atherosclerosis and vascular remodeling.

1981 Increased proportion of circulating progenitor cells in the early phase of acute myocardial infarction

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Recent papers suggest a role for stem/progenitor cells (SPC) in the repairing process of damaged myocardium after acute myocardial infarction (AMI). The most of the data were generated in animal models; rare reports suggest that such a process happens in humans. To evaluate the spontaneous mobilization of SPC in the early phase of AMI, we studied 12 patients (pts) with ST segment elevation AMI (10 men, age 46-68 years) who underwent primary percutaneous transluminal coronary angioplasty (PTCA) within 6 hours from the onset of symptoms. EDTA blood samples were drawn at admission (T0) and immediately after PTCA. The membrane expression of the cell antigens CD34, CD117, CD33, CD38 and vascular endothelial growth factor receptor-2 (VEGFR-2/KDR) was evaluated by cytofluorimetric analysis. The results were compared with those obtained from 12 age-matched healthy subjects (CTR) and 10 pts with dilated cardiomyopathy (DCM). Data are expressed as percentage (median and range). Statistic analysis was performed by Kruskall Wallis ANOVA test and post-hoc test. At T0 the percentage of CD34+ cells was higher in AMI pts than in CTR or DCM (1.69, 0.29-6.7 vs 0.5, 0.25-1.32, p= 0.045, or vs 0.3, 0.0-1.46, p=0.007, respectively). Similarly, in AMI pts both the percentages of CD33+ and CD38+ were increased if compared with CTR and DCM (CD33+: 79.8, 72.2-86.9 vs 53.7, 33.2-73.9, p=0.0001, or vs 63.8, 40.5-72.2, p=0.0001; CD38+: 88.4, 83.7-92 vs 79.9, 46.6-87.8, p=0.0006, or vs 79.0, 71.7-96.6, p=0.015). In AMI pts the percentage of CD34+CD33+ and CD34+CD38+ cells were also significantly increased if compared with CTR or DCM (CD34+CD33+: p=0.013 and p=0.056; CD34+CD38+: p=0.045 and p=0.0038, respectively). At T0 no difference was observed in the percentage of CD117+ or VEGFR-2+ cells between AMI pts and CTR subjects. However, in AMI pts the percentage of CD117+ and CD117+CD34+ cells significantly increased after PTCA with respect to T0 (from 2.7, 0.02-5.98 to 3.3, 0.54-9.4, p=0.046, and from 0.34, 0.02-0.75 to 0.77, 0.14-1.47, p=0.006, respectively).
In conclusion, our preliminary data suggest that the early phase of AMI is associated with a significant elevation of the percentage of circulating subsets of SPC. The CD117+ cells seem to be rapidly increased after myocardial reperfusion obtained by PTCA.

1982 Influence of mobilized stem cells on myocardial infarct repair in a non-human primate model of acute myocardial infarction

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Aim: Although previous findings have suggested that some adult stem cells are pluripotent and could differentiate in an appropriate microenvironment, the fate conversion of adult stem cells is currently being debated. The present study was undertaken to evaluate the ability of mobilized stem cells to repair cardiac tissue injury in a nonhuman primate model of acute myocardial infarction.
Methods: Mobilization was carried out with Stem Cell Factor (SCF), 100 mcg/kg/Day (D) and Granulocyte Colony Stimulating Factor, (G-CSF), 25 mcg/kg/D administered 5 days before (D-5 group; n=3) or 4 hours after (H+4 group; n=4) circumflex coronary artery ligation; no growth factor was administered to 3 baboons of the control group. Animals' follow-up was assessed in vivo by 2-dimensional echocardiography and Positron Emission Tomography (PET) with [11C]-acetate performed twice: 2 days (D2) and 30 days (D30) after AMI.
Results: No adverse effect relating to growth factor administration was observed. Mobilization involved cells of the endothelial and cardiac lineage. When comparing Positron Emission Tomography (PET) with [11C]-Acetate between examinations from D2 and D30, a relative increase (perfusion ratio between infarct and non-infarct regions) of 26% (p=0.01) in myocardial blood flow was found in the H+4 group; the relative rate of oxidative metabolism remained unaltered in the three groups. No change was observed in the echographic indices of the left ventricular (LV) enlargement or systolic function in the three animal groups during the 2 months follow-up. The PET findings concurred with the immunohistochemistry analysis of left ventricular myocardial sections with evidence of endothelial cells but no myocyte differentiation; few cycling cells were observed at this time.
Conclusion: The present data suggest that, in nonhuman primates submitted to coronary artery ligation, mobilization by hematopoietic growth factors could promote angiogenesis in the infarcted myocardium, without detectable myocardial repair.

ADVANCES IN CARDIOVERSION/DEFIBRILLATION OF ATRIAL TACHYARRHYTHMIAS

1992 Atropine-facilitated electrical cardioversion of persistent atrial fibrillation

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Objectives: To assess the efficacy of Atropine administration in facilitating electrical cardioversion of electrical refractory chronic atrial fibrillation (CAF).
Background: Electrical cardioversion for patients with CAF meets failure rates of 10-25%.
Methods: We enrolled 364 patients who underwent synchronized electrical cardioversion for CAF. After > 4 weeks of adequate oral anti-coagulation and failed attempts of pharmacological cardioversion, patients were subjected to electrical cardioversion. Under brief general anesthesia, escalating doses of synchronized transthoracic electrical shocks were deployed. A total of 254 patients received sequential monophasic shocks of 100, 200 and two 360 joules, while 110 patients received biphasic shocks of 50, 100 and two 200 joules.
Results: Forty nine patients (13.5%) failed to restore sinus rhythm after 2 sequential cardioversions shocks of 360 joules (monophasic) or 200 joules (biphasic). After receiving up to 2 mg of Atropine, patients were subjected to 2 additional attempts of synchronized transthoracic electrical shocks of 360 Joules (monophasic) or 200 joules (biphasic) each, 40 of the 49 (81%) were successfully cardioverted to sinus rhythm and maintained sinus rhythm for at least 24 hours. The use of Atropine was not associated with high incidence of early recurrence of atrial fibrillation or any substantial adverse events.
Conclusion: Atropine facilitates successful cardioversion in drug and electrical refractory CAF, and reduces failure rate from 13.5% to 2.5%. Therefore, Atropine should be considered in algorithms of electrical cardioversion of patients in CAF.

1993 Energy requirements for transthoracic electrical cardioversion of atrial tachyarrhythmias with biphasic shocks

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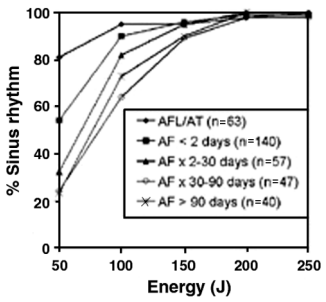
The purpose of this prospective study was to evaluate the relation between the type and duration of the atrial tachyarrhythmia and the probability of successful cardioversion with biphasic shocks in order to formulate recommendations for the initial energy setting aiming at a success rate of at least 80%.
Methods: We analyzed 347 consecutive electrical cardioversions including 63 attempts for atrial flutter (AFL) or atrial tachycardia (AT) and 284 attempts for atrial fibrillation (AF). A biphasic shock waveform (Medtronic Physio-Control Lifepak 12 or 20) was employed using sequential shocks of 50, 100, 150, 200 and 250 J, if necessary. All patients (except 6 with right-sided pectorally implanted pacemaker) were treated by an anterior-lateral electrode position.
Results: Cardioversion was successful in 344 of 347 attempts (cumulative efficacy 99%). The probability of conversion to sinus rhythm at the different levels of energy was determined by type and duration of the atrial tachyarrhythmia (Figure).



Conclusion: Based on our results, we recommend an initial energy setting of 50 J in patients with AFL/AT, an initial energy setting of at least 100 J in patients with a duration of AF of less than 30 days and an initial energy setting of at least 150 J in patients with a duration of AF of more than 30 days.

1994 Stroke prevention by rhythm versus rate control in atrial fibrillation: insight from the randomized studies

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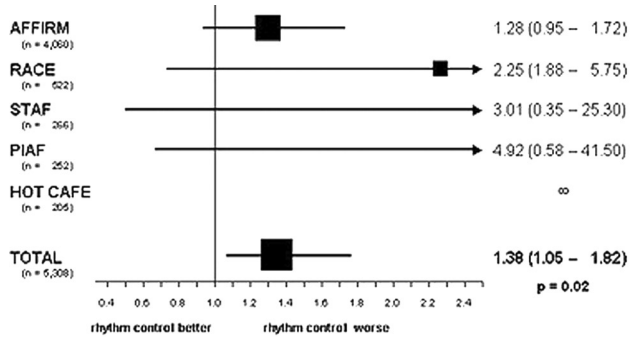
Background: In patients with atrial fibrillation return to sinus rhythm is believed to decrease arrhythmic symptoms, heart failure and systemic embolism. In the past years 5 major randomized trials on rate versus rhythm control have addressed these issues and their results have been published or presented. We specifically have analysed stroke prevention by a strategy of rhythm control.
Results: A total of 5,305 patients with persistent or paroxysmal atrial fibrillation were randomized to rate or rhythm control in the AFFIRM, RACE, STAF, PIAF and HOT CAFE trials. Follow-up varied from 1 to 6 years. Oral anticoagulation was administered to almost all (94%) patients in the rate control strata and in all patients undergoing electrical cardioversion. The majority of rhythm control patients were anticoagulated during follow-up. Ischemic strokes (including TIA) occurred in 195 patients (87 with rate (4.4%) and 111 (6.1%) with rhythm control, RR 1.38, 95% CI 1.05 - 1.82, p = 0.02, see figure) and cerebral bleeding in 39 (23 with rate and 16 with rhythm control p = 0.48). The risk of ischemic stroke is consistently increased in the rhythm control arms of the trials compared to the rate control groups.



Ischemic stroke.

Conclusion: A routine strategy of rhythm control in atrial fibrillation increases the risk of ischemic stroke significantly by nearly 40%. Besides the risk of side-effects of antiarrhythmics, the increased risk of stroke should be incorporated in the decision to rhythm or rate control. These data support also a more extensive use of prolonged oral anticoagulation, even when long-term sinus rhythm has been achieved.

1995 Anticoagulant treatment is often inadequate when administered in prevention of thrombotic complications before direct current cardioversion

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Direct current cardioversion (DCC) is commonly used for restoration of sinus rhythm in patients with atrial fibrillation (AF). Despite widespread recommendations for antithrombotic covering of DCC, the risks of thromboembolic and haemorrhagic events still persist. In a multicenter French survey we tried to assess the quality of anticoagulant treatment in patients treated with DCC for restoration of sinus rhythm.
During a three months period (January-April 2000), 801 case of DCC were collected in four geographic regions (Lille, Marseille, Paris, Toulouse) in teaching and private centres and 684 fulfilled the quality control criteria. The mean age of the patients was 68,5 $\pm$ 10,9 years and 61% were male. The duration of AF was less than one month in 31% of the patients and 20% were asymptomatics. The immediate success rate was 86% and sinus rhythm was present in 79% of patients at discharge. 35% of the patients had transesophageal echocardiography which was performed only in few patients immediately before DCC to avoid prolonged anticoagulant treatment. 39% of the patients were treated with a low molecular weight heparin at anytime, alone or in combination in relay of an oral anticoagulant.
Only 41,1% of the patients had adequate anticoagulation (INR 2.0-3.0 or APTT 1.5-2.5) immediately before DCC and this rate increased to 54,8% when a less strict criterion was applied (INR 2.0-3.5 or APTT 1.5-3.0). Anticoagulation was insufficient in 8,3% of patients with INR $<$ 2.0 and APTT $<$ 1,5 and there was an excess of bleeding risk in 28.1% others with INR $>$ 3.5 and/or APTT $>$ 3.0. Seven haemorrhagic episodes were reported of which 3 were severe (one death from cranial bleeding; one haematoma requiring surgery and another haematoma with severe haemoglobin fall). No patient suffered thromboembolic complication.
In daily practice, as compared to widely admitted recommendations, anticoagulant treatment before DCC is inadequate in a very important proportion of patients, both with an increased risk of bleeding or, in a lesser extend, of thrombosis. Further investigations aimed at improving efficacy and safety of the anticoagulant regimen before DCC in daily practice are urgently required.

1996 Effects of carvedilol and amiodarone on persistent atrial fibrillation conversion and recurrence rates. A randomized controlled study

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Purpose: Carvedilol is a multiple action cardiovascular drug with blocking effects on beta and alpha receptors, Ca+2-channels, Na^+-channels and various cardiac K^+-channels. Such electrophysiological effects of carvedilol would be beneficial for cardioversion outcome and prevention of recurrences in atrial fibrillation (AF) patients.
In this prospective trial we examined the effects of carvedilol and amiodarone on persistent AF conversion and recurrence rates and we measured several electrophysiological parameters of the pre- and post-electroversion period in order to assess the possible effects of these drugs on atrial electrical remodeling and whether these actions have any clinical implications.
Methods: We evaluated 49 patients (66$\pm$9 years) with persistent AF (mean duration 30$\pm$34 months). They were randomly assigned to three treatment groups over a period from 6 weeks before to 6 weeks after external biphasic cardioversion: group A (16 pts, Carvedilol, at a daily oral dose not less than 12,5 mg titrated up to a maximum of 50 mg), group B (17 patients, Amiodarone, 600 mg per day the first two weeks and subsequently 200 mg per day up to the end of the study) and group C (13 patients, no antiarrhythmic drugs). Several electrophysiological parameters were assessed 5 min and 24 h after cardioversion. Relapses of AF were recorded after 24 hours and 7 days.
Results: All three groups had similar clinical and echocardiographical data. Cardioversion rates were 14/17 (87%) in group A, 16/17 (94%) in group B and 9/15 (69%) in group C. These rates differed significantly between controls (C) and groups A and B (F=5.848, p=0.050). Patients of groups A and B had longer fibrillatory cycle length intervals in the immediate preconversion period than patients of group C (180$\pm$18 ms and 186$\pm$14 ms vs. 165$\pm$19 ms, p=0.001) and longer atrial effective refractory periods (211$\pm$22 ms and 208$\pm$16 ms vs. 188$\pm$17 ms, p=0.003) as assessed 5 min after conversion. There was a more marked trend towards a higher incidence of AF relapses after 7 days in group C (4/9 44%) than in groups A (4/14, 29%) and B (3/16, 19%).
Conclusions: Carvedilol seems to have effects similar to those of amiodarone regarding the conversion rates, prolongation of fibrillatory cycle length and atrial effective refractory period in AF patients. These preliminary results of our study provide the first clinical and electrophysiological evidence suggesting that carvedilol may have a beneficial effect on cardioversion outcome and preservation of sinus rhythm after cardioversion of persistent AF.

1997 Incidence of atrial thrombus in patients with auricular arrhythmias. Study of a cohort of patients with transoesophageal echocardiography

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Introduction: The potential presence of atrial thrombus in patients with auricular arrhythmias(AA)of more than 48 hours duration and the risk of embolization after cardioversion in this patients have determined a precardioversion anticoagulation strategy. In the last decade a new strategy, Transesophageal Echocardiography (TEE)-guided cardioversion has emerged as an alternative approach, allowing an immediate cardioversion in those patients without thrombus.
Purpose: To analyse our Centre's experience in the last four years with this TEE-guided cardioversion strategy. We sought to determine the incidence of atrial thrombus in our patients and its relation with clinical and echo variables.
Methods: We analysed 114 consecutive TEEs in patients with AA of more than 48 hours duration, candidates to electrical cardioversion. The mean age of our patients was 64 years, 62% of them were men and 54% had some kind of cardiopathy. Atrial fibrillation (AF) was the most common arrhythmia (72%), the rest of patients had atrial flutter (AFL), common in 56% of them. We recorded clinical and echo variables (atrial size, spontaneous echo contrast (SEC), and atrial appendage emptying velocity).
Results: We found atrial thrombi in 27 patients (24%). The incidence of thrombus was 25,6% in patients with AF, 21% in patients with uncommon AFL and 16,7% in patients with common AFL. Among clinical variables we found the presence of cardiopathy as a strong predictor of atrial thrombus, among echo variables, left atrial enlargement (>4,2cm), the presence of SEC and an emptying velocity of left atrial appendage below 0,20cm/seg.

Predictors of left atrial thrombus

	Incidence of thrombi	p
Cardiopathy (y/n)	30% vs. 15%	0,05
LA>4,2 (y/n)	32% vs. 10%	0,008
SEC (y/n)	39% vs. 0%	0,001
Low emptying vel. (y/n)	50% vs. 5%	0,001

Incidence of left atrial thrombus in patients with or without clinical an echo predictors.

Conclusions: 1)The incidence of atrial thrombus in patients with AA of more than 48 hours duration was 24% in our series. 2)The presence of cardiopathy, left atrial enlargement, SEC, and a low emptying velocity of left atrial appendage were strong predictors of atrial thrombus.

TREATMENT STRATEGIES FOR ATRIAL FIBRILLATION

1998 Rate control versus electrical cardioversion for persistent atrial fibrillation in patients with heart failure: results of the RACE study

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Background: Rate control (RC) is not inferior to rhythm control (RhC) in preventing mortality and morbidity in patients with atrial fibrillation (AF). In heart failure patients, restoration of sinus rhythm (SR) seems beneficial due to improvement of ventricular function. However, despite intensive RhC, recurrence of AF is frequent, offsetting the beneficial effects of SR.
Hypothesis: RC is not inferior to RhC in preventing mortality and morbidity in patients with heart failure.
Methods: In RACE (rate control versus electrical cardioversion in persistent atrial fibrillation) 522 patients with persistent AF with at least one previous cardioversion were included. RC patients received permanent oral anticoagulation and negative chronotropic drugs (heart rate < 100 bpm). RhC patients received cardioversion and antiarrhythmic drugs, and oral anticoagulation as needed. A total of 261 patients (130 in RC and 131 in RhC) had heart failure NYHA class II or III at baseline, with reduced left ventricular fractional shortening. The primary endpoint was a composite of cardiovascular mortality, heart failure, thromboembolic complications (TEC), bleeding, pacemaker implantation and life threatening drug side effects. Mean age was 69±8 years, median AF duration 375 days. Hypertension was present in 49%, coronary artery disease in 36%. Characteristics were well comparable between both groups.
Results: After 2.3±0.6 years SR was present in 14% vs 36% in the RC and RhC group, respectively. The number of primary endpoints was the same in RC and RhC groups: 29/130 (22.3%) vs 32/131 (24.4%). The 95% one-sided upper boundary of the absolute difference in the primary endpoint was 6.5%, which met the non-inferiority criterion (10%). The distribution of the components of the primary endpoint was different between both groups. More cardiovascular death (11.5% vs 6.1%), progression of heart failure (5.4% vs 3.8%) and bleeding (8.5% vs 3.1%) occurred in the RC group. TEC (6.1% vs 8.4%), side effects of AAD (0.8% vs 5.3%) and pacemaker implantation (0% vs 4.6%) were more frequent under RhC. The causes of death were bleeding (6 vs 2), heart failure (3 vs 0), TEC (0 vs 2), and sudden death (6 vs 4).
Conclusion: In patients with heart failure, rate control is not inferior to rhythm control. However, rate control is associated with higher mortality and more severe morbidity due to bleeding and progression of heart failure.

1999 One-year cost-effectiveness of rhythm and rate control strategy in persistent atrial fibrillation

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The clinical trials on rhythm or rate control in persistent AF revealed no significant differences between compared strategies. Our study was aimed at analyzing the cost of alternative strategies to determine effective allocation of limited resources. Therefore, we conducted a prospective, detailed costs analysis using data gathered alongside HOT CAFE Polish Study. The retrospective cost for 205 pts randomly assigned to rhythm or rate control arm of a study was calculated over the time horizon of 12 months. A cost minimization analysis was implemented because both strategies are associated with similar clinical benefits. The cost of diagnostic and treatment procedures, hospitalization, outpatient visits, drugs and physicians consultations were estimated for both groups. Expected costs, and incremental cost were identified. The sensitivity analysis on unit cost driver items was performed.
Results: Our study population comprised 205 pts (F/M 71/134; mean age 60.8±11.2 year). 101 pts were randomly assigned to the rate control group. The treatment goal in this group was optimizing the heart rate frequency by 24-hours Holter monitoring using pharmacological therapy. 104 pts were randomized to SR restoration by CV and its subsequent maintenance with serial antiarrhythmic drug usage (disopiramide, propafenone, sotalol and amiodarone). At the end of follow-up SR was presented in 75% pts. There was no significant difference in composite end-point such as: all-cause mortality and number of thromboembolic and major bleeding between study groups (2.0% vs. 3.8%). The incidence of hospital admission was higher in rhythm control in comparison to rate control arm (12% vs. 74%; $p<0.001$). No thromboembolic complications were observed in pts left with AF. 3 pts suffered ischemic stroke in rhythm control arm: 2 cases were associated with CV, the third one with late AF recurrence. The conservative strategy with pharmacological ventricular rate control was less costly than rhythm control (1350 vs 2850 USD, $p<0.001$). The cost driver contributing to observed difference was the cost of CV. Additional cost drivers were the cost of echocardiography, 24 hours ECG recording, cardiologists consultations, hospitalization costs including intensive care and cardiology unit services. The sensitivity analysis performed on the cost drivers confirmed the domination of the conservative strategy.
Conclusions: rhythm control is more costly than ventricular rate control in pts with persistent AF.

2000 Sudden cardiac death in patients with persistent atrial fibrillation. Results of the RACE study

V.E. Hagens[1], I.C. Van Gelder[1], H.A. Bosker[2], O. Kamp[3], J.G. Tijssen[4], J.H. Kingma[5], D.J. Van Veldhuisen[1], H.J. Crijns[6]. *[1]University Hospital, Thoraxcenter, Cardiology, Groningen, Netherlands; [2]Rijnstate Hospital, Cardiology, Arnhem, Netherlands; [3]Academic Hospital VU, Cardiology, Amsterdam, Netherlands; [4]Academic Medical Center, Clinical Epidemiology, Amsterdam, Netherlands; [5]St. Antonius Hospital, Cardiology, Nieuwegein, Netherlands; [6]University Hospital, Cardiology, Maastricht, Netherlands*

Background: In most patients with persistent atrial fibrillation (AF), underlying heart disease is present exposing this population to sudden and non-sudden cardiovascular mortality. The mechanism of sudden cardiac death (SCD) in patients with AF is largely unknown.
Objective: To determine the mechanism of SCD in patients with persistent AF included in the RACE study (rate control versus electrical cardioversion in persistent atrial fibrillation).
Methods: In RACE, patients were randomized to rate control (n=256, negative chronotropic drugs aimed at a heart rate $<$ 100 bpm and oral anticoagulation (OAC) as needed) or rhythm control (n=266, serial electrical cardioversions, antiarrhythmic drugs and OAC).
Results: During a follow-up of 2.3$\pm$0.6 years SCD occurred in 16 patients. All were on OAC, 14 (88%) patients were in AF at the time of event. One was on flecainide, one on sotalol and 2 patients used amiodarone. Non-SCD was due to heart failure (5 patients), thromboembolic complication (TEC) (6) and bleeding (9). Death due to bleeding and heart failure was more frequent under rate control and TEC under rhythm control. The table shows patient characteristics according to outcome. In the 3 groups, the number of stroke risk factors (median 2, range 0-5), presence of hypertension (49%, 44%, and 55%) and heart failure NYHA I/II/III (%) (51/46/3, 38/62/0, 35/50/15), all respectively, were comparable.

Patient characteristics

	Alive (n=486)	Sudden cardiac death (n=16)	Non-sudden cardiac death (n=20)
Rate vs rhythm control (n)	238 vs 248	8 vs 8	10 vs 10
Diabetes	44 (9%)	5 (31%)*#	3 (15%)
Coronary artery disease	129 (27%)	9 (56%)*	5 (26%)
Previous myocardial infarction	69 (14%)	7 (44%)*#	2 (11%)
Lone AF	105 (22%)	0 (0%)	3 (15%)
Left ventricular end diastolic and systolic diameter, mm (mean, SD)	52 (7)/37 (8)	56 (7)/42 (9)	54 (6)/37 (9)

P$<$ 0.05 compared to alive (*univariate, #multivariate)

Conclusion: Sudden cardiac death in patients treated for persistent atrial fibrillation is associated with diabetes and previous myocardial infarction and does not depend on treatment strategy.

2001 Atrial fibrillation suppression reduces atrial fibrillation burden on patients with paroxysmal atrial fibrillation and class 1 & 2 pacemaker indication – the OASES study

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Alternative site atrial pacing was introduced to prevent atrial fibrillation (AF) as a mono-therapy and in combination with several modalities of atrial overdrive pacing. An alternative site of pacing is the intra atrial septum at the posterior site of the triangle of Koch (ASP). The aim of this site is to synchronize atrial depolarization and therefore prevent repolarization time dispersion. The comparison between ASP and Right Atrial Appendage (RAA) pacing was studied in 285 patients with a class 1 and 2 pacemaker indication. Protocol violations were noted in 30 patient case report forms and therefore rejected for data inclusion. The group for final data analysis: 170 patients with a history of paroxysmal AF for the study group (85 patients with ASP and 85 with RAA) and 85 without paroxysmal AF for the control group. All atrial leads were successfully implanted with a Locator and a Tendril 1388T/1488T extendable and rectable screw-in lead. After Integrity DAO (AF suppression) implant, Far Field R-wave sensing was excluded by blanking on an individual basis, in all patients. Enrolment and randomization (AF suppression ON or OFF in a crossover design) started 6 weeks post implant. AF Burden is defined as minutes AF/day, using the total time in AF divided by the number of days between two consecutive follow-up intervals. Data were derived from the Automatic Mode Switch histograms of the pacemaker.

Data (mean $\pm$ SD) after 3-month intervals

Lead Location	AF History	Number	DAO OFF	DAO ON	P
RAA	Yes	85	76.0 $\pm$ 36.0	38.9 $\pm$ 39.5	0.033
ASP	Yes	85	74.1 $\pm$ 29.9	22.0 $\pm$ 18.6	0.027
RAA-ASP	No (control)	85	0.5 $\pm$ 0.5	0.6 $\pm$ 0.4	ns

Conclusions: A combination of an AF suppression algorithm with ASP reduces AF burden in patients with a history of atrial fibrillation and a class 1 or 2 pacemaker indication in a most optimal way.

2002 Haemodynamic instability and atrial fibrillation: is always direct current cardioversion the only alternative? Analysis of clinical presentation and management in the acute setting (the GEFAUR-3 study)

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Objectives: To analyse the real magnitude, clinical presentation, management strategies (MS) and its influence on outcome of patients (pts) with atrial fibrillation (AF) and hemodynamic instability (HI) in the acute setting.
Methods: prospective multicenter study carried out in 12 emergency departments during July-2000, February-2001 and May-2002. HI: symptomatic drop of BP ($<$90/50 or $<$30mm previous BP) and/or organ dysfunction or others with immediate vital risk).
Results: 2550 pts included, 59% female, age 75$\pm$12y. (58%$>$75y). HI was diagnosed in 4.5%, with a higher prevalence of cardiopathy (63vs51%, p=0.005, OR=1.2), CAD (37vs28%, p=0.05, OR=1.3), HF (34vs24%, p=0.02, OR=1.4), secondary (non-cardiac origin) AF (8vs3%, p=0.01, OR=2.5) and rapid HR (64vs50%, p=0.02, OR=1.4). They attended more frequently due to dyspnea (50vs33%, p=0.001, OR=1.6) and syncope (10vs3%, p=0.02, OR=3.3). In the multivariate analysis HI was associated with syncope (OR=3.8), HF (OR=1.8), HR$<$60 (OR=0.2) or$>$100bpm (OR=2.2). IH was attributable to non-cardiac diseases in 33% (56% sepsis, 8% thyrotoxicosis, 7% pulmonary tromboembolism). Rate control (RC) was more frequently performed (50vs31%, p$<$0.001, OR=1.6) with higher use of calcium-blockers (21vs11%, p=0.005, OR=2) as were anticoagulation (72vs58%, p=0.04, OR=1.4) and cardioversion (CV) (20vs8%, p=0.05, OR=2), higher use of DC-CV (18vs7%, NS) and amiodarone (90vs45%, p$<$0.001, OR=2.1). No MS were applied if HR$<$60bpm. In the multivariate analysis RC was associated with age$<$75(OR=2.9), HR$>$100bpm (OR=5), disability (OR=10), hypertension (OR=3.3) and absence of syncope (OR=9) or stroke (OR=7) as was CV with HF (OR=5.1), age$<$75 (OR=1.2) and hypertension (OR=5). Symptom control was more frequently achieved if IH was related with AF (55vs35%, p=0.007, OR=1.8), calcium-blockers were used for RC (60vs28%, p=0.05, OR=2.2) or CV was effective (66vs14%, p=0.05, OR=4.7). IH was associated with more admissions (77vs49%, OR=1.6). Overall mortality was 6.25% (25% due to non-cardiac disease), no differences between MS.
Conclusions: IH is an uncommon feature of AF in the acute setting, usually manifested as dyspnea or syncope. RC (calcium-blockers) and pharmacological-CV (amiodarone) are more used MS but the "gold standard" (DC-CV) is underused. Despite of this, symptom control is frequently achieved and overall mortality is surprisingly low. Although DC-CV is the best MS in most of pts, our data suggest that RC could be an acceptable alternative when there are very few possibilities to restaurate sinus rhythm and in IH attributable to non-cardiac diseases.

2003 Combined antiarrhythmic therapy for refractory atrial fibrillation: plays still a role in the ablation era?

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Aim: We assessed whether or not the combined antiarrhythmic (AA) therapy (CAT) for atrial fibrillation (AF) refractory to at least two AA drugs (TAD) used alone, still plays a role alternative to ablation.
Methods: 62 pts (33 m, mean age 66 ±18) with recurrent symptomatic AF (>10 episodes/year) without heart disease (HD) (27%), ischemic HD (16%), valvular HD (21%), hypertensive HD (31%), refractory to at least TAD tested alone, underwent CAT to assess its risk/benefit, taking into consideration the efficacy in the prophylaxis of recurrences (RE) and the occurrence of side effects (SE). Pts were given the following oral AA associations: flecainide + amiodarone (F+A), F+ sotalol (F+S), propafenone + A (P+A), P + S, decreasing the dose of one of the two TAD and, in any case, administering the maximum dose tolerated. Pts were randomized in 4 groups: F+A, F+ S, P+A, P+S. In case of RE pts switched to the 2nd step to another CAT and, if it failed, to the 3rd step. In case of SE pts withdrew from the study. F-UP was 6-month.
Results: are reported in the table. R = responder, NR = non responder.

Table 1

1st step	F+A	F+S	P+A	P+S	All pts	r	nr
N# pts	15	16	14	17	62		
SE	-1	-2	-3	-2	-8 (13%)		
	8r 6nr	6r 8nr	6r 5nr	7r 8nr		27/52 (50%)	27/52(50%)
2nd step	P+S	P+A	F+S	F+A			
N# pts	6	8	5	8	27		
SE	-2	-1	-1	-2	-6(22%)		
	1r 3nr	4r 3nr	1r 3nr	4r 2nr		10/21 (48%)	11/21(52%)
3rd step	P+A	F+A	P+S	F+S			
N#pts	3	3	3	2	11		
SE	-1	-1	-2	-1	-5(45%)		
	2nr	1r 1nr	1nr	1nr		1/6 (17%)	5/6(83%)

Conclusions: SE occurred in 13% of pts at the first steps of CAT, and successively in 22% and 45%, so that CAT was not well tolerated. Half of pts responded to the 1st step of CAT, with lower success rate of CAT during the further steps, even with a quite short F-UP. Our results would seem disappointing as to the use of CAT in AF refractory to single AA drug.

RESISTANCE TO ASPIRIN AND CLOPIDOGREL: A CALL FOR CAUTION

2004 Efficiency of antiplatelet therapy in vascular patients

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Background: Antiplatelet therapy is a basic element of treatment and prevention of the ischemic vascular diseases. Besides the old acetyl salicylic acid, novel agents are also available. The lack of effectiveness of the therapy is well-known for acetyl salicylic acid in a remarkable part of the patients and could be suspected in connection with the other drugs. Recently, platelet aggregometers became more and more widespread and their results have set antiplatelet therapy into a new perspective.
Methods: Data of 1264 cases coming from our region last year were evaluated in this study. Platelet aggregometry was performed at patients with ischemic cardio-, cerebro- and peripheral vascular diseases treated regularly with an antiplatelet drug. 776 patients were treated with 100 mg acetyl salicylic acid, 144 patients were on 300-325 mg acetyl salicylic acid; 118 patients were on ticlopidine and 226 patients were on clopidogrel treatment. The effectiveness of the treatment was measured in Carat TX4 optical platelet aggregometer using epinephrine (10 μM), ADP (5 és 10 μM) and collagen (10 μg/ml) as inductors.
Results: In the group of patients taking 100 mg acetyl salicylic acid the lack of effective therapy was as high as 49%. This ratio was 33% in the group with higher dosage of acetyl salicylic acid. Ineffective antiplatelet treatment could be found in 21% of the ticlopidine group, and clopidogrel was also not sufficient in 31%.
Conclusions: Our results indicate the necessity of the individually adjusted, controlled antiplatelet treatment; otherwise a large number of patients could be treated insufficiently as a consequence of real resistance to a drug or low compliance of the patient. From the point of view of evidence-based medicine there is a need of performing a multicenter study on antiplatelet therapy controlled by aggregometry with morbidity and mortality end-points.

2005 Aspirin resistance is related to high-density lipoprotein cholesterol levels and total cholesterol/high-density lipoprotein ratio

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Aspirin protects from cardiovascular events. However, a number of patients who take aspirin suffer events, probably due to aspirin resistance. This has been measured with different methods and related to different causes. Recently, hypercholesterolemia has been found to be associated with aspirin resistance.
Aim: In order to know the prevalence and possible causes of aspirin resistance, platelet function was studied in a number of patients and related to different variables.
Methods: Platelet function was studied in 74 patients aged 36 to 84, mean 63±10 (59 men) with the the platelet function analyser (PFA-100). They were taking aspirin (100 to 300 mg/day) due to ischemic heart disease (n= 53), hypertension (n= 13), or other reasons (n = 8). The normal epinephrine cartridge closure time was <161 sec and the normal ADP closure time was < 126 sec. The maximum value measured for both, epinephrine and ADP was 300 sec. SPSS package was used for statistical analysis.
Results: In the entire group of patients the epinephrine closure time ranged between 97 and 300 sec, mean 220±79. No significant correlation was found between epinephrine closure time and the following variables: age, aspirin dose/m^2, total cholesterol (TC), LDL-cholesterol, HDL-cholesterol, triglycerides or C reactive protein. A significant correlation was found with the ratio TC/HDL (Rs = -0.27, p = 0.029). Aspirin resistance, defined as epinephrine closure time <161 sec, was found in 25 patients (33.8%). A significant difference (Mann-Whitney U test, p = 0.043) in HDL levels was found according to the presence (median HDL = 40.5 mg/dL, Q1-Q3 = 37.5-48), or absence (median HDL = 47 mg/dL, Q1-Q3 = 39-54.5) of aspirin resistance. The ratio TC/HDL also showed a significant difference (p = 0.034) between patients with (median TC/HDL = 4.18, Q1-Q3 = 3.75-4.94) and those without (median TC/HDL = 3.85, Q1-Q3 =3.18-4.26) aspirin resistance. Only 8 patients had a prolonged ADP closure time (>125 sec). These also had a prolonged epinephrine closure time.
Conclusion: aspirin resistance was found in 33.8% of patients taking aspirin. These patients had significantly lower HDL-cholesterol levels and higher total cholesterol/HDL ratio. Further studies are needed to ascertain whether changes in lipid levels improve the response to aspirin.

2006 The history of coronary artery bypass graft procedure is connected with the aspirin resistance phenomenon in patients with ischaemic heart disease

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Background: The aspirin resistance phenomenon is well known from many years now, but still there is a lack of information who and why can develop it. Last Antithrombotic Trialists' Collaboration report showed that small doses of aspirin (75 to 150 mg) are the most appropriate for the secondary prevention of thrombotic complications in cardiovascular disorders.
Aim: The aim of this study was to assess the frequency of aspirin resistance in patients with ischaemic heart disease on 75 mg dose of the drug and to find out clinical predictors of such a status.
Material: The study included 200 patients (100 men and 100 women) age 65 ± 10 years hospitalized from January to December 2002 in Cardiology Department of Wroclaw Medical Academy due to the diagnosis and treatment of ischaemic heart disease.
Methods: All patients were on 75 mg aspirin daily for at least 7 days according to patient's interview and used no other antiplatelet agents. Platelet response to aspirin was estimated with the use of optical aggregation method after addition of arachidonic acid (AA) 0,5 mg/ml, ADP 10 μM and collagen (COL) 2 μg/ml. Aspirin resistance was defined as a mean aggregation of more than 80% with ADP and more than 80% with COL. Aggregation with AA was used to ensure aspirin use. Controls to establish laboratory norm included 30 healthy persons without any medication.
Results: In the studied group there were 25% of patient after CABG, 15% after PTCA, 55% with history of myocardial infarction, 70% with arterial hypertension and 60% with diabetes mellitus. There were 40 patients (20%) with aspirin resistance according to the criteria used. No patient has platelet aggregation more than 5% after AA addition. Patients who were aspirin resistant were more likely to have history of previous revascularisation (36.1% vs. 10,2%, p<0,001). With the use of multiple regression model including age, sex, concomitant medications, revascularisation procedures, history of other cardiovascular disorders, history of CABG were still strongly correlated with the presence of aspirin resistance in the studied group (beta=0,71, p<0,05).
Conclusions: 1. Aspirin resistance defined on the basis of optical aggregation method is present in 20% of patients with ischaemic heart disease. 2. Aspirin resistance is more frequent in patients with the history of previous CABG. 3. Presence of this phenomenon in this group of patients indicates the use of higher doses of aspirin or adding platelet ADP receptor blockers.

2007 Aspirin and ticlopidine resistance in cardiovascular patients. Multicentre database of 2425 patients aimed to standardize the laboratory control of antiplatelet therapy

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Tailored, sustained and combined antiplatelet therapy is a common task in present cardiovascular medicine. Laboratory and/or clinical definition of effective platelet inhibition for the clinician, and methods for routine screening evaluation for the laboratory were studied.Platelet aggregatory results of 150 untreated and 2275 patients treated with antiplatelet agents were evaluated in nine cardiovascular hospitals. Platelet aggregation measurements were performed under same conditions in all centers. Platelet aggregation was measured on a computerized Carat TX4 platelet aggregometer. For the interest of mass-screening, fix doses of different inductors were used (ADP 5 μM, collagen 2 μg/ml, epinephrine 10 μM, arachidonic acid 0,5 mM). The threshold of the measurable inhibition was postulated as mean of maximal aggregation% minus 2xS.D. of the 150 untreated controls. Threshold values of measurable inhibiton (Mean of controls minus 2xS.D of controls): ADP 62%, collagen 64%, epinephrine 59%. Treated patients were considered resistant to aspirin or ticlopidine, if results of their maximal aggregation was higher than the postulated threshold value. Arachidonic acid was used as a control of drug compliance of aspirin. Epinephrine and collagen were used to evaluate aspirin monotherapy (maximal aggregation beyond threshold to any of these two inductors considered aspirin resistant). ADP was used to evaluate ticlopidine monotherapy. Epinephrine, collagen and ADP simultaneously were used to evaluate the combination therapy of aspirin and ticlopidine.Aspirin or ticlopidine monotherapy, and aspirin and ticlopidine combination therapy were evaluated and resistant cases were identified. Out of 2215 cardiovascular patients taking aspirin (100-325mg) alone for secondary prevention 26.9% (596) showed resistance. 4 of 60 patients taking ticlopidine (500 mg) alone were found to be resistant. Patients, who were changed to a combination therapy of aspirin and ticlopidine (n:62) all became responder under the criteria listed above. Tailored antiplatelet therapy is possible with a relatively easy routine screening method. Patients who are resistant to any oral antiplatelet drug should take a combination therapy which proved superior in recent acute coronary syndrome trials.

2008 Aspirin resistance in patients with acute myocardial infarction: is it of any clinical importance?

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Purpose: Aspirin resistance can be divided in biochemical and clinical aspirin resistance. Biochemical resistance is defined as a diminished or absent response to aspirin, when measuring the effect by different platelet aggregation methods. Clinical resistance is defined as a "breakthrough" event despite aspirin therapy. Whether an association between the two phenomena exits has not yet been clarified. With this study we wanted to describe and compare the prevalence of biochemical aspirin resistance in patients with and without acute myocardial infarction.
Methods: Patients with a suspected acute coronary syndrome were eligible. Treatment with aspirin 150 mg daily for a minimum of seven days prior to admission was required for inclusion. The patients were included consecutively. Blood samples for assessment of platelet function were taken immediately on hospital admission before any additional antiplatelet therapy was initiated. Platelet function was measured by a Platelet Function Analyzer - 100. Biochemical aspirin resistance was defined as a Closure Time $<$165 seconds. Acute myocardial infarction was defined as an elevation of Troponin T $>$0.10 μg/l and/or CK-MB $>$10.0 μg/l.
Results: Two-hundred-and-eighty-three patients (age 68.5 $\pm$12.2 years (SD)), fulfilled the inclusion criteria. Sixty-one patients had a definite myocardial infarction and of these, 38% demonstrated biochemical aspirin resistance (table). Only 18% of the remaining 222 patients were biochemically aspirin resistant (p=0.0015).
Conclusion: This is the first study to show an association between biochemical aspirin resistance and acute myocardial infarction. Whether any causality exits between biochemical aspirin resistance and acute myocardial infarction needs to be clarified.

Prevalence of aspirin resistance (* p=0.0015.)

	With acute myocardial infarction	Without acute myocardial infarction
Aspirin resistance	38% (23 pts)*	18% (41 pts)*
No aspirin resistance	62% (38 pts)	82% (181 pts)

NEUROHORMONES IN HEART FAILURE

2010 Haemodynamic, morphological and molecular effects of chronic administration of ghrelin in monocrotaline-induced pulmonary hypertension

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Ghrelin (GR) has cardiovascular effects by acting directly or indirectly through growth hormone (GH) release. The potent vasodilator effect of GR can antagonize endothelin-1 (ET-1) induced vasoconstriction, a peptide whose release is elevated in pulmonary hypertension. The present study investigated the effects of chronic administration of GR in the monocrotaline (MCT) model of pulmonary hypertension. Adult Wistar rats received a single injection of MCT (60 mg/kg, sc) or just the vehicle (day 0). One week later, MCT treated animals were randomly divided and injected with GR (100 μg/kg, BID, sc) or with a similar volume of vehicle. The study resulted in 3 groups: (i) control (Ctrl, n=7), MCT (n=9), MCT+GR (n=9). At days 21-25 the animals were anaesthetized, ventilated and instrumented with a tip micromanometer to record right ventricular (RV) pressures. End-diastolic (EDP) and peak systolic (RVPmax) pressures, dP/dtmax, and time constant Tau were measured. RV-to-LV ratio and myocyte fiber diameter estimated RV hypertrophy and % medial wall thickness of peripheral pulmonary arteries evaluated pulmonary vascular remodelling (Olympus, 400x). Additionally, RV transmural free-wall samples were collected to quantify SERCA2a and calsequestrin (housekeeping gene) mRNA by competitive RT-PCR. Results, presented as mean$\pm$SEM, are summarized in the table ($P<0.05$: a vs. Ctrl; b vs. MCT).

	Ctrl	MCT	MCT+GR
EDP (mmHg)	1.3 $\pm$ 0.3	3.0 $\pm$ 0.2 a	1.7 $\pm$ 0.2
RVPmax (mmHg)	25.4 $\pm$ 1.7	49.1 $\pm$ 1.6 a	36.4 $\pm$ 1.8 a,b
dP/dtmax (mmHg/s)	1228 $\pm$ 67	1602 $\pm$ 91 a	1692 $\pm$ 113 a
Tau (ms)	6.6 $\pm$ 0.9	27.8 $\pm$ 2.5 a	17.1 $\pm$ 1.9 a,b
RV-to-LV ratio (g/g)	0.208 $\pm$ 0.010	0.584 $\pm$ 0.032 a	0.398 $\pm$ 0.033 a,b
Myocyte Diameter (mm)	59 $\pm$ 2	172 $\pm$ 20 a	114 $\pm$ 6 a,b
% Wall thickness	32 $\pm$ 2	62 $\pm$ 4 a	46 $\pm$ 4 a,b
SERCA2a/CSQ	0.77 $\pm$ 0.08	0.345 $\pm$ 0.04 a	0.512 $\pm$ 0.06 a,b

Chronic GR administration attenuates pulmonary hypertension, partially prevents the development of the morphological and molecular phenotype of RV hypertrophy and ameliorates RV haemodynamics. Based in these results it is tempting to suggest that the GR-GH axis is a potential new therapeutic target in pulmonary hypertension.

2011 Are aldosterone tissue levels more important than circulating levels in congestive heart failure?

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Purpose: In RALES study, spironolactone, an aldosterone receptor antagonist, decreased mortality in patients with severe congestive heart failure.
Methods: To evaluate if this beneficial effect was also present in patients with low baseline aldosterone plasma levels, aldosterone plasma concentrations (normal value:$<$0.4 nmol.mL-1) were measured in 125 patients (mean ejection fraction: 25%), randomly assigned to placebo (n=64) and spironolactone (n=61). All patients were in NYHA III-IV functional class and treated with ACE-Inhibitors.
Results: After 2-year follow-up, 25% of spironolactone patients had died versus 42% of placebo patients ($p<0.05$). Further, when patients were divided according to baseline aldosterone levels, superior or equal to median (0.38 nmol.mL-1), the benefit of spironolactone was present in all patients regardless of baseline values. Considering the baseline aldosterone levels greater/equal or inferior to median, the death rates were 27.6 and 21.9% respectively in the spironolactone group compared to 48.6 and 34.5% in the placebo group. Indeed, although overall mortality tended to be higher in placebo patients with high baseline values than those with low baseline values, mortality was also higher in the two placebo groups when compared to patients treated with spironolactone (RR for placebo vs spironolactone: 1.76 [0.85-3.93] and 1.58 [0.63-4.13], [95%CI] for high and low baseline values respectively). Given the 95%CI overlap, these RR indicate comparable risk reduction in both spironolactone groups.
Conclusion: The beneficial effects of spironolactone in congestive heart failure are independent of baseline aldosterone levels and not limited to patients with high circulating aldosterone levels. This suggests that tissue concentration might play a key role in the pathophysiology of congestive heart failure.

2012 Myocardial effects of selective ETB receptor stimulation are modulated by ETA receptor activity

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Background: Endothelin-1 (ET-1) acts through the binding to ETA and ETB receptors. We have recently reported that selective ETB receptor stimulation promotes a negative inotropic effect, which is reversed after selective removal of the endocardial endothelium (EE). The present study investigated the influence of ETA receptor inhibition on those effects.
Methods: The study was performed in right papillary muscles (n=27) from New Zealand White rabbits (Krebs-Ringer: 1.8 mM CaCl2, 35°C). The effects of selective ETB receptor stimulation by Sarafotoxin S6c (SRTXc; 0.2 μM) were evaluated in the following groups: (i) intact EE (n=6); (ii) absence of EE (Triton X-100; 0.5%; n=6); (iii) intact EE in the presence of BQ-123 (selective ETA receptor antagonist, 0.1 μM; n=7); (iv) absence of EE in the presence of BQ-123 (0.1 μM; n=8). Only significant results (mean$\pm$SEM, $p<0.05$) are given, expressed as % change from baseline.
Results: SRTXc induced a negative inotropic effect in papillary muscles with intact EE, reducing 11.0$\pm$5.6% active tension (AT) and 11.2$\pm$5.9% peak rate of tension development (dT/dtmax). This effect was exacerbated by ETA receptor inhibition (AT decreased 27.0$\pm$7.4% and dT/dtmax 13.3$\pm$4.9%). On the contrary, in the absence of EE, SRTXc increased contractility (AT increased 35.2$\pm$11.7% and dT/dtmax 29.5$\pm$7.9%), an effect that was reversed by ETA receptor inhibition (AT decreased 9.0$\pm$1.8% and dT/dtmax 4.1$\pm$3.5%).
Conclusions: This study showed that the negative inotropic effect induced by selective ETB receptor activation is enhanced by ETA antagonism in the presence of an intact EE. On the other hand, the positive inotropic effect elicited by ETB receptor stimulation in the absence of EE requires the presence of active ETA receptors. These results reveal that the effects mediated by endothelial and myocardial ETB receptors are modulated by ETA receptors activity, suggesting significant ETA/ETB interaction, which might have pathophysiologic and therapeutic implications.

2013 Activation of the cardiac renin-angiotensin-system is essential for tumour necrosis factor-induced cardiac hypertrophy

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Objective: Activation of the renin-angiotensin-system (RAS) and release of tumor necrosis factor (TNF) play a pivotal role for the progression of cardiac hypertrophy and chronic heart failure. The aim of this study was to determine whether effects of TNF in the heart are mediated by activation of the cardiac RAS.
Methods and Results: Experiments were performed in a newly created murine model for cardiac restricted overexpression of TNF (MHCsTNF). At 8 weeks of age, MCHsTNF mice revealed a significant increase in heart weight ($p<0.05$) as well as in LV mass and posterior wall thickness as determined by cardiac MRI ($p<0.05$). In addition, there was an increase in myocardial collagen content ($p<0.05$) and an increased incidence of apoptotic cardiac myocytes ($p<0.05$)as determined by picrosirius red staining and ligase assay, respectively. Also, TNF overexpression led to an increase in ACE mRNA content and ACE acitivity and an increase in myocardial angiotensin II levels (all parameter $p<0.05$ vs. controls) as determined by RNAse protection assay, kinase assay and radioligand binding experiments, respectively. RAS activation was accompanied by a reduction of myocardial AT1-receptor mRNA and protein levels($p<0.05$, RNAse protection assay and radioligand binding experiments), indicating homologous or heterologous receptor downregulation. The functional relevance of RAS activiation was determined by treatment of MHCsTNF mice with the AT1-receptor antagonist losartan (30 mg/kg) from week 4 to 8 of age. AT1-receptor blockade normalized cardiac mass and LV collagen content and reduced the incidence of cardiac myocyte apoptosis by 50% (all parameters $p<0.05$).
Conclusion: Cardiac restricted overexpression of TNF leads to cardiac hypertrophy, fibrosis and cardiac myocyte apoptosis. The effects of TNF are mediated by an activation of the cardiac RAS. In consequence, effective blockade of the cardiac RAS might be sufficient to inhibit TNF induced LV remodeling in cardiac hypertrophy and heart failure.

2014 Increased water intake and plasma arginine vasopressin in rats with congestive heart failure are mediated by angiotensin II receptors

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Aims: To examine the involvement of the angiotensin system on water deprivation (WD) induced thirst and AVP secretion in a rat myocardial infarction (MI) model of CHF.
Methods: Seven days after coronary artery ligation (CAL) (n=33), or a sham procedure (n=31), Sprague-Dawley male (200-250g) rats (CAL n=12, sham n=12) were subjected to a 24-hr WD test. Rats (CAL n=7, sham n=6) were also subjected to a 24-hr WD but Telmisartan 30mg/kg (p.o) was administered 2 hrs prior to the end of the WD period. Water intake recorded for the first 6 hrs after WD. Angiotensin II (30 pmol & 100 pmol) was administered intracerebroventricularly (ICV) (CAL n=7, sham n=6) and water intake was recorded for an hour.
One week later, rats that had received Telmisartan (CAL n=7, sham n=6) went through the identical 24-hr WD and Telmisartan administration and trunk blood was collected after 24-hr WD. Another group of rats (CAL n=7, sham n=7) were also subjected to a 24-hr WD and trunk blood was collected. Plasma AVP and sodium were measured from the trunk blood.
Results: CHF rats have elevated AVP ($P<0.05$) and drank significantly more water in the 6 hrs after WD than controls (ANOVA, F1,22=9.0, P=0.007). The increase in AVP and water intake in CHF rats were attenuated by Telmisartan (ANOVA, F1,17=18.8, $P<0.001$). AVP and water intake after Telmisartan were similar in CHF and controls (ANOVA, F1,11=3.4, $p>0.09$). CHF rats drank significantly more water than controls after the lower dose of ICV Ang II (30 pmol) (5.1 $\pm$ 0.5ml CHF vs. 3.2 $\pm$ 0.4ml Control, $P<0.05$). At the higher dose of ICV Ang II (100 pmol), water intake was similar in the CHF and controls (8.3 $\pm$ 0.4ml CHF vs. 9.4 $\pm$ 0.8ml Control, $p>0.2$).

	CHF	Control	CHF + Telmisartan (n=7)	Control + Telmisartan (n=6)
Water Intake (ml $\pm$ SEM)	19.5 $\pm$ 1.3 (n=12)	15 $\pm$ 0.8 (n=12)	11.9 $\pm$ 0.1	10.5 $\pm$ 0.1
Plasma AVP (pmol/l)	7.8 $\pm$ 1.4 (n=7)	4.2 $\pm$ 0.2* (n=7)	3.7 $\pm$ 0.2**	3.1 $\pm$ 0.3
Plasma Na (mmol/l)	137.1 $\pm$ 0.9 (n=7)	137.4 $\pm$ 0.4 (n=7)	136.9 $\pm$ 0.6	137.5 $\pm$ 0.8

Cumulative 6-hr water intake, plasma AVP and sodium after 24-hr WD. *$P<0.05$ CHF vs control. **$P<0.05$ CHF+Telmisartan vs CHF.

Conclusion: CHF results in an increase in plasma AVP and thirst after a standard 24-hr WD stimulus and Telmisartan attenuates these effects. CHF rats were more sensitive to the dypsogenic effects of central Ang II. The increase in plasma AVP and thirst in CHF rats are mediated by the renin-angiotensin system.

2015 Aldosterone receptor blockade improves left-ventricular remodelling and increases ventricular fibrillation threshold in experimental heart failure

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Objectives: To investigate the effects of aldosterone receptor blockade in postinfarction heart failure.
Methods: Eighty-seven rats with moderate myocardial infarction were randomized to receive either no drug or canrenone, the active metabolite of spironolactone, 20 mg/kg/die, or ramipril, 1 mg/kg/die, or a combination of the two drugs. Treatment was initiated 1 month after coronary ligation and lasted 4 weeks. Echocardiography was performed at baseline and after 4 weeks. LV catheterization, isolated heart studies, morphometric histology, myocardial norepinephrine and SERCA-2 mRNA were assessed at the end of the treatment period.
Results: Infarct size was 33$\pm$3%, 32$\pm$3%, 34$\pm$3%, and 34$\pm$4% in the placebo, canrenone, ramipril, and combination group, respectively. Canrenone attenuated LV remodeling, improved LV systolic and diastolic function, and markedly reduced interstitial and perivascular fibrosis. These effects were increased by concomitant ramipril therapy. Moreover, myocardial norepinephrine content was decreased while ventricular fibrillation threshold significantly augmented by canrenone. SERCA-2 levels remained unchanged.
Conclusions: Canrenone attenuated LV dilation and interstitial remodeling, and improved LV filling dynamics and systolic function in the rat model of postinfarction heart failure. Addition of ramipril conferred further cardioprotection. Canrenone also reduced myocardial norepinephrine content and increased ventricular fibrillation threshold. The data provide a potential explanation for the decreased sudden death observed in the RALES study.

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR THERAPY: NEW PERSPECTIVES

2028 Comparative evaluation of implantable cardioverter-defribrillator efficacy in Europe and the United States in the MADIT II trial

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MADIT II has demonstrated that the prophylactic implantation of a defibrillator (ICD) improves survival among patients (pts) with remote myocardial infarction (MI) and LV-EF of </= 30%. Pts were enrolled from 76 centers, 71 from the US and five from Europe (EU). EU centers enrolled 109 (9%) of the total 1232 pts. In order to assess potential differences in outcome or clinical characteristics between US and EU pts enrolled in MADIT II ICD efficacy in the EU pts was compared with US pts.

EU-Pts were younger (62 vs 65 years), had a higher prevalence of heart failure NYHA II/III (79% vs 61%), but had a higher LV-EF (25% vs 23%) and a less broad QRS width (114 ms vs 123 ms) in the standard ECG. Time between last MI and enrollment was shorter (3.2 years vs 5 years). EU-Pts were treated with less digitalis (47% vs 60%), and had less diuretics (66% vs 76%); all differences being significant at $p < 0.05$.

Overall mortality of EU-Pts was slightly higher in the conventional group (CON) (23.8% vs 19.4%) and lower in the ICD group (7.5% vs 14.8%) compared to US-Pts, without reaching significance. Hazard ratios (ICD:CON) for mortality in EU and US were 0.32 and 0.71 respectively, and not significantly different ($p = 0.15$). Incidence of arrhythmic death was not significantly different between EU- and US-Pts. Heart failure (CHF) death of EU vs US Pts was lower in the CON arm (0% vs 5%, $p = 0.05$) but equal in the ICD arm (6% both, $p = 0.1$). Hospitalization for CHF during follow up in the ICD arm was less for EU Pts (15% vs 26%, $p = 0.03$) but not different for the CON arm (10% vs 21%, $p = 0.07$). Appropriate ICD therapy was similar in both study populations (24% vs 23%). Mean incidence of appropriate ICD intervention per patient in EU Pts was 3.5 ± 2.8 and 7 ± 16 in US-Pts ($p < 0.5$). EU-Pts received more single chamber ICDs (86%) than US-Pts (53%) ($p < 0.001$). Revascularization procedures during follow-up were not different between EU-Pts and US-Pts (2% vs 5%).

Conclusion: The efficacy of ICD therapy was not different among pts enrolled in MADIT II from EU vs US despite several clinical differences between both patient groups.

2029 Prevalence of patients with MUSTT and MADIT II indications for prophylactic implantable cardioverter-defribrillator treatment after myocardial infarction

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Background: The results of recent primary prevention studies (MUSST, MADIT I & II) have indicated a need to expand ICD therapy to high-risk patients after myocardial infarction (MI). However, the incidence of the patients fulfilling the inclusion criteria of these studies is largely unknown. The Cardiac Arrhythmia and Risk Stratification after Myocardial Infarction (CARISMA) is a multicenter study enrolling patients with an acute MI and an ejection fraction (EF) <40% in whom an insertable loop recorder is implanted to document the arrhythmia episodes and various risk stratification tests are performed at 6 weeks post-MI. The CARISMA screening logs were analyzed to estimate the incidence of patients fulfilling the MUSTT and MADIT II criteria for prophylactic ICD implantation.

Methods and Results: Of 3224 consecutive acute MI patients, 2143 (66%) underwent a screening echocardiography to assess their eligibility for CARISMA: 473 patients (22%) had an EF <40%, and 117 of these were eligible into the CARISMA study after exclusions, mainly due to planned revascularization, life-expectancy < 1 year for non-cardiac causes, and unwillingness to consent. The EF of these patients was re-assessed after 6 weeks, and 35% of the patients had an EF <30% (1.9% prevalence of MADIT II pts). When analyzed from the total population without exclusions, the prevalence of MADIT II pts would have been 7.7%. Nearly half of these (45%) also showed a QRS complex >120 ms. Only 8/117 patients (6.8%) had NSVT on the 24-h Holter test and inducible sustained VT during the EP study performed at 6 weeks, in addition to an EF <40% (0.4% prevalence of MUSTT patients). Without exclusions, the prevalence of MUSTT pts would have been approximately 1.5%.

Conclusion: A relatively small proportion of post-MI patients diagnosed and treated according to the current MI management guidelines fulfill MADIT II and MUSTT criteria. It is likely that the use of troponin as a marker of acute MI, improved treatment of post-MI patients and the relatively high number of excluded patients have reduced the prevalence values compared to historical post-MI data.

2030 New detection algorithms in single chamber implantable cardioverter-defribrillator devices for prevention of inappropriate therapies

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Purpose: Currently available implantable cardioverter defibrillator (ICD) devices protect patients reliably against sudden cardiac death. Nevertheless the discrimination of ventricular (VT) and supraventricular (SVT) tachycardia in order to avoid unnecessary and inappropriate therapies is still an issue.

Methods: Two new detection algorithms for discrimination between VT and SVT available in newly introduced ICD from Guidant (GDT) and Medtronic (MDT). Whereas the Wavelet® criterion of MDT compares the intracardiac electrogram (IEGM) during an episode with an IEGM stored during sinus rhythm with regard to the signal morphology and the area below the IEGM curve the GDT RhythmID® algorithm uses a vector analysis from the rate sensing IEGM and the shock IEGM. Both systems update the reference IEGM periodically and automatically during normal sinus rhythm. The rhythm classification of the algorithms (CA) was compared to the stored episode IEGM manually in order to evaluate the algorithm performance.

Results: The main results are shown in tables 1 and 2. There were 2 SVTs from one patient classified as VT by the Vitality and 1 VT classified as SVT by the Marquis. In both cases an instable IEGM was found in the patients.

Table 1

ICD device	# of pts	Age [a]	LVEF [%]	FU [months]	# of episodes	# of VT: CA vs IEGM	# of SVT: CA vs IEGM	Sensitivity	Specifity
MDT Marquis	15	63.5	32	4.6	31	26 vs 27	5 vs 4	96%	100%
GDT Vitality	11	66.0	33	2.5	32	10 vs 8	22 vs 24	100%	92%

FU: follow-up.

Conclusions: Both new algorithms expand the variety of detection enhancements successfully. Problems were observed if the patient has an instable IEGM for any reason. A reprogramming of the parameters in these cases is possible only for the MDT algorithm which may help to improve the discrimination of tachycardia and appropriate detection of VT. Nevertheless the GDT algorithm showed a superior sensitivity for VT in our investigation without VT undersensing as seen with the MDT algorithm which is clinically very important.

2031 The one + one-trial: should patients with slow ventricular tachycardias receive a dual-chamber implantable-defibrillator for detection enhancement? A prospective multicentre randomized cross-over trial

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Background: The tachycardia detection interval (TDI) in implatable defibrillators (ICD) is conventionally programmed according to the slowest documented ventricular tachycardia (VT) with a safety margin of 30-60ms. This may imply a risk of VTs below the detection rate during follow-up. Longer TDIs are however associated with an increased risk of inappropriate therapies (IT) in a single chamber (SCH) ICDs. A dual chamber (DCH) ICD with an increased specificity may compensate the increased tachycardia burden due to an increased TDI. Study hypothesis. Patients with slow VTs (<200bpm) have a benefit from a long TDI and a DCH detection algorithm compared with a conventionally programmed SCH-ICD.
Methods: Patients with VTs < 200bpm were implanted a DCH-ICD (Defender III/IV, ELA medical) which was randomly programmed to 1. a DCH algorithm (PARAD, ELA medical) and a TDI of 469 ms or more, and 2. to a SCH algorithm with a TDI 30 to 60 ms above the slowest documented VT cycle length plus the SCH enhancement criteria cycle length variation and acceleration. The primary combined endpoint was the number of all inappopriate therapies (ITs) for supraventricular tachycardias, VTs above the TDI, VTs with significant therapy delay (>2min). After 6 months a cross-over was performed. Total follow-up was one year.
Results: 102 patients were included in the study. Programmed detection interval was 500±36 ms during the DCH- and 424±63 ms during the SCH-phase. During SCH detection 78 ITs occurred in 30 pts, 32 VTs with detection delay in 4 pts and 31 VTs above the TDI in 10 pts. During DCH detection 62 ITs occurred in 16 pts, 10 VTs with detection delay in 4 pts and 4 VTs above the TDI in 4 pts. For the comparison of VTs not detected, a medium sized advantage was found for the patients in the DCH mode (MW = 0.6647; CI 0.5347- 0.7946; Pexcact = 0.0175). For the number of ITs, the robust two-sided cross-over test revealed a benefit of the DCH mode with Pexcact = 0.0079. Yet, there was indication for a carry-over- and a period-effect. For the first period, the test for treatment effect already revealed a more than medium sized superiority of the DCH mode (MW = 0.6628; CI 0.5642-0.7614; Pexcact = 0.0023).
Conclusion: The DCH algorithm with a long TDI was associated with a low number of VTs not detected. The DCH algorithm could compensate the increased tachycardia burden and the longer TDI was not associated with an increased risk of ITs. This may favour a long TDI and the implantation of a DCH-ICD in patients with slow monomorphic VTs merely for detection sake.

2032 Long-term experiences with subcutaneous implantable cardioverter-defribrillator leads: a comparison between three different types of subcutaneous leads

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Efficacy of defibrillation remains an important issue to guarantee the future safety of patients who receive an ICD. Up to 5% of patients need an additional subcutaneous (SQ) lead to obtain a defibrillation safety margin of at least 10 J between the maximum output of the ICD and the energy needed for ventricular defibrillation (DFT). However, few data exists about the long-term outcome of different types of SQ leads. Therefore, the aim of our study was to analyse our long-term experiences with three different types of SQ leads.
Methods: One hundred and thirty-two patients were evaluated (109 men, 23 women; mean age 59.8 years (SD 10.7 years)). All patients had received an ICD with an additional SQ lead at our department between 1990 and 2002. A defibrillation threshold testing was performed at implant, at 1 year and at 3 years after implant. All lead-related complications were analysed.
Results: Eighty-two single element subcutaneous array electrodes (SQ-A1), 31 subcutaneous three-finger array electrodes (SQ-A3) and 21 subcutaneous patch electrodes (SQ-P) were implanted during the study period. Only leads manufactured by Medtronic or Guidant were enrolled in the study. The mean follow-up was 1378 days (SD 710 days) in the SQ-A1 group, 1926 days (SD 990 days) in the SQ-A3 group and 1704 days (SD 1122 days) in the SQ-P group. In none of the three groups there was a significant change of the DFT during follow-up compared to baseline. In group SQ-A1, the mean DFT was 9.0 J at implant. The mean DFT was 9.7 J at 1-year follow-up and 9.8 J at 3-year follow-up, respectively (p=0.15). In group SQ-A3, the mean DFT was 11.8 J at 1-year follow-up and 11.8 J at 3-year follow-up compared to 11.7 J at implant (p=0.95). For SQ-P, the mean defibrillation threshold was 17.9 J at 1-year follow-up and 18.0 J at 3-year follow-up compared to a baseline value of 17.1 J (p=0.67). A major complication (e.g. lead fracture) occurred in 6 patients (7.3%) in group SQ-A1 and in 2 patients (9.5%) in group SQ-P. Kaplan-Meier curves analysing freedom from subcutaneous lead-related complications did not show a significant difference between the three study groups (p=0.16).
Conclusions: SQ-A1 leads, SQ-A3 leads and SQ-P leads provide stable DFTs during long-term follow-up. Major complications are rare. However, a careful follow-up including chest radiographs at regular intervals is needed to detect potentially fatal complications such as lead fractures.

2033 Multiple appropriate consecutive defibrillator discharges are frequently caused by monomorphic ventricular tachycardia

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Some patients with an automatic implantable cardioverter-defibrillator (ICD) present appropriate multiple consecutive discharges (MCD) during follow-up, that, according with previous studies, are a marker of a poor prognosis (up to 40% mortality). The arrhythmic mechanisms involved in MCD are unknown.
Methods and Results: 179 patients with an ICD with the capacity of storing intracardiac electrograms (IEGM) were followed-up for a mean of 39±51 months. During the follow-up, 29 patients (16%) presented MCD (>1 discharge needed to terminate an arrhythmia episode, according to the device information). After analyzing the IEGM, MCD were considered appropriate in 16 patients (9%). According to IEGM information: 1) 8 different types of sequences of arrhythmic events [ventricular tachycardia (VT) vs fibrillation (VF), VT of similar vs different morphology] accounted for appropriate MCD; 2) monomorphic VT rather than VF was the initial arrhythmia in 14/16 cases (87%); 3) real failure of stopping ventricular arrhythmia (with or without change in morphology), as opposed to termination and immediate reinitiation, occurred in the majority of cases (12/16, 75%).
Conclusions: Appropriate MCD can be accounted for by a variety of arrhythmic sequences. Contrary to what could be expected in view of the usually lower threshold for termination of VT as opposed to VF, monomorphic VT (rather than fibrillation) was the arrhythmia most frequently involved in the MCD event.

ADVANCED ECHOCARDIOGRAPHY: NEW TOOLS, NEW INSIGHTS?

2034 Can we predict coronary lesion severity by transthoracic Doppler echocardiography in diabetic patients?

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Background: Historically diabetic patients appear to be at increased risk for coronary artery disease and require frequent clinical observation. Transthoracic Doppler echocardiography (TTDE) is a suitable method for serial assessment of coronary flow velocity reserve (CFVR) in left anterior descending artery (LAD). A value of CFVR < 2 predicts a severe(> 70%) angiographic stenosis in patients without microvascular disorder. Efficacy of this method in prediction of severe epicardial coronary stenosis in diabetic patients has not been tested yet, due to potential disorder of microcirculation. This study sought to evaluate the diagnostic potential of CFVR by TTDE in detecting severe coronary stenosis in diabetic patients and in control subjects.
Methods: we performed TTDE in 30 consecutive well controlled (Hb A1c<7) diabetic and in 70 control patients who underwent elective coronary angiography for routine indications. We measured by TTDE basal CFV in the distal LAD and during continuos intravenous infusion of adenosine triphosphate(140 mcg/kg/min). CFVR was defined as the ratio of hyperemic to basal flow. For all patients we assessed coronary lesion severity by quantitative coronary angiography (QCA).
Results: Adequate quality of CFV at baseline and during hyperemia was obtained in all patients. In 46 non diabetic and in 23 diabetic patients, CFVR > 2 was associated with non severe stenosis (QCA stenosis < 70%) p=0.001. The predictive value of CFVR for angiographic stenosis >70% was high for both diabetics and non diabetics (AUC 0,953±0.2, 94% sensitivity and 84% specificity, and AUC 0.952±0.46, 90% sensitivity and 98% specificity, respectively).
Conclusion: A normal CFVR value >2 predicts absence of critical stenosis also in patients with well controlled diabetes mellitus. CFVR can be used as a potent non invasive test in clinical decision making of these high risk patients for cardiovascular disease.

2035 Rapid and accurate measurement of left-ventricular function with a new second-harmonic fast-rotating transducer and semi-automated border detection

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Background: Measurement of left ventricular (LV) volume and function is the most common clinical referral question to the echocardiography laboratory. A fast, practical and accurate method is a prerequisite to obtain this important information.
Objective: To develop and validate a new method for rapid, accurate and cost-effective measurement of LV volume and function.
Methods: We developed a continuous fast-rotating transducer, with second-harmonic capabilities, for three-dimensional echocardiography (3DE), connected to a GE-Vingmed Vivid V echosystem. The individual images were post-processed with MatLab software using multi-beat data fusion. Subsequently, with these images 12 datasets per cardiac cycle were reconstructed each comprising 7 equidistant cross-sectional images for analysis in new TomTec® 4DLV analysis software. This TomTec software uses a semi automated border detection (ABD) algorithm. Magnetic resonance imaging (MRI) was used as the reference method.
Results: 15 cardiac patients underwent both MRI and 3DE on the same day. Image acquisition was performed in 10 s. with a frame rate of 100/s and a rotational speed of 8/s. The ABD allowed an average analysis time of 15 min. per patient. A strong correlation was found between LV end-diastolic volume (r = 0.98; bias = 22.7 ml; SEE = 13.4 ml), LV end-systolic volume (r = 0.99; bias = 12.6 ml; SEE = 8.7 ml) and ejection fraction (r = 0.97; bias = 0.7%; SEE = 3.1%). Inter-observer agreement for all measurements was good (r > 0.95).

The fast-rotating utrasound transducer.

Conclusion: The fast-rotating transducer with new ABD software is a dedicated tool for rapid and accurate analysis of LV volume and function.

2036 Recovery of stunned myocardium in acute myocardial infarction quantified by strain rate imaging. A clinical study

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Purpose: Strain rate imaging (SRI) is a new tissue Doppler based method that can quantify regional myocardial deformation. The aim of the study was to evaluate if SRI could quantify changes in myocardial mechanical function after acute myocardial infarction (AMI), and to follow the timecourse of these changes.
Methods: Twenty-five patients (mean age 66±10 years) with first myocardial infarction (16 inferior/9 anterior, 16 Q-wave/9 non Q-wave) were examined with 2D echo and SRI after 1 day, 7 days and 3 months. One infarcted segment was studied and compared to a remote control segment. All values are given as mean (SD).
Results: Peak systolic strain rate (SRs) in infarcted segments increased significantly in magnitude from day 1 to 7, but not after day 7 (see table).

Table	Acute	One week	Three months
SRs (1/s)	-0,25 (0,2)	-0,49 (0,32)***	-0,51 (0,31)
SRps (1/s)	-0,75 (0,23)	-0,62 (0,38)	-0,2 (0,3)**
EF (%)	50,6 (8,7)	51,5 (8,9)	54,4 (8,4)*
* p<0,05	** p<0,01	*** p<0,001	Paired t Test

In the remote segments there was no significant change (mean -1,58 (0,29) 1/s). The infarcted segments showed post-systolic shortening, in 18 patients at first day and in 17 after 7 days. Peak post-systolic strain rate (SRps) was unchanged between day 1 and 7 and decreased significantly in magnitude after day 7 (see table). Six patients had remaining post-systolic shortening at 3 months, but SRps in these six, decreased in magnitude from -1,02 (0,14) 1/s at baseline to -0,61 (0,18) 1/s, p<0,05.
There was no change in peak early diastolic strain rate in the infarcted segments over time (mean 1,0 (0,42) 1/s) compared to remote segments (mean 1,83 (0,45) 1/s).
Ejection fraction (EF) increased significantly, but with no change in left ventricular enddiastolic volume.
Conclusions: Strain rate imaging can quantify early contractility improvement due to recovery of stunned myocardium after acute myocardial infarction. No late improvement in contractility could be seen.
Postsystolic shortening disappeared mainly between 7 days and 3 months, probably due to fibrosis and reduced elasticity.
Diastolic function is relatively less reduced in the acute phase than systolic, but with no subsequent recovery.

2037 Myocardial regional right-ventricular relaxation time in patients with pulmonary arterial hypertension: a Doppler myocardial imaging study

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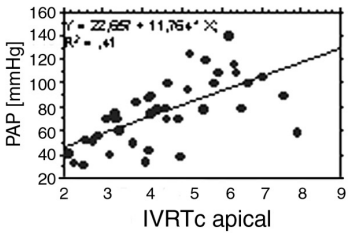
That a low-pressure right ventricle (RV) has virtually no isovolumic relaxation time (IVRT) has been reported in both experimental and clinical studies. This is due the combination of low pulmonary resistance and a small tricuspid (TV) end-systolic pressure gradient. Furthermore, a prolongation of IVRT has been related to an increase in pulmonary systolic pressure (PAPs). If the increase in PAP would correlate with the increase in IVRT, this could offer a easy measure of PAP in pts who had uninterpretable TR signals. Previously RVIVRT was measured by blood pool Doppler. However, Doppler Myocardial Imaging (DMI) now offers a simple reliable approach to RVIVRT measurement.
Aims: 1)To evaluate the duration of regional IVRT in the RV free wall (RVFW) segments in normals and pts with pulmonary arterial hypertension (PAH); 2)To investigate if a relationship exists between regional IVRTs and PAP.
Methods: TTE, blood pool Doppler and 2-D DMI examinations were performed in 46 pts with varying degrees of PAH (PAPs ranged from 35 to 140 mmHg). IVRT was measured for the TV annulus (TVA) and basal and apical RVFW segments.
Results: TVA IVRT and basal RV IVRT were not statistically different (94±32ms and 106±36ms). However, apical IVRT was consistently longer (126±38ms; p<0.0001 vs TVA IVRT, p<0.05 vs basal IVRT). Heart rate corrected IVRT values (divided by the cycle length square root) were correlated with PAP. Only apical IVRT values correlated significantly with PAP (p<0.0001; R=0,64).



Conclusions: 1) RV regional IVRT can be accurately measured from regional velocity curves for all RV FW segments; 2) apical IVRT is significantly longer compared to other RV FW segments-this held true over the range of PAP; 3) apical IVRT correlates significantly with PAP in PAH (figure).

2038 Exploring the complexity of cardiac motion by multiscale motion mapping, a novel quantitative echocardiograpic technique

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Background: Measuring motion is fundamental for echo. Conventionally, this is done by "eyeballing", i.e. visual inspection, with strong intraobserver variability. More recently, tissue Doppler echo and border detection algorithms have been introduced, but their limited impact on routine echo reflects some of their weaknesses, including a limitation to strict 1D motion vectors, the angle dependence of Doppler, and the inability to directly measure wall thickening.
Methods and Results: Multiscale Motion Mapping is a novel echocardiographic technique for measuring motion. This technique is able to assess cardiac motion at arbitrary locations in the echocardiogram, based on exhaustive mathematical analysis of the images using so-called "optical flow" techniques, spline-based imaging, and hierarchical image decomposition. In contrast to conventional techniques, it allows quantitative assessment of true 2 D motion, and quantitative measurement of thickening independent of translation. After successful testing of this new technique in synthetic echocardiograms constructed to contain defined motion patterns, and in a physical phantom of heart motion, we explored its potential in clinical echocardiograms. The ability to display motion independent of the ultrasound beam angle was assessed in the short axis views of the left ventricle. We found that the resulting color motion map showed systolic inward- and diastolic outward motion at all locations of the short axis view, in strong contrast to tissue Doppler that failed to show motion at 90 and 270 degrees of the short axis circle.
The ability of Multiscale Motion Mapping to analyze complex 2D motion was tested in short axis views using a novel vector motion display: in this case, apical rotation/twisting could clearly be shown, a phenomenon difficult to observe in echocardiograms.
To validate quantification of wall thickening, synthetic echocardiograms containing predefined wall thickening were constructed digitally; in this model, multiscale motion mapping was able to detect direction and extent of instantaneous wall thickening (true 2D strain rate) reliably.
Conclusion: Multiscale Motion Mapping, a novel method for objective and quantitative determination of myocardial motion, has been validated in vitro and is applicable to clinical echocardiograms. Its unprecedented ability to measure full 2D motion including wall thickening at arbitrary locations in the echo opens a new window to the complexity of cardiac motion in health and disease, and highlights the limitations of current quantitative methods.

2039 Detection of carotid artery endothelial function with intravenous microbubbles

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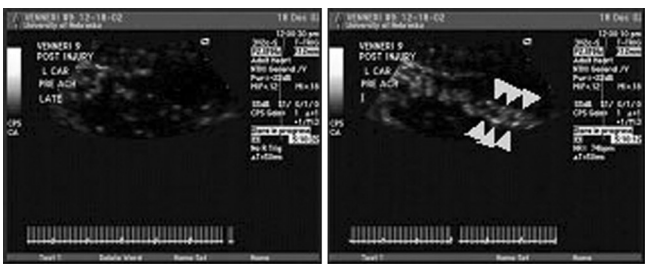
Microbubbles adhere to sites of endothelial dysfunction. Our aim was to test whether intra-arterial endothelial dysfunction (ED) could be detected by intravenous (IV) microbubbles and new highly sensitive low mechanical index (MI) transcutaneous imaging techniques.
Methods: Endothelial responses to incremental local infusions of the endothelium dependent vasodilator acetylcholine (ACH) from 10-7 to 10-5 Molar in the carotid artery (CA) were assessed in seven pigs. Following this, CA ED was created by balloon injury (BI). Following BI, the same ACH infusion was repeated. Intravenous perfluorocarbon exposed sonicated dextrose albumin (PESDA) microbubbles were injected prior to and following BI. The vessels were imaged transcutaneously with a low MI real time pulse sequence scheme (Contrast Pulse Sequencing; Acuson Sequoia; Siemens Medical Solutions). Vessels were also analyzed for degree of endothelial damage at histology.
Results: Prior to BI, CA flow increased in response to 10^{-7} Molar ACH (20 $\pm$ 17%; $p<0.001$ compared to baseline flow). Following BI, CA flow decreased in response to the same ACH infusion (-3 $\pm$ 8%; $p<0.001$). While virtually no PESDA was observed adherent to CA walls prior to BI, adherent microbubbles were evident following BI (figure). The number of adherent microbubbles correlated inversely with flow responses to 10-7 M ACH ($r=0.84$, $p<0.05$). Endothelial injury by histology was equivalent for all vessels.
Conclusions: transcutaneous low MI imaging of carotid arteries can detect adherent microbubbles attached to sites of intravascular carotid artery ED. The functional severity of ED correlated with the number of adherent microbubbles. This technique could be used to localize sites where endothelial dysfunction is present, and quantify its severity.



LATEST NEWS IN THE TREATMENT OF ACUTE CORONARY SYNDROMES

2046 Safety of sirolimus-eluting stent implantation in patients with acute coronary syndromes – insights from the RESEARCH registry

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Background: The safety of sirolimus-eluting stents (SES) implantation in patients with a high risk for early thrombotic complications is currently unknown. In this study we evaluated the early outcomes of patients with acute coronary syndromes (ACS) treated with SES.
Methods and Study Population: SES implantation has been utilized as the default strategy for all procedures in our institution, as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. At 4 months, 311 patients with ACS had been enrolled and compared to a control group composed by 320 consecutive patients treated in the same time period immediately prior. The impact of SES implantation on major adverse cardiac events (MACE) in the first month was evaluated (death, non-fatal MI, or re-intervention).
Results: Clinical syndrome was unstable angina in 67% and 69% and acute MI in 33% and 31% in the RESEARCH and control groups respectively (p=NS for all). As compared to controls, patients treated during the RESEARCH period had more primary angioplasty (90% vs 77%; $p<0.05$), less previous MI (34% vs 46%; $p<0.05$), less IIb/IIIa inhibitor utilization (32% vs 40%; $p<0.05$), and more bifurcation stenting (14% vs 4%, $p<0.05$). At least one SES was utilized in 74% in the RESEARCH group. The incidence of 30-day MACE was similar between both groups (RESEARCH: 6.8% vs controls: 6.9%; p=1.0), with most complications occurring in the first week. Stent thrombosis occurred in 0.6% in the RESEARCH group and in 1.6% of controls (p=0.5). At multivariate analysis, SES utilization did not influence the incidence of MACE (OR 0.81 [95% CI: 0.4 – 1.6]).
Conclusions: Sirolimus-eluting stent implantation for patients with acute coronary syndromes is safe, with early outcomes comparable to conventional percutaneous techniques.

2047 Consistent benefit of clopidogrel in patients with non-ST-elevation acute coronary syndromes undergoing very early, early or later percutaneous coronary intervention in the CURE study

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Background: The CURE study demonstrated the overall benefit of clopidogrel when added to standard therapy in patients with non-ST segment elevation acute coronary syndromes (ACS), including those undergoing percutaneous coronary intervention (PCI). This analysis explored the treatment benefit of clopidogrel according to timing of PCI after clinical presentation with ACS.
Methods: Pts undergoing PCI in CURE were divided into 3 groups according to timing of intervention: very early (<72 hrs from randomization) (N=535), early (between 72 hrs and initial hospital discharge) (N=1195), and later (after initial hospital discharge) (N=928). All pts were treated with clopidogrel/placebo in addition to aspirin and standard therapy before PCI and for mean follow-up of 9 mths. Outcome events included cardiovascular (CV) death and myocardial infarction (MI). Analysis was by intention to treat.
Results: Clopidogrel reduced the overall rate of CV death/MI at 12 (mean 9) mths in the total group of patients undergoing PCI (RRR -31%). There were consistent reductions in events regardless of the timing of intervention, with the greatest benefit in the very early (<72 hr) group: very early RRR -41%, early RRR -28%, after initial hospital discharge RRR -30% (Table 1).

Table 1. Benefit of clopidogrel in pts with non-STE ACS undergoing very early, early and later coronary intervention in the CURE study

Timing of PCI	Placebo	Clopidogrel	Relative risk (95% CI)	p value
Overall group	169/1345 (12.6%)	116/1313 (8.8%)	0.69 (0.54-0.87)	0.002
PCI <72h after randomization	36/270 (13.3%)	21/265 (7.9%)	0.59 (0.34-1.01)	0.050
PCI >72h after randomization	73/639 (11.4%)	47/556 (8.5%)	0.72 (0.50-1.04)	0.080
PCI after initial hospital discharge	60/436 (13.8%)	48/492 (9.8%)	0.70 (0.48-1.02)	0.062

Conclusions: In pts undergoing PCI in the CURE study, 1. Clopidogrel showed consistent benefit in reducing CV death/MI in pts undergoing PCI very early, early and later during follow-up. 2. These data add further support for the use of clopidogrel (pre-treatment and long-term usage) in all pts with ACS undergoing PCI, irrespective of timing of intervention.

2048 Meta-analysis of low molecular weight heparin versus unfractionated heparin in acute coronary syndromes without ST-elevation

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In order to assess efficacy of low molecular weight heparin (LMWH) versus unfractionnated (UFH) in acute coronary syndromes without ST elevation (ACS), we performed the meta-analysis of trials comparing the two classes of heparin. Randomised trials were identified using Medline and Cochrane database. Pooled Relative Risk of the combined criteria of death (D) or myocardial infarction (MI) was calculated with published data. Seven trials including 15998 patients fulfilled the inclusion criteria (Gurfinkel, FRIC, FRISC, FRISC II, ESSENCE, TIMI 11B, FRAXIS).
During the acute phase (7 days), LMWH demonstrated superiority to reduce D or MI versus UFH [RR=0.83; 95%CI(0.70-0.99); p=0.042] in the meta-analysis of five trials including 12169 patients (Gurfinkel, FRIC, ESSENCE, TIMI 11B, FRAXIS). Heterogeneity test was non significant (p=0.47) but subgroup analysis according to the type of LMWH, showed that amplitude of benefit was highest with enoxaparin [RR=0.78; (0.62-0.96); p=0.02] compared to other LMWHs. Long term LMWH administration did not show any additional benefit [RR=0.98; (0.82-1.16); p=0.78] when considering only events occurring after the acute phase in the meta-analysis of five trials (FRIC, FRISC, FRISCII, TIMI11B, FRAXIS). During the acute phase, no significant difference was observed for major bleedings [RR=1.01; (0.81-1.26)]. However minor bleedings were increased by LMWH [RR=1.96; (1.65-2,61); p<0.001]. Prolonged administration increased significantly major bleeding rate by two folds (p<0,001) and minor bleeding by three folds (p<0,001). During the first week of ACS, there is a significant favorable class effect for LMWH compared to UFH to reduce ischemic events. However, prolonged LMWH treatment increases major bleedings without significant additional benefit on ischemic events.

2049 Early invasive management of acute coronary syndromes without ST-elevation does not improve long-term mortality: insights from the randomized trials

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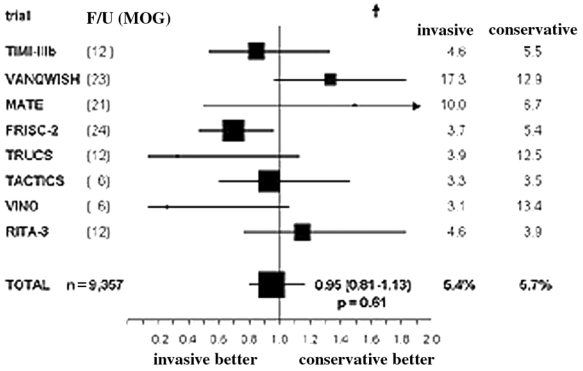
Background: Randomized trials from the 80s and early 90s evaluating an early invasive strategy failed to show a benefit over a conservative approach, but in recent studies the composite of death, MI and revascularisation/recurrent ischemia has been reduced by early intervention. However, by the necessarily open design MI and revascularisation/recurrent ischemia are relatively weak endpoints. Since MI is both an entry criterion and an endpoint, it is difficult to evaluate, since it may be induced by intervention and, therefore, its definition in the trials is cumbersome. Thus, long-term mortality is the best outcome parameter to evaluate the above strategies.
Methods and Results: The 9 randomized trials were carried out between 1996 and 2001 and included 9,357 patients with non-ST-elevation acute coronary syndromes randomized to an early invasive or an ischemia-guided conservative strategy. Long- term mortality (figure) from completed follow-up data (11,633 patients-years) are 5.4% for invasive and 5.7% for conservative (RR 0.95, 95%CI 0.81-1.13, p=0.61)



Long term mortality.

Conclusion: Although most trials on non ST-elevation ACS reported a reduction in the composite of death, MI and revascularisation/recurrent ischemia, an early invasive strategy does not lead to improved survival on the long-term. These findings should be clearly mentioned in current and future guidelines.

2050 Effects of antithrombotic regimen on the early outcome in the FRACAS study: incremental beneficial effects of low molecular weight heparin and thienopyridine in patients undergoing subsequent percutaneous coronary intervention

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Background: Most of the available data about acute coronary syndromes (ACS) were provided by randomised trials. We therefore sought to investigate current management and early outcome of ACS without ST elevation in French centres with on-site percutaneous coronary intervention (PCI) facilities.
Methods: 89 centres, selected on a geographic basis, were asked to complete a prospective record for 10 consecutive patients (pts) admitted in their coronary care unit for an ACS without persistent ST elevation (chest pain<48 hours with ECG changes and/or myocardial damage marker elevation).
Results: Among the 873 pts included in the registry, 804 had complete FU at 30-day. Of those, 441 underwent subsequent PCI during index hospitalisation. Initial antithrombotic therapy included unfractionated heparin (UFH) (42%), low molecular weight heparin (LMWH) (55%), aspirin (95%), thienopyridines (thieno) (either ticlopidine or clopidogrel: 33%, in combination with aspirin in 94%) and GP IIB/IIIA receptor inhibitors (8.6%). The 30-day predefined combined endpoint of death, Q-wave MI or refractory ischemia occurred in 10.1% of the pts. Considering the whole population, the endpoint rate was lower among pts on LMWH (8.2 vs 12.3%) or thieno (7.3 vs 11.4%), but the difference did not reach statistical significance (0.054 and 0.06 respectively). In the pts not submitted to PCI, there was no difference in the outcome regarding initial antithromotic regimen. In contrast, in pts undergoing PCI, both LMWH and thieno uses were associated with an improved outcome (7.6 vs 12.8, $p<0.03$ and 6.3 vs 12.8, $p<0.02$, respectively). Both LMWH (RR 0.42, 95% CI (0.21 to 0.84)) and thieno (RR 0.49, 95% CI (0.24 to 0.99)) remained independent predictors in the multivariate analysis as well as other clinical indicators (prior CABG, 3-vessel disease and CK or troponin elevation). Moreover, the association of thieno+LMWH provided the lowest endpoint rate (3.5%) as compared with LMWH+aspirin (10.3%), UFH+thieno (9.1%) and UFH+aspirin (17.5%).
Conclusion: Initial antithrombotic regimen greatly influences the early outcome of pts admitted for an ACS without persistent ST elevation in case of subsequent PCI. The combination of thieno+LMWH (with aspirin) seems to be the most effective antithrombotic therapy to prevent the occurrence of adverse cardiac events in a population with a low GP IIB/IIIA receptor inhibitors use.

2051 Comparative efficacy of once daily parnaparin and unfractionated heparin in unstable angina pectoris: parnaparin indian multicentric evaluation of cardiac events (PRIME CARE) study

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Several studies have established the efficacy of low molecular weight heparin (LMWH) in the treatment of unstable angina. All these studies have employed twice daily dosing of LMWH.
Parnaparin sodium is a LMWH extensively studied in the treatment and prevention of deep vein thrombosis. The pharmacokinetic studies of a single dose of Parnaparin 6400 IU s. c. indicate that anti Xa activity is present upto 24 hours.
In this first Indian multicentric study, 897 patients of unstable angina were randomised to Group A (UFH) and Group B (Parnaparin). All of them received antiplatelet agent and adequate antianginal treatment as per their needs. UFH was administered as an i. v. bolus of 5000 IU followed by an infusion of 800 to 1000 IU/hour for 48 hours followed by 5000 IU 6 hourly for 5 days or Parnaparin [Fluxum (M/S ASW, Italy)] 6400 IU s. c. once daily for 7 days.
Primary end-points of death, myocardial infarction (Q wave/non-Q wave myocardial infarction), need for revascularisation and major bleeding were monitored during 7 days after enrollment and at the end of 30 days of follow up. Thirty-day follow up data was available from 664 patients.
In Group A there were 446 patients (310 males, 136 females) with a mean age of 55.9 $\pm$ 12.27 years and in Group B 451 patients (311 males, 139 females) with a mean age of 57.6 $\pm$ 11.19 years. Both the groups were similar with respect to age, sex and weight distribution ($p > 0.05$).
At the end of 7 days, primary end points were reported in 53 patients (11.8%) in group A and in 35 patients (7.8%) in Group B (odds ratio 0.62, 95% CI 0.39 to 0.97 p=0.037). At the end of 30 day follow up the cumulative events were seen in 75 patients (22.5%) in Group A (n=334) and 42 patients (12.7%) in Group B [n=330 (Odds ratio 0.50, 95% C I 0.33 to 0.76 p=0.001)]
During the 7-day follow up, episodes of minor bleeding were reported in 115 patients from Group A and 12 patients from Group B (Odds ratio 0.08, 95% C I 0.043 to 0.15). In both the groups, 2 episodes each of major bleeding were reported.
Thus, once daily administration of Parnaparin 6400 IU as a fixed dose is a safe and effective alternative to UFH in the treatment of unstable angina.

PERCUTANEOUS CORONARY INTERVENTION IN ST-ELEVATION MYOCARDIAL INFARCTION

2052 Differences in diagnostic and therapeutic management strategies in diabetic patients experiencing acute myocardial infarction: analysis of a large United States database

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Purpose: Diabetes mellitus (DM) has been associated with adverse cardiovascular outcomes, but its impact on patients hospitalized with a primary diagnosis of acute myocardial infarction (AMI) is not well understood. We compare the in-hospital treatment and clinical outcomes of DM and non-DM AMI patients in a large US community practice database.
Methods: The clinical outcomes of 171,414 consecutive patients hospitalized with a primary diagnosis of AMI from 1998 to 2002, were analyzed from the HCA Casemix Database using univariate and multivariate logistic regression. Patient characteristics, complications, and co-morbid conditions were identified using ICD9 codes. The impact of DM on the following adverse outcomes (mortality, shock, acute renal failure, neurologic and cardiac complications, and adult respiratory distress syndrome) was analyzed using logistic regression analysis, controlling for age, gender, and 23 co-morbid conditions.
Results: Overall, 29.5% of the AMI patients were DM. Men represented 56% of the DM population and 63% of the non-DM AMI population. Unadjusted analysis demonstrated DM patients were significantly more likely to die (9.9% vs. 8.2%, $p<0.001$) and almost two-times more likely to develop acute renal failure (ARF) (7.7% vs. 4.3%, $p<0.001$). DM patients were significantly less likely to undergo a diagnostic cath (52.2% vs. 59.2%, $p<0.001$) or percutaneous coronary intervention (PCI) (25.2% vs. 34.5%, $p<0.001$). Despite this, DM patients were more likely to undergo CABG (12.3% vs. 10.8%, $p<0.001$). Controlling for age, gender, and co-morbidity, IDDM AMI patients were 40% ($p<0.001$) more likely to die and 95% ($p<0.001$) more likely to develop ARF than non-DM patients. NIDDM patients were 15% ($p<0.001$) and 35% ($p<0.001$) more likely to die and develop ARF than non-DM patients. With multivariate logistic regression, all DM patients are significantly more likely to receive a CABG (IDDM OR 1.19, $p<0.001$: NIDDM OR 1.26, $p<0.001$) and significantly less likely to undergo diagnostic cath (IDDM OR 0.65, $p<0.001$: NIDDM OR 0.90, $p<0.001$) or PCI (IDDM OR 0.56, $p<0.001$: NIDDM OR 0.82, $p<0.001$).
Conclusions: Adjusted for age, gender and co-morbidity DM patients admitted with a primary diagnosis of AMI experience significantly worse outcomes than non-DM patients. Although this increased risk is particularly true for IDDM, NIDDM also have heightened risk. Additional study is necessary to determine the influence of diagnostic and therapeutic strategies on the outcomes of these patients.

2053 The clinical impact of percutaneous intervention as first-line therapy of ST-elevation acute myocardial infarction in the practice of a tertiary-care hospital

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Background: Front-loaded thrombolisis (alteplase 100 mg. in 90 min.) within 12 hours of symptoms onset (extended time window of 24 hours in the case of shock or ongoing ischemia) has been the standard treatment of ST-elevation AMI (SteMI) at our Hospital since 1993. Based on the results of a number of randomised controlled trials in which primary PCI was followed by lower morbidity and mortality compared to thrombolisis, the former became our first-line therapy in the year 2000. Since then, we usually perform PCI with or without stenting in every patient who is admitted within 12 hours of symptoms onset, and up to 24 hours whether shock, overt heart failure or ongoing, potentially reversible ischemia are identified.
Methods: A retrospective comparison was made of the clinical records of 200 consecutive patients in a "thrombolisis first" year (1995) and 200 consecutive patients in a "PCI first" year (2001) at our Hospital. Every patient who received the diagnosis of AMI in the Emergency Room was included in the year cohort.
Results: Patients' age (67 ± 14 vs. 63 ± 13 years) and Killip class (1.7 ± 1 vs. 1.3 ± 1) did not differ between the two cohorts. In 1995, 39% of the patients received the first-choice therapy (thrombolisis), while in 2001 71% was the proportion of those treated with PCI, with 88% recanalization (TIMI 2 & 3 flow) rate. The in-hospital mortality rate among the patients who underwent the index therapy was similar (7.7% in 1995, 7% in 2001), but the introduction of PCI as first-line therapy significantly reduced the mortality of the whole cohort (from 19.5% to 12.5%, $p<0.01$), due to a more extensive utilization of PCI compared to thrombolisis. The incidence of two major in-hospital events significantly decreased in 2001: reinfarction (from 6.4% to 1.4%, $p< 0.01$) and heart failure (from 9% to 6.4%, $p< 0.01$).
Conclusion: The introduction of PCI as first-choice therapy in SteMI favourably affected mortality and morbidity in the daily practice of our Hospital.

2054 Clinical features and in-hospital mortality of patients with TIMI 3 flow after percutaneous coronary intervention in acute myocardial infarction but lack of ST-segment resolution

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Background: Percutaneous coronary intervention (PCI) in ST elevation acute myocardial infarction (STEAMI) has proved to be effective in restoring TIMI 3 flow in a high proportion of patients (pts). However, discrepancies have been observed between recanalization of the epicardial vessel and effective tissue perfusion. A persistent ST segment elevation is considered the most readily available clinical tool to evaluate this discrepancy.
Methods: We analyzed data of consecutive prospectively enrolled pts with PCI for STEAMI who had: 1) a post-procedural TIMI 3 flow - as assessed by an independent observer-; 2) an available 12 lead electrocardiogram (ecg) performed before and immediately after PCI, with comparable heart rates and absence of confounders (intraventricular conduction delay, persistent idioventricular rhythm, paced beats, etc). In this cohort, the ST segment variation between pre- and post-PCI were measured manually by an operator blinded to the angiographic results. Patients were divided according to an ST segment resolution in the worst lead $>$ 50% (group A, achieved reperfusion) or $<$ 50% (group B, failed reperfusion). Clinical and angiographic findings and in-hospital outcome were compared in the 2 groups.
Results: The study population includes 221 pts (mean age 62 ± 13 yrs, 78% males) treated in the period 1999-2001. Of these pts, 164 (74%) had ST segment resolution (Group A) while 57 (26%) had not (Group B). There was a trend for a more severe clinical profile in Group B compared to group A (age: 64 ± 13 yrs vs 61 ± 14 yrs; p=0.290; diabetes: 14% vs 5.5%; p=0.066; ejection fraction: 44 ± 12% vs 47 ± 11%; p=0.075; time-to-treatment: 5.4 ± 3.3 hrs vs 4.5 ± 3 hrs; p=0.059; Killip class 3-4: 18% vs 9%; p=0.138). The 2 groups differed significantly for baseline TIMI flow, which was lower in group B compared to group A (TIMI 0: 70% vs 54%; TIMI 1: 2% vs 13%; TIMI 2: 23% vs 21%; TIMI 3: 5% vs 12%; p for trend: 0.044). Infarct location, use of IIb/IIIa receptor antagonists and intra-aortic balloon pumping were almost identical in the 2 groups. Peak Troponin I was quantitatively similar, but occurred later in group B compared to group A (16 ± 7 hrs vs 13 ± 5 hrs; p=0.002). In-hospital mortality was 1.8% in group A and 8.8% in group B (p=0.045).
Conclusions: Our data show that 1/4 to 1/5 of pts with TIMI 3 flow after successful PCI in STEAMI do not show resolution of ST segment elevation. Early mortality in these pts is $>$ 4 times higher compared to pts with normalized ST. These data emphasize the need for more effective therapeutic strategies aimed at restoring tissue reperfusion.

2055 Which factors determine the application of reperfusion therapy in ST-elevation acute coronary syndromes? Lessons from the Euro-Heart acute coronary syndromes survey

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Background: In the Euro-Heart ACS survey a large proportion of patients with ST-elevation acute coronary syndromes (ACS) did not receive PCI or did not receive reperfusion therapy at all. In order to optimize treatment in these patients clear insight in which factors influence the choice for administrating reperfusion therapy and the choice for mode of therapy is warranted.
Methods and Results: The Euro-Heart ACS survey enrolled 4,431 consecutive patients with a confirmed diagnosis of ST-elevation ACS in 25 European and Mediterranean countries, and 2,472 (56%) received immediate reperfusion therapy. Among these 916 (37%) were treated with primary angioplasty, 665 (27%) with streptokinase, and 891 (36%) with another lytic agent.

Patient Characteristics

	Reperfusion therapy			Mode of therapy			Lytic agent		
	Yes	No	p	PCI	Lytic	p	SK	Other	p
Number of Patients	2472	1959	¶	916	1556		665	891	
Arrival $>$ 6 hours	14%	34%	¶	24%	15%	¶	12%	11%	
Age $>$ 70 years	28%	43%	¶	26%	29%		31%	26%	*
Female Gender	24%	34%	¶	23%	26%		27%	24%	
Diabetes	18%	25%	¶	18%	18%		18%	19%	
Hypertension	49%	55%	¶	53%	47%	¶	47%	46%	
Coronary Angioplasty	7%	8%		11%	5%	¶	3%	6%	*
Coronary Bypass Surgery	2%	5%	¶	3%	2%		2%	2%	
Myocardial Infarction	17%	29%	¶	19%	17%		16%	16%	
Heart Failure	4%	14%	¶	4%	4%		4%	3%	
Cerebrovascular Accident	4%	8%	¶	4%	4%		5%	4%	
Renal Failure	2%	5%	¶	3%	2%		2%	2%	
Pulmonary Disease	7%	10%	#	6%	8%	*	9%	8%	

* $p<0.05$; # $p<0.01$; ¶ $p<0.001$

Conclusion: Patients who received reperfusion therapy were younger, less often females, more likely to have arrived in the hospital within 6 hours after the onset of symptoms and constituted a healthier population. PCI is preferred to thrombolysis in patients arriving later than 6 hours after the onset of symptoms.

2056 Incidence and outcome of percutaneous coronary intervention in ASSENT-3 and ASSENT-3 Plus

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Background: It is well known that patients with ST-elevation acute myocardial infarction (AMI) in whom fibrinolytic reperfusion therapy is initiated in the ambulance are a higher risk population compared with patients treated in the emergency department. The effect of this prehospital treatment on incidence of and outcome after percutaneous coronary interventions (PCI) is not known.
Methods: Incidence of elective and urgent PCI in ASSENT-3 and ASSENT-3 Plus in the patients treated with tenecteplase (TNK-tPA) and unfractionated heparin (UFH) or enoxaparin (ENOX) co-therapy were compared using a Chi-square test. Clinical outcomes after PCI in both trials were also assessed.
Results: Incidence of and mortality after PCI are shown in the table. A significant excess of invasive procedures was seen in the ASSENT-3 Plus population. No major differences in clinical outcomes were seen after PCI in ASSENT-3 Plus compared with ASSENT 3. Caution is needed in the interpretation of these results since study populations and study designs were different. Patients in ASSENT-3 Plus were older, more likely to be female and presented more frequently with anterior AMI.

	ASSENT-3 Plus	ASSENT-3	P-value
TNK-tPA + UFH	n=813	n=2035	
Incidence of elective PCI	176 (21.6%)	332 (16.3%)	0.0008
Incidence of urgent PCI	239 (29.4%)	292 (14.3%)	<0.0001
TNK-tPA + ENOX	n=815	n=2036	
Incidence of elective PCI	184 (22.6%)	348 (17.1%)	0.0007
Incidence of urgent PCI	204 (25.0%)	242 (11.9%)	<0.0001
TNK-tPA + UFH			
Death at 30d elective PCI	1/176 (0.6%)	4/332 (1.2%)	NS
Death at 30d urgent PCI	13/239 (5.4%)	13/292 (4.5%)	NS
TNK-tPA + ENOX			
Death at 30d elective PCI	1/184 (0.5%)	2/348 (0.6%)	NS
Death at 30d urgent PCI	10/204 (4.9%)	13/242 (5.4%)	NS

Incidence of and 30 day mortality after PCI in ASSENT-3 Plus/ASSENT-3

Conclusions: Significantly more patients underwent PCI in ASSENT-3 Plus when compared with ASSENT-3, potentially reflecting a selection of sicker patients receiving prehospital treatment, however outcomes after PCI were similar in both trials.

2057 Totally occluded infarct-related artery: a bad omen?

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Direct infarct intervention (d-PCI) in totally occluded (TO) infarct-related arteries (IRA) poses a challenge to the interventional cardiologist, both in terms of re-establishing patency and maintaining it. Limited data is available on immediate and long-term clinical outcomes following d-PCI. We compared baseline clinical profile, angiographic characteristics, procedural, in-hospital and 12-month clinical outcomes in 1,181 consecutive patients (494 had TO; 687 had non-occluded IRA; N-O) undergoing d-PCI within 12 hours of onset of acute MI. Results: Patients in both groups were well-matched for age, gender and cardiac risk factors. Patients who had N-O IRA were more likely to have prior episodes of unstable angina (6.0% versus 3.4%; p=0.034*) or prior MI (21.4% versus 17%; p<0.0001*). On angiographic comparison, patients with TO had a significantly higher incidence of ostial/proximal disease (55% versus 46%; p=0.0003*), implying large myocardial volume subtended by the IRA. Non-O IRA lesions were longer (>20 mm, 21% versus 16%; p=0.01*) and associated more frequently with multivessel disease (19.6% versus 8.3%; p<0.0001*). Use of adjunctive IABP support (62% versus 29%; p<0.0001*) and transvenous pacing (7.5% versus 2%; p<0.0001*) were significantly greater in the TO group. Procedural success (residual stenosis <20%; epicardial TIMI grade 3 flow) was achieved less frequently in the TO artery (95.7% versus 98.7%; p=0.0036*). This group also demonstrated a higher incidence of ventricular tachycardia during the procedure (1.2% versus 0.7%; p=0.03*), acute reclosure (1.0% versus 0.1%; p<0.0001*), in-hospital CABG (2.6% versus 0.6%; p=0.009*) and death (1.2% versus 0.4%; p<0.0001*). At 12-month follow-up, the TO group showed less myocardial salvage (change in LVEF 3.3% versus 7.9% in the N-O group; p<0.0001*) and had a greater incidence of target vessel revascularization (8.0% versus 5.3%; p=0.003*). Reinfarction rate (1.8% versus 1.0%) and mortality at 1 year (4.6% versus 3.5%) were higher but did not reach statistical significance. Conclusions: Our experience indicates that patients with totally occluded IRA at the time of direct infarct intervention are more likely to present with proximal lesions, more likely to develop periprocedural complications and require hemodynamic support, than patients with nonoccluded IRAs. Following successful revascularization, they continue to be at greater risk for MACE, both acutely and in the long-term. Thus, the strategy of direct-PCI in total occlusions represents an imposing challenge to the interventional cardiologist.

POSTER DISPLAY IV

MECHANISMS OF ARRHYTHMIAS I

P2061 Transgenic ccs/lacz expression in the pulmonary venous area in murine embryos; source of atrial arrhythmias?

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Background: Atrial arrhythmias often originate in the pulmonary veins (PV). With the CCS(cardiac conductive system)/lacZ construct it has been possible to delineate the developing and mature cardiac conduction system. Expression in the area of the PV however, has not been described.
Purpose: To explore the presence of lacZ-expression in the area surrounding the PV in order to determine whether these structures relate to the CCS during embryology.
Methods: Analysis of lacZ-expression during sequential stages of cardiogenesis was performed in a line of CCS/LacZ transgenic mice (E 9,5-15,5). Embryos were stained for beta-galactosidase activity. An immunohistochemical staining with the myocardial marker HHF35 was performed to produce a double staining with the lacZ reporter construct. Results were 3-D-reconstructed and morphed to allow optimal insight.
Results: CCS/lacZ-expression was broadly present in the embryonic heart tube in the youngest embryos and remained visible in subsequent stages. Expression became gradually confined to the primitive conduction system. In the right atrium CCS/lacZ expression was observed in the putative sinu-atrial node and internodal pathways (left and right venous valves and septum spurium). Furthermore, expression was present in the right and left atrioventricular ring, His bundle, bundle branches and the moderator band in the RV. LacZ positive cells could be demonstrated in the LA, also encircling the pulmonary venous entrance. These cells were continuous with the left venous valve in the RA. The RV inflow and the distal part of the outflow tract did not show lacZ expression.
Conclusion: Lac Z reporter gene expression is able to delineate the developing murine cardiac conduction system. New details have been found, such as the embedding of the PV in an area of lacZ-positive cells, which may be significant in the participation of the PV in atrial arrhythmogenesis.

P2062 Extracellular matrix proteins in left atrial tissue of patients with atrial fibrillation of different causes

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Background: Mitral valve disease (MVD) is usually associated with increased atrial fibrosis. Additionally it is often combined with atrial fibrillation (AF). To test the hypothesis that even AF alone leads to atrial fibrosis which is enhanced by additional MVD we analyzed the protein expression of the extracellular matrix proteins (ECM) collagen I, III (coll I, III) and fibronectin in left atrial tissue of patients (pt.) with lone AF, MVD and AF and sinus rhythm control pt. (SR).
Methods: Left atrial tissue samples of pt. with lone AF (n = 40), pt. with MVD and AF (n = 35) and pt. in SR without and with MVD (n = 15) were obtained during surgery and the coll I, III and fibronectin protein content measured by Western blot analysis. In addition samples
Results: Compared to SR the coll I, coll III and fibronectin content was increased in all forms of AF (p = 0,002, p = 0,022 and p = 0,08, respectively). The increase in coll I and fibronectin showed the same extent in the lone AF and MVA and AF group whereas the coll III content was significantly higher in the MVD and AF group than in the lone AF group (p = 0,044 vs. lone AF). Within the groups there were no differences in the expression of ECM proteins between pt. in paroxysmal and chronic AF.
Conclusion: With this data it could shown for the first time that even lone AF leads to an increase in ECM protein expression and therefore increased fibrosis. An additionally present mitral valve disease causes only an additional increase in coll III. The enhanced fibrosis in MVD is not only caused by the MVD but also the AF. The demonstrated changes support the perpetuation of AF.

P2063 Heart-rate variability reflects the severity of coronary artery disease

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Purpose: Reduced heart-rate variability is associated with increased risk of coronary events. Whether it is associated with the severity of coronary atherosclerosis is unknown. The aim of the study was to evaluate the relationship among heart rate variability, cardiovascular risk factors and coronary artery disease (CAD) and to investigate whether heart rate variability patterns are different in chronic or acute coronary syndromes. Methods. 24-hour ECG monitoring was used to define autonomic activity by time domain measures of heart-rate variability in a multicenter study addressed to patients undergoing angiography for symptoms and ECG signs of ischemic heart disease. We evaluated 137 patients. The percent of differences of adjacent RR intervals $>$ 50 ms (pNN50) and the root-mean square of differences of successive RR intervals (RMSSD) are measures of the modulation of parasympathetic tone by respiratory activity. The standard deviation of all normal RR intervals (SDNN) and the standard deviation of the means of all normal RR intervals during each 5-minute segment (SDANN) indices are measures of both parasympathetic and sympathetic tone as mediated by baroreflex activity. We assessed the mean and the following cut off values: (1) SDNN $>$50 and $>$100 ms. (2) SDANN $>$50 and $>$100 ms. (3) RMSSD $<$25 ms. (4) PNN50 $<$3%. Diabetic patients were excluded because at high risk of autonomic nervous system unbalance, independently of CAD. Measurements of heart rate variability were related to age, gender, history of CAD, smoking, hypertension, hypercholesterolemia and severity of CAD. Severity of CAD was assessed as the presence of lumen stenosis ($>$ 50%) in one or more epicardial vessels. Results PNN50$<$ 3% and RMSSD $<$25 ms were significantly associated with multivessel coronary artery disease in both patients with chronic (n=20) and acute (n=117) coronary syndromes (Pearson test, r = 0.627 and r = 0.611, respectively, p$<$0.003). Conversely they were not associated with the quality and quantity of coronary risk factors in CAD patients. No significant relationship was found in SDNN or SDANN. Conclusion. These preliminary findings on a carefully selected group of patients with documented coronary atherosclerosis indicate that analysis of heart rate variability, namely PPN50 and RMSSD, can select patients with severe chronic or acute disease for a more aggressive approach. PPN50 and RMSSD reflect low vagal activity. Partial vagotomy induced by the atherosclerotic involvement of the vessel wall may result in low parasympathetic indices of heart rate variability.

P2064 Prognostic value of heart rate variability after ST-segment elevation myocardial infarction treated with fibrinolysis versus primary angioplasty

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Purpose: A low 24-hour heart rate variability(HRV) is a prooven predictor of mortality after myocardial infarction. However, this relation is based on data from fibrinolysed patients only, and in patients with a low prevalence of betablocker treatment. In the present study we investigated the prognostic value of HRV in patients with ST segment elevation infarction(STEMI) randomized to treatment with either fibrinolysis or primary angioplasty(PA).
Methods: HRV was measured as the HRV triangular index in a 24-hour ECG recording performed at discharge from hospital in 964 patients treated in a randomized fashion with either fibrinolysis(n=477) or PA(n=487), as a part of the DANAMI-2 trial. HRV was dichotomized according to a previously documented cutpoint of the HRV index $<$ 20. A HRV index $<$ 20 was present in 25% of patients. Patients treated with betablockers were 87% and 89% in the fibrinolysis and PA group respectively. The primary endpoint was all cause mortality during follow-up at one year.
Results: HRV was not different for fibrinolysed as compared with PA treated patients(28.7(10.1) vs. 27.8(9.7); p=0.13) neither was ejection fraction(49.8%(10.7) vs. 50.7%(10.5); p=0.13. Mortality was also not different, 2.9% as compared to 2.5% for PA treated patients. For fibrinolysed patients a HRV index $<$ 20 was associated with a significantly increased mortality of 8.2%, versus 1.9% for patients with HRV index $\geq$ 20(p=0.008), whereas in PA treated patients mortality was not different(HRV index $<$ 20: 4.4% vs. 2.1%; p=0.19).
Conclusions: The selection of an invasive treatment for STEMI had no impact on HRV as compared to fibrinolysis. However, after fibrinolysis a low HRV was associated with an adverse prognosis, as previously documented, whereas this was not the case after PA. This indicate that PA may affect the arrhythmic substrate, and this finding have implications for risk evaluation after PA treated STEMI.

P2065 Prognostic factors of patients with history of myocardial infarction and unexplained syncope

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The purpose of the study was to evaluate the clinical and electrophysiological factors useful to predict the prognosis of patients with previous myocardial infarction (MI) and syncope; these patients are generally considered at risk of sudden death. **Methods:** 229 patients with history of MI ($>$ 1 month) and without documented ventricular tachycardia (VT) were admitted for syncope. Holter monitoring and programmed ventricular stimulation up to 3 extrastimuli in 2 sites were systematic. Left ventricular ejection fraction (LVEF) was measured by 2D echocardiogram or radionuclide methods. The patients were followed up to 5 years or up to heart transplantation (mean 3$\pm$1 years). **Results:** patients were divided into 2 groups according to LVEF, 119 patients with LVEF $<$ 40% (group I) and 110 patients with LVEF $>$ 40%(group II). Sustained monomorphic VT ($<$ 280 b/min) was induced in 44 group I patients (37%) and 18 group II patients (16%) (p $<$ 0.05); ventricular flutter ($>$ 270 b/min) or fibrillation (VF) was induced in 24 group I patients (19%) and 19 group II patients (17%) (NS). Various other causes of syncope (conduction disturbances, severe coronary ischemia, neurally-mediated syncope or rapid atrial tachyarrhythmias) were identified in 23 group I patients (19%) and in 32 group II patients (29%) (p $<$ 0.05). Syncope remained unexplained in 43 group I (36%) and in 40 group II patients (36%) (NS). The prognosis differed in both groups: in group I, cardiac mortality was 49% in patients with inducible VT $<$ 280 b/min, 35% in those with inducible VF and 9% in those without inducible VT/VF; in group II, the prognosis was independent on the results of programmed ventricular stimulation and was favourable; cardiac mortality was 5. 5% in patients with inducible VT, 5% in those with inducible VF and 4% in those without VT/VF. The prognosis was also independent on the presence of nonsustained (NS) VT on Holter monitoring, but in group II, NS VT were noted in 46% of patients with inducible VT or VF and only 14% of patients without VT/VF (p $<$ 0.05%); the differences were not significant in group I (NSVT present in 52% in patients with induced VT, 46% in those with VF and 36.5% in those without VT/VF). **Conclusion:** LVEF, at first, should be considered in patients with myocardial infarction and syncope. Only those with a LVEF $<$ 40% and with inducible ventricular arrhythmias have a high risk of cardiac mortality; the prognosis of those with preserved LVEF is favourable and does not depend on the results of programmed ventricular stimulation.

P2066 Genotype specific natural history in the long QT syndrome: identification of a novel risk stratification scheme

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The three most prevalent genetic variants of Long QT Syndrome (LQTS) are caused by mutations in the potassium channels genes KCNQ1 (LQT1) and KCNH2 (LQT2) and in the sodium channel gene SCN5A (LQT3). Despite genotype-specific clinical manifestations have been outlined in several studies, the value of genotyping for risk stratification is still unclear. In this study, we evaluated the predictors of outcome before treatment in the world's largest single-center series of consecutively genotyped LQTS patients, in the attempt to develop a novel risk stratification scheme based on genotype, heart-rate corrected QT interval (QTc) and gender. The study population included 647 patients (386 LQT1, 206 LQT2, 55 LQT3): 193 probands presenting with a clinical diagnosis of Romano-Ward variant of LQTS, 387 genotyped family members and 67 LQTS-related sudden cardiac deaths. Cardiac events (CE) were defined as syncope, documented Torsade de Pointes, cardiac arrest and sudden death occurring below age 40 and before initiation of therapy. Duration of QTc, gender, familial history of sudden death and genotype were assessed as possible predictors of a first CE in both univariate and multivariate survivorship analyses. The frequency of a first CE was lower among LQT1 (30%) than among LQT2 (47%) or LQT3 (43%), p$<$0.001, while a QTc interval $>$/=500ms (upper quartile; 24% of the population) was significantly associated with a worse outcome compared with patients with QTc $<$500ms (p$<$0.0001). The independent predictors of CE identified by multivariate analysis were genotype and QTc. Gender differences were observed for selected groups of patients. Overall the results allowed the definition of a novel risk stratification scheme (table). In conclusion, these data demonstrate for the first time that risk stratification should be based on the genetic variant of LQTS and that clinical parameters contribute to modulate the risk of cardiac events.

Risk stratification in LQTS

QTc	High Risk ($\geq$50%)	Intermediate risk (30%-50%)	Lower risk ($<$30%)
$\geq$500ms	All LQT1; All LQT2; Males LQT3	Females LQT3	-
$<$500ms	-	Females LQT2; All LQT3	Males LQT2; All LQT1

Cumulative probability of a first cardiac event by age 40 before therapy

P2067 Natural history in patients with the Brugada syndrome

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Background: The prognosis of patients with the syndrome of right bundle branch block and ST segment elevation in the right precordial leads (Brugada syndrome) has been somewhat controversial, particularly for asymptomatic individuals. In this study, the largest cohort of patients with Brugada syndrome are reported and the prognostic significance of clinical and electrophysiological data are analyzed.
Patients: A total of 667 patients with an electrocardiogram (ECG) characteristic of Brugada syndrome were analyzed.
Results: Mean age at diagnosis was 41±15 years, 160 were female and 507 male. The diagnosis was made due to the presence of a basal diagnostic ECG in 499 patients and in 168 the diagnostic ECG was noted only after antiarrhythmic drug administration. Sustained ventricular arrhythmias were induced during electrophysiological study in 231 out of 493 patients. During their lifetime 164 patients (25%) presented at least one episode of sudden cardiac death or documented ventricular fibrillation at a mean age of 43±15 years (2 to 77 years). Using multivariate Cox regression models, inducibility of sustained ventricular arrhythmias ($p<0.0001$, Hazard ratio 3.8, 95% CI 2.4-6.25), a male gender ($p<0.02$, Hazard ratio 1.9, 95% CI 1.03-3.4) and a basal abnormal ECG ($p<0.05$, Hazard ratio 1.9, 95% CI 1.01-3.7) were all predictors of occurrence of sudden cardiac death or ventricular fibrillation. Using a logistic regression model, the probability that a male, with a basal abnormal ECG and inducible to sustained ventricular arrhythmias has an event is 45% (CI 38-53%).
Conclusions: Patients with an ECG showing right bundle branch block and ST segment elevation in the right precordial have a high risk of ventricular arrhythmias and sudden death. Inducibility of sustained ventricular arrhythmias, male gender and a spontaneously abnormal ECG are markers of poor prognosis.

P2068 Human cardiac inward rectifier Kir2.2/Kir2.1b (KCNJ12) potassium channels are antagonistically regulated by protein kinase A and protein kinase C

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Human Kir2.2/Kir2.1b (KCNJ12) potassium channels contribute significantly to the cardiac inwardly rectifying IK1 current. Recently, we have demonstrated that protein kinase C (PKC) causes a strong inhibition of Kir2.2 channels via a direct phosporylation of the channel protein. In this study, we focused on the regulation of Kir2.2 by protein kinase A which has not been analysed before.
Human Kir2.2 channels were expressed in Xenopus oocytes and experiments were performed using double electrode voltage clamp.
In modified Kir2.2 channels lacking PKC consensus sites, the unspecific protein kinase activator PMA (100 nmol/l) surprisingly induced a strong activation of the currents: Peak inward currents were increased to 171.8 ± 15.1% (n=6) of the control values after 30 minutes.
This effect could be suppressed by coapplication of protein kinase A inhibitors. KT-5720 (2.5 μmol/l) attenuated the increase to 121.4 ± 2.8% (n=6) and H-89 (50 μmol/l) to 120.1 ± 5.4% (n=5), respectively.
In wild type Kir2.2 channels, activation of protein kinase A induced an increase of the currents. Incubation with Forskolin (100 μM) and the PDE-IV-Inhibitor Ro-20-1724 (100 μM) resulted in an increase of Kir2.2 currents to 170.3 ± 11.0% (n=9) and 155.2 ± 7.9% (n=11), respectively, after 40 minutes. This was significantly different from control experiments ($p<0.01$).
Kir2.2 channels have a single PKA consensus site at S430. However, mutated Kir2.2-S430A channels showed the same response to PKA activation as wild type channels. With 193.8 ± 9.8% (Forskolin) and 152.6 ± 7.1% (Ro-20-1724), respectively, the results were not significantly different. Therefore, the molecular basis of the effect is not entirely clear.
In summary, we have shown that PKA and PKC antagonistically regulate human Kir2.2 channels. This is an interesting physiological mechanism which may contribute to the regulation of the resting potential and the excitability of cardiomyocytes. It could be a promising target for future pharmacologic or genetic interventions in patients with cardiac arrythmia.

P2069 T-wave morphology analysis in patients with implantable cardioverter defibrillator

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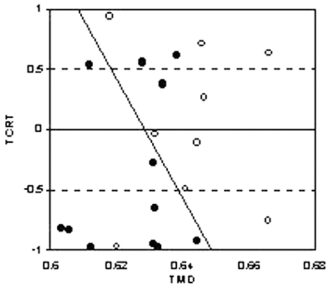
Early studies demonstrated that T-wave morphology (TWM) analysis was a powerful risk predictor after myocardial infarction and abnormality in TWM may be indicator of arrhythmic complications in patients (pts) with ischaemic heart disease (IHD). This study evaluated the relation of TWM analysis to arrhythmic events in pts with IHD who had an implantable cardioverter defibrillator (ICD) in situ (n=21, age 60±9 yrs, 20 men). Ten consecutive standard 12-lead ECGs were recorded from each patient using a digital electrocardiograph (MAC VU, GE Medical Systems, WI, USA) with a sampling rate of 500 Hz. An analytical program performed a singular value decomposition of the ECG signal into a minimum dimensional space. Two TWM descriptors were calculated: TWM dispersion (TMD) which evaluated the spatial and temporal variations of TWM, and the total cosine R-to-T (TCRT), which evaluated repolarisation wavefront direction by describing the global angle between repolarisation and depolarisation loops. Twelve of 21 study pts had ≥1 ICD therapy (shock, anti-tachycardia pacing) after implantation of ICD while others remained free of therapy. TCRT in pts who had ICD therapy tended to be lower (-0.36±0.68 v 0.02±0.67, p=ns) than in those who did not have such therapy. TMD was similar in both groups (0.63±0.01 v 0.64±0.02, p=ns). Pts who had negative value of TCRT associated with lower value of TMD were more likely to have ICD therapy. Linear combination of both factors separated both groups with a sensitivity of 75% and specificity of 89% (p=0.008, Fisher's exact test) (figure: dots = pts with ICD therapy, open circles = pts without ICD therapy.).



TWM analysis in relation to ICD therapy.

Our findings suggest that evaluation of TWM might identify pts with IHD at high risk of significant arrhythmic complications.

P2070 Ventricular sensing of implantable cardioverter defibrillators is significantly reduced during exercise-testing

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Aims: Transvenous implantable cardioverter defibrillators (ICDs) are usually programmed at rest, at the supine position. However, usually ICDs detect and treat life-threatening arrhythmias during exercise. We investigated the effects of treadmill exercise on ventricular sensing in patients with ICDs.
Methods: We studied 16 consecutive patients (mean age 50±19 years, 75% males) with a dcICD implanted 11±11 months before examination, who were regularly followed in the outpatients department of our hospital and were willing to undergo treadmill exercise by the modified Bruce protocol. The patients were exercised for an average of 9±3 minutes achieving 6±2 METS of workload. Tip to tip, sensed R wave amplitude was monitored continuously, and the intracardiac electrograms from 8 consecutive cardiac cycles in each phase of the exercise testing were recorded on paper, scanned through a flatbed scanner, scale adjusted, magnified and measured onscreen using a previously described computer-based method in order to improve accuracy and reproducibility of the measurements.
Results: Sensed R wave amplitude was significantly lower at peak exercise compared to baseline values at rest (8.7±2.4 vs 9.9±2.6mV,P=0.002) and compared to the third minute of recovery (8.7±2.4 vs 9.3±2.7mV,P=0.032). R wave at peak exercise was reduced by 12±11% (range -5 to 33%), and values at implantation were not significantly correlated to the observed changes at peak exercise (R=-0.17,P=0.65). In 6 of the studied patients, changes concerning rate response pacing, rate adaptive AV, or mode switch parameters were reprogrammed according to the patients' response to exercise.
Conclusions: Our results suggest that sensed R-wave is significantly reduced during exercise by an average of 12%. Taking into consideration the high incidence of device-related adverse effects and the expanding indications for the use of ICDs in the prevention of sudden cardiac death, this observation could have profound clinical implications, if verified by other studies. Furthermore, exercise-testing in this study was proved to be a valuable tool for the final adjustments of ICDs programming.

QT DISPERSION AND OTHER ELECTROCARDIOGRAPHY FEATURES I

P2071 The comparison of principal component analysis ratio with QT dispersion and T-wave alternans in patients with old myocardial infarction

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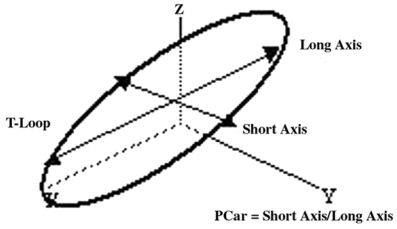
Background: PCA ratio was a significant univariate predictor of cardiovascular mortality in both men and women, whereas QTd significantly predicted cardiovascular death in women only. Increased QT interval dispersion (QTd) is a proposed ECG marker of vulnerability to ventricular arrhythmias and of cardiovascular (CV) mortality. However, principal component analysis (PCA) of the T-wave vector loop may more accurately represent repolarization abnormalities than QTd. Principal-component-analysis-ratio(PCAr) has been reported as new ventricular heterogeneity-marker. Relation of PCAr with QT-dispersion(QTd) and T-wave-alternans(TWA) is unclear.
Methods: In patients(pts) with old myocardial infarction (OMI,66 ± 8yrs,M/F=14/11), surface-ECG was recorded by Standard 12-lead ECGs were recorded with digital holter recorder. QT interval measurements were performed using interactive software (QT-Guard, GE Medical Systems) that detects QRS onset and uses a least-squares fitting method to identify T-wave offset from the intersection of the maximal slope of the terminal T wave with a threshold defined by the T-P segment.
Results: There were no significant clinical-characteristics-differences between TWA positive(+,n=13) and negative(-,n=12) groups. The PCAr of TWA+group was significantly higher than that of TWA-group(32 ± 19 vs 25 ± 10%, $p<0.05$). QTd in TWA+ group was significantly higher than that of TWA- group (49 ± 36vs26 ± 9ms,$p<0.05$).The PCAr correlated with TWA micro voltage (r=0.35, $p<0.05$) but there was no significant correlation between QTd and TWA-micro-voltage.

PS arprovides information that can be visualized by analogy as the long and short axis of the three-dimendional T-wave loop



Conclusions: PCAr represented ventricular heterogeneity more strongly than QTd, because it correlated with TWA micro voltage better than QTd. PCAr might be useful marker to predict malignant arrhythmia in OMI pts.

P2072 Prognostic value of QRS distorsion in acute myocardial infarction patients undergoing primary angioplasty

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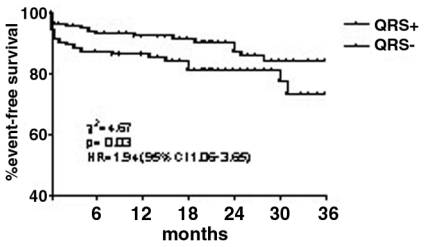
Background: QRS distorsion (J point ≥50% of R-wave voltage in leads with QR pattern; no S-wave in leads with RS pattern) indicates poor in-hospital and 30-day outcome in ST elevation acute myocardial infarction (AMI), likely due to more severe ischemia and faster progression of necrosis.
Methods: We evaluated clinical and prognostic correlates of QRS distorsion in 246 pts with extensive (ST elevation in ≥4 leads) AMI undergoing primary angioplasty (PTCA).
Results: QRS distorsion was present (QRS+) in 107 (43%) pts. QRS+ and QRS- groups did not differ as for age, sex, diabetes, hypertension, previous cardiac events, AMI site, peak CK-MB, symptom onset-to-balloon time, use of GPIIbIIIa inhibitors, number of stenotic vessels and collateral flow. QRS+ pts. had greater ST elevation (7±3.6 vs 4.4±1.7 $p<0.0001$), higher number of infarct-related leads (6.1±1.6 vs 4.4±1.7 $p<0.001$), less pre-infarction angina (56% vs 64% $p<0.05$), and more frequent occlusion of culprit vessel (81% vs 64% $p<0.001$) and TIMI flow <3 following PTCA (33% vs 20% $p<0.01$). In addition, QRS+ pts. had higher heart rate (87±20 vs 77±16 $p<0.01$), and more frequent Killip class >3 (19% vs 8% $p<0.005$) and ventricular fibrillation (26% vs 14% $p<0.05$)on admission. QRS+ pts. showed lower event-free survival for the combined end point of death and congestive heart failure at 20±13 months f.u. (figure). Ejection fraction and WMSI were similar in the 2 groups on admission; a significant ($p<0.005$) improvement was observed in QRS- group at 6-month evaluation as compared to baseline.



Conclusion: QRS distorsion identifies worse in-hospital and long-term outcome following primary PTCA and is associated to higher incidence of occluded infarct vessel and less functional recovery.

P2073 Electrocardiogram and symptoms correlation in a large family of Brugada syndrome related to a SCN5A mutation

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Purpose: Brugada syndrome (BS) is an inherited syndrome defined by an ST segment elevation and a risk of ventricular fibrillation. Genetic screening was proposed in a large family with BS and correlation between molecular findings and clinical data was assessed.
Methods: Clinical data were recorded for medical history, physical examination and ECG parameters in a 69-year old male proband and 25 family members (5 to 74 years old). Mutation analysis in SCN5A was performed by PCR-SSCP. Flecainide challenge and electrophysiological study (EPS) were proposed to family members in case of ST elevation (STE) in V1-V2 leads or positive genetic testing.
Results: SCN5A mutation (2850delT) was detected in the proband and 11 family members. Mutation led to a premature stop codon and produced a non functional protein missing domains III and IV. Among the 12 carriers, 5 were symptomatic (32-57 years old at first symptom) with various spontaneous documented ventricular arrhythmias (monomorphic or polymorphic VT and VF with late ventricular extrasystole coupling onset) and 7 were asymptomatic (14-73 years old). 92% (11/12) of carriers had an abnormal ECG - transient BS pattern (4/5 in symptomatic and 1/7 in asymptomatic carriers) or permanent conduction disorders (11/12) - whereas 100% (14/14) of non carriers had normal ECG. In carriers, PR interval was prolonged (203.5±43.1 vs 137.8±18.6 ms, $p<0.001$), QRS axis was deviated (4/12), QRS duration was higher (116.7±25.3 vs 85.6±8.8 ms, $p<0.01$) and STE was higher in V2 lead (+1.25±1.25 vs +0.39±0.65 mm, $p<0.05$). Among 3 asymptomatic carriers submitted to electrophysiological or pharmacological tests, 2 (aged 51 and 73 years) were considered silent carriers as flecainide challenge was negative and they were non-inducible at EPS and 1 had dome-shape ECG at screening but non-inducible at EPS and received an ICD.
Conclusions: Genetic screening in BS was effective in this family to diagnose carriers. Inter-individual variability was observed in ECG appearance and ventricular arrhythmias from the severe symptomatic proband to the silent carriers. Carriers had frequently conduction disorders at baseline in absence of STE. These permanent conduction disorders (prolonged PR interval or QRS duration and left anterior or left posterior fascicular blocks) need to be considered for diagnosis of BS.

P2074 Distortion of the terminal portion of the QRS on the admission electrocardiogram in acute myocardial infarction provide worse long-term prognosis

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Purpose: The value of admission electrocardiogram (ECG) for the diagnosis of acute myocardial infarction (AMI) and in-hospital prognosis is well established. However, its prognostic ability for long-term prognosis was not clarify and this is the aim of the study.
Methods: In a prospective study 288 (217 men) consecutive post AMI patients (pts) aged 64.2±0.7 (SE) years with a first anterior AMI were studied. Pts with atrial fibrillation, bundle branch block, intraventricular conduction defects or ventricular rhythm were excluded. According to admission ECG pts were allocated in 3 groups: Group A contained pts with tall symmetric T waves without ST-segment elevation. Group B comprised pts with tall symmetric T waves and ST-segment elevation in >2 adjacent leads and Group C comprised pts with tall symmetric T waves, ST-segment elevation and distortion of the terminal portion of QRS (emergence of J point >50% of the R wave in leads with qR configuration or disappearance of the S wave in leads with Rs configuration) in >2 adjacent leads; 192 pts were treated with thrombolytic treatment. Infarct size was estimated on 12-lead ECG by QRS score based on Q and R wave duration and R/S and R/Q ratio before hospital discharge. Signal averaged ECG (SAECG) was assessed on 3rd day in time domain by late potentials (LP) and frequency domain by spectral temporal mapping. Killip class on admission, maxCPK and maxCPK-MB and echo-left ventricular ejection fraction (LVEF) were also determined.
Results: During a follow-up period of 39+0.8 (SE) months there were 93 (82.2%) cardiac deaths. In univariate analysis group C pts vs group A and B pts differ in age, LVEF, LP, maxCPK and maxCPK-MB, QRS score and Killip class. In multivariate logistic regression analysis age (p=0.001), LVEF (p=0.001), Killip class on admission (p=0.001), LP (p=0.001) and type C ECG were independent predictors of cardiac long-term mortality. The probability for cardiac death was 5.7%, 32.7% and 58.6% in groups A, B and C respectively.
Conclusions: The distortion of terminal portion of QRS on the admission ECG provide an early estimation of long-term prognosis and would justify more aggressive reperfusion measures.

P2075 QRS dispersion: an electrocardiographic index of systolic left-ventricular dysfunction in patients with left bundle branch block

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Purpose: The presence of complete left bundle branch block (LBBB) in patients with congestive heart failure (CHF) has been proposed to be a factor that negatively affects left ventricular (LV) systolic function. Recently, the interlead dispersion of QRS interval (QRSD) has been suggested to be associated with mortality in CHF patients. The aim of this study was to evaluate the relative predictive value of QRSD and QRS duration (QRSd) in relation to systolic functional status of the left ventricle.
Methods: In this prospective study the ejection fraction (EF) of 130 consecutive patients with LBBB was evaluated by standard echocardiographic methods, whereas QRSd and QRSD were measured manually on surface electrocardiograms that recorded simultaneously the 12 standard leads. The relationship between QRSd, QRSD and EF was then studied.
Results: Sixty-eight (52%) patients had had CHF, 31 (24%) structural heart disease without CHF, and 31 (24%) isolated LBBB. The LVEF was negatively related to: QRSD (r= -0.625, p <0.0001), QRSd (r= -0.376, p <0.0001) and age (r= -0.207, p =0.019). Linear regression analysis identified QRSD (r= -0.622, p <0.0001) and age (r= -0.163, p=0.019) as the only independent predictors of LVEF, with the former having the strongest relationship. By using a QRSD value of 40 ms as a dichotomus, patients could be divided into 2 groups differed significantly and independently in LVEF (34 ± 12 vs 52 ± 12, p <0.0001).
Conclusions: The interlead dispersion of QRS-interval in patients with complete LBBB is strongly related to left ventricular contractility. We therefore suggest that this simple electrocardiographic index may serve as a useful screening test for detection of patients with LV systolic dysfunction.

P2076 Exercise-induced QTc dispersion as a maker of the viability of infarct-related myocardium after successful coronary angioplasty

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It is not clarified whether QT dispersion is useful to detect the viability of infarct-related myocardium after successful coronary angioplasty. The aim of this study was to evaluate the relationship between QT dispersion and viability of reperfused infarct-related myocardium. Methods: In sixty-seven patients (60.6 ± 11.5 years) with Q wave myocardial infarction after successful direct angioplasty and without the stenosis of coronary artery excluding the infarct-related vessel, exercise thallium-201 single photon emission computed tomography (SPECT) and cardiac catheterization were performed at 6 months after reperfusion. The number of perfusion defect areas (DS) on SPECT images and the QT interval on 12 ECG leads were measured at rest and exercise simultaneously. The QT intervals were corrected for heart rate (QTc), and the QTc dispersion was calculated from the difference between the maximum and minimum QTc intervals. The regional motion in the infarct-related wall was visually scored as follows: 0 - akinesis or dyskinesis to 3 - normal. Results: In fifty-six patients with resting perfusion defects, the QT dispersion was not related to the DS at both rest and exercise, but the change in DS from rest to exercise was related to the change in QTc dispersion (y=0.6-4.4X, r=0.515, p<0.0001). When the patients were divided into 2 groups as follows: group A, 29 patients with the increase of QTc dispersion from rest to exercise, and group B, 27 patients with the decrease of QTc dispersion, the DS was reversible at exercise significantly in the group A (6.0 ± 4.2 at rest to 4.8 ± 3.7 at exercise, p<0.05), but not the group B (5.0 ± 3.8 at rest to 5.3 ± 4.4 at exercise, p=not significance). Although the peak creatine kinase in the acute phase and the DS at rest and exercise were comparable between 2 groups, the regional wall motion (the wall motion score) and the left ventricular ejection fraction (LVEF) was improved significantly in the group A (score: 0.5 ± 0.6 to 1.4 ± 1.2, p<0.01, and LVEF: 45.1 ± 11.9% to 53.2 ± 11.4%, p<0.05) but not the group B (score: 0.4 ± 0.7 to 0.9 to 1.0, and LVEF: 47.7% ± 8.1% to 51.5 ± 10.2%, p= not significance). Conclusions: The change in QTc dispersion during exercise may be a good indicator of the viability of infarct-related myocardium and the functional recovery.

P2077 The diagnostic value of negative U-wave in acute coronary syndromes without ST-segment elevation

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Background: The negative U wave is frequentlly considered as a subtil diagnosic marker during myocardial ischemia but it has a high specificity but low sensitivity.
Aim: We tried to establish the true significance of negative U wave in patients with acute coronary syndromes (ACS) without ST segment elevation. In adition,we studied the prevalence of negative U wave in this patients (pts.).
Methods: We studied ECGs of 112 consecutive patients admitted with diagnosis of ACS without ST elevation and in patients who presented transitory negative U wave on ECGs we examined coronary angiographies and evaluated the extent of severity of coronary artery disease.
Results: We found transitory negative U waves at 19% pts. with ACS without ST elevation. Coronarographic analysis showed 74% pts with multivessel disease, 86% had proximal left anterior descendent (LAD) lesions, 72% had kinetic change, 59%had collateral circulation and 84% had important sistolic disfunction (ejection fraction less than 35%), all sugested a large myocardial involvement.
Conclusions: The rate of prevalence of negative U wave in pts. with ACS without ST sgment elevation was 19%. Our study sugested that a transitory negative U wave is asociated with estensive coronary and ventriculary involment. Its presence seems to be a noninvasive marker of proximal LAD lesions and indicated altered ventricular kinesis secondary to ischaemia of a large myocardial infarction.

P2078 Localization and stimulation rate-dependence of the U-wave in intracoronary electrocardiogram. Are M cells the basis of the U-wave?

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Background and Purpose: In general, body surface U wave is most frequently detected in leads V2-V4 by standard body surface electrocardiogram (S-ECG), but the mechanism of U wave formation is not clearly understood. Although intracoronary electrocardiogram (IC-ECG) using a PTCA guide-wire (GW) is known to be more sensitive in documenting U wave and detecting the local ECG changes compared to S-ECG, there have been no detailed reports on the localization of U wave by IC-ECG. So we investigated the localization of U waves with epicardial and intramural IC-ECG mapping.
Subjects and Methods: We developed a new PTFE-covered PTCA guide-wire (GW) with the entire GW shaft insulated by PTFE tube except for 3 mm at the tip, which allows for IC-ECG only from the GW tip to be obtained so that mapping in various coronary artery sites can be performed. We studied the distribution and incidence of U wave in 34 cases of elective PTCA using this GW. U wave according to IC-ECG was defined as positive or negative deflection of more than 1 mm (0.1 mV) in height, detected after T wave. In some cases we examined the relationship between stimulation rate and time to peak T wave (QaT) and U wave (QaU).
Results: The incidences of U wave at various coronary sites (in AHA segmentation) were as follows. QaT and QaU at stimulation rate 60, 80 and 100/min were 319 $\pm$ 21(100%), 309 $\pm$ 17(97 $\pm$ 3%),287 $\pm$ 11(90 $\pm$ 6%) msec and 542 $\pm$ 28(100%), 460 $\pm$ 31(85 $\pm$ 4%),387 $\pm$ 27(72 $\pm$ 6%) msec, respectively (n=8, $p<0.001$)
Conclusion: The present study confirms that U wave is observed very high frequently at various sites of the left ventricle, and QaU is more strongly affected by stimulation rate than QaT. These findings may indicate that heterogeneity of repolarization exists within the various sites of the left ventricular wall, which may be based on M cells.

P2079 Quantitative T-wave analysis predicts 1-year prognosis and benefit from early invasive treatment in the FRISC II-study

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Purpose: T-wave abnormalities are the most common electrocardiographic occurrences in patients with non-ST-segment elevation acute coronary syndromes. Although these abnormalities are currently considered relatively benign, a more quantitative approach to analysis of T-wave changes could improve its diagnostic and prognostic value. The purpose of this study was to investigate the prognostic value of T-wave abnormality in patients with non-ST-segment elevation acute coronary syndromes. And further, to evaluate T-wave abnormality as an instrument to predict benefit from an early invasive treatment strategy.
Methods: In 1609 patients with non-ST-segment elevation acute coronary syndromes the T waves in the admission electrocardiogram were quantitatively analysed in relation to normal amplitude values. The study endpoints were death and myocardial infarction in a 1-year follow-up period.
Results: The results confirmed the prognostic importance of certain T-wave abnormality categories in patients with non-ST-segment elevation acute coronary syndromes. Patients with more than 4 leads with abnormal T waves had a higher risk when not treated with an early invasive therapy, but could be brought the same level of risk as the remaining patients with this treatment regime.
Conclusions: Although ST-segment depression remains one of the strongest predictors of outcome in patients with non-ST-segment elevation acute coronary syndromes, a new quantitative approach to T-wave analysis on admission adds to the predictive information on the electrocardiogram, and predicts benefit from invasive treatment. The results suggest that early risk stratification in these patients should include quantitative T-wave analysis. Whether these new T-wave criteria can further improve existing multivariate predictive models remains to be shown.

P2080 P-wave dispersion and left atrial appendage function for predicting recurrence after conversion of atrial fibrillation and relation of P-wave dispersion to appendage function

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Objectives: We investigated P wave dispersion and left atrial appendage (LAA) function for predicting atrial fibrillation (AF) relapse and the relation of P wave dispersion to LAA function.
Methods: Sixty-four consecutive patients with AF $<$3 months (30 men, mean age:61$\pm$10 years) were analyzed to predict the six-month AF recurrence after conversion of AF. P wave duration and dispersion were measured in all 12 leads of electrocardiogram. Transthoracic and transesophageal echocardiography were used to evaluate the functions of the left ventricle, left atrium (LA) and atrial appendage (LAA).
Results: At six-month follow-up, 28 patients (mean age:62$\pm$11 years) had AF relapse and 36 patients (mean age:61$\pm$10 years) remained in sinus rhythm. There was no difference between patients with and without AF relapse in gender, age, and underlying heart disease, AF patterns, left ventricular function and maximal LAA area. AF duration $>$ 5 days, LA size $>$ 45 mm, maximal P wave duration $>$ 112 ms, P wave dispersion $>$ 47 ms, presence of spontaneous echo contrast, minimal LAA area $>$ 166 mm^2 and LAA emptying velocity $<$36 cm/s were univariate predictors for relapsing AF (each $p<0.05$). By multivariate analysis, LA size ($p=0.02$), P wave dispersion ($p<0.001$) and LAA emptying flow ($p=0.01$) identified the patients who had recurrent AF. The accuracy values of these three parameters were 91%, 97% and 72% respectively.
Conclusion: The dilated LA, prolonged P wave dispersion and depressed LAA emptying flow can identify the patients at risk for recurrence after conversion of AF during six months.

P2081 T-wave morphology analysis in hypertrophic cardiomyopathy

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This study investigated the association between T wave morphology analysis and risk factors (RF) for sudden death (SD) (i.e. previous cardiac arrest, non-sustained ventricular tachycardia (VT) on Holter monitoring, abnormal exertional blood pressure response (ABPR), unexplained syncope, a family history of premature SD, and severe left ventricular hypertrophy $\geq$30 mm) and clinical outcome in patients with hypertrophic cardiomyopathy (HC).
Method: Ten consecutive 12-lead ECGs were recorded from each of 157 patients with HC (107 men, age 43$\pm$15, 14-79 years) using a digital electrocardiograph (MACVU, GE Medical Systems, WI, USA) with a sampling rate of 500 Hz. Study patients were followed up for 60$\pm$44 months. Analysis of the digital ECG recordings was performed in a fully automatic manner with custom-developed software implemented on a personal computer. The analysis program performed a singular value decomposition of the ECG signal into a minimum dimensional space calculated 3 indices: complexity ratio (CR), the total cosine R-to-T (TCRT), and relative T-wave residuum (TWR%), which evaluated the ratio of the singular value of the second most important component to the square root of the sum of the squares of all 8 singular values, repolarisation wavefront direction, and local electrical heterogeneity, respectively.
Results: TWR% and CR were significantly increased in patients with any risk factor (RFpos) and in those with 2 or more risk factors (RF2) (table). TCRT was not associated with RF but with cardiac events (cardiac death, VF, ICD discharge, n=14) and cardiac death (n=9) compared with survivors without any cardiac events (-0.67$\pm$0.35 v -0.43$\pm$0.47, p=0.03; -0.71$\pm$0.36 v -0.43$\pm$0.47, p=0.035, respectively). A weak and statistically significant correlation was found between TCRT and maximum left ventricular wall thickness (r=-0.23, p=0.004).

	CR	TCRT	TWR%
RF0	0.20 (0.09)	-0.41 (0.48)	0.06 (0.07)
RFpos	0.25 (0.14)*	-0.48 (0.45)	0.14 (0.17)**
RF2	0.23 (0.12)	-0.46 (0.50)	0.11 (0.08)**

*$p<0.05$, **$p<0.01$ for comparison between RF0 v RFpos or RF2

Conclusion: Abnormalities in T wave morphology are associated with risk factors and clinical outcome in HC patients.

HEART RATE VARIABILITY AND MAPPING TECHNIQUES II

P2082 Increased heart rate and reduced heart rate variability are associated with subclinical inflammation in healthy middle-aged and elderly subjects

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Background: Increase in inflammatory markers, heart rate and reduced hear rate variability (HRV) are all strong markers of mortality in various studies of cardiovascular and epidemiological studies. The associations between these markers have not been investigated before.
Methods and Results: 643 healthy men and women between 55 and 75 years of age and with no prior history of cardiovascular disease or stroke were included in the study. Baseline examination included physical examination, fasting laboratory testing and 48-hour ambulatory ECG monitoring. We selected the time domain components of HRV for further analyses. C-reactive protein and white blood cell (WBC) count were selected as markers of inflammation. After identification of parameters related to measures of HRV we used regression analyses (with forced entry of sex and age) for evaluating the independent associations. A low HRV as measured by decreased standard deviation of the time between normal complexes was associated with smoking, C-reactive protein, WBC count, blood sugar, triglyceride concentration, female gender and diabetes. Physical activity in contrary was strongly associated with a high HRV. In multivariate regression analyses both increased heart rate and reduced HRV were significantly related to WBC count or C-reactive protein after correction for relevant covariates.
Conclusions: Reduced HRV and increased heart rate are associated with subclinical inflammation in healthy middle-aged and elderly subjects. This may suggest that sympathetic overactivity could enhance inflammation and may have a more important role in the pathogenesis of atherosclerosis than previously anticipated.

P2083 Abnormal turbulence slope as a cardiac death predictor in patients undergoing coronary revascularization

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Background: Heart rate turbulence (HRT) is considered as one of the most promising Holter-derived predictors of cardiac death. Coronary artery bypass grafting (CABG) has been proved to decrease the risk of cardiac death. So far, there is no data concerning the predictive value of HRT parameters in patients undergoing CABG.
Methods In 111 pts (97 males, 14 females, mean age 63 yrs) undergoing CABG, 24-hour Holter monitoring with HRT analysis was performed before CABG. HRT parameters included turbulence onset (TO) and turbulence slope (TS). Death was considered as the endpoint of the study.
Results: During 1-year follow-up 13 pts (12%) died, all of them of cardiac causes. Median values of clinical data, HRT parameters as well as p- values (U- Mann Whitney test) are shown in a Table
After adjustment for clinical covariates in a multivariate Cox model, TS was significantly and independently associated with cardiac death in patients undergoing CABG: HR=1.25 per 1 ms/RR decrease (95%CI =1.06-1.45; p=0.012). When dichotomized TS (at $<$4.25ms/RR – in first quartile) was tested in the Cox model HR = 8.93 (95%CI = 2.14-37.33; p=0.003).

Comparison of survivors and non-survivor

	Survivors	Non-survivors	p
	N=98	N=13	
Age (yrs)	62	69	0.001
LVEF (%)	54	48	0.110
TO (%)	-1.39	-1.01	0.260
TS (%)	8.75	2.94	0.0001

Conclusions: Abnormal TS evaluated pre-operatively in coronary patients undergoing CABG surgery identifies individuals with an increased risk of mortality during long-term follow-up. TO does not have predictive value in CABG patients.

P2084 Severe bradyarrhythmias in patients with sleep apnea syndrome: the effect of n-CPAP therapy. A long-term study with the use of implantable loop recorders

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Purpose:
Several studies have described severe bradyarrhythmias in patients with obstructive sleep apnoea hypopnea syndrome(OSAHS) but there is a great variation in their incidence, mainly because they were evaluted by means of short-term Holter ECG recordings. The aim of this study was to clarify the incidence of extreme bradyarrhythmias in such patients and to evaluate the effect of long-term Continuous Positive Airway Pressure (CPAP) treatment.
Methods: We prospectively enrolled 23 patients (16 men, 50$\pm$ 11 years) after the diagnosis of OSAHS. In all of them an implantable loop recorder with the ability to record the heart rhythm for 18 months was implanted. In this part of the study, we looked for cardiac pauses $>$ 3 sec, two months before the treatment was initiated and two months after. During the same time interval, the patients underwent two 48 hour Holter recordings.
Results: During the 2 month period before treatment, the implantable loop recorder revealed that 35% of patients demonstrated extreme bradyarrhythmias. The percentage by 48 hour Holter was only 9%. In the two months following the initiation of treatment, the incidence of pauses recorded by the implantable loop recorder was reduced to 13% (p=0.06) and by 48 hour Holter, to 4% (p=NS). The Holter recorded pauses only in patients with very frequent episodes recorded by the implantable loop recorder.
Conclusion: About one third of patients with OSAHS evidence long periods of asystole, which tend to reduce by CPAP treatment. Holter recordings used until now seem unable to precisely describe the incidence of severe bradyarrhythmias and the effect of treatment.

P2085 Evolution of the arrhythmia burden following ablation of atrial fibrillation: significance of early recurrences

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The temporal evolution of the arrhythmia burden after radiofrequency catheter ablation (RCA) in patients with focal atrial fibrillation (AF) is not well known. Specifically, there has been contradictory opinions concerning the predictive role of early AF recurrences.
Methods: We studied prospectively these issues by performing serial 24-hour Holter recordings before and after 30 consecutive RCA procedures on drug-refractory AF of presumed focal origin, and correlated these findings with the clinical outcome of each procedure. The RCA was considered successful if the patient's overall symptoms improved in a specific arrhythmia-related symptoms questionnaire obtained during the follow-up (median 8.3 months after RCA).
Results: Spontaneous or induced ectopic activity was used to guide the RCA. Empirical pulmonary vein isolation was performed only in 2 procedures. A median of 1.5 substrates were ablated per patient (P25, P75 = 1, 2). Twenty two procedures (73%) were successful. In these procedures atrial ectopic beats (AEB), atrial tachycardia (AT) runs and the maximal number of consecutive AT beats were reduced progressively (Table). On the contrary, unsuccessful procedures had no significant changes in the arrhythmia burden. Immediate post-RCA AF was recorded in 14% of successful and in 71% of unsuccessful procedures; odds ratio (95% confidence interval)=0.07 (0.01 to 0.45); p=0.005.

	Pre-RCA	Immediate post-RCA	Late post-RCA
Recording day (relative to RCA day)	-47 (-76, -27)	1 (1, 2)	41 (34, 94)
AEB (n)	409 (37, 8025)	80 (33, 1036)	17 (1, 119)
AT (n)	18 (1, 145)	0 (0, 3)	0 (0, 1)
Consecutive AT beats (n)	6 (0, 20)	0 (0, 6)	0 (0, 2)
AF time (min)	17 (1, 1200)	0 (0, 0)	0 (0, 0)

Data are median (P25, P75) per 24-hour recording. Al p values are $<$0.01.

Conclusions: Early Holter recordings are useful to assess the clinical outcome of RCA in patients with focal AF. Successful procedures are followed by an immediate great reduction of the AEB and AT runs. AEB also exhibits an additional lesser reduction in the following weeks. Although early AF recurrences may be observed after effective procedures, they are a strong predictor of an unsuccessful RCA.

P2086 Documentation of life-threatening ventricular tachyarrhythmias by means of an insertable loop recorder

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Background: CARISMA is a multicenter study enrolling patients with acute myocardial infarction (AMI) and ejection fraction =< 40% in whom an insertable loop recorder (ILR, Reveal™ Plus 9526, Medtronic Inc.) is implanted to assess the incidence of tachy- and bradyarrhythmia episodes during a 2-year follow-up period. Various risk stratification tests, including electrophysiological (EP) testing, are performed at 6 six weeks post-AMI. The feasibility of using the ILR to automatically document ventricular tachycardia (VT) or fibrillation (VF) was assessed during the EP testing.
Results: Sustained ventricular tachyarrhythmias were induced in 18 of 84 CARISMA patients. All VT episodes (9 monomorphic, 1 polymorphic) and 6 of 8 VF episodes were automatically detected by the ILR. Two VF episodes were not detected, probably due to the built-in ILR noise detection feature: this algorithm prolongs the ILR refractory period when signals with a cycle length shorter than 150 ms are detected. Fast ventricular rhythms might therefore have been classified as noise and not stored in the ILR memory. In 7 of 10 VTs, the ILR was activated through the tachycardia counter. In the other cases (3 VT, 6 VF), the arrhythmia-associated changes in QRS axis and amplitude resulted in a temporary loss of R wave detection and in the activation of the asystole counter.
Conclusions: The ILR successfully detects the majority of induced ventricular tachyarrhythmias and may therefore be used for continuous monitoring of post-MI patients deemed at high risk for life-threatening arrhythmias. However, coarse VFs with a short cycle length, which do not degenerate into asystole, may remain undetected.

P2087 Influence of coronary revascularization on heart rate turbulence parameters: 1 year follow-up

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Background: Coronary artery patients may benefit from revascularization, that decreases the risk of sudden death. As heart rate turbulence (HRT) is a new method of cardiac death risk prediction, so far there are no data concerning the influence of coronary artery bypass graft (CABG) surgery on its parameters. The aim of this study was to evaluate the influence of CABG on HRT parameters assessed in one-year follow up.
Methods: A group of 76 pts (62 M, 14 F, mean age 63 yrs) with multivessel coronary artery disease, who underwent CABG was studied. In all these patients 24-hour Holter ECG monitoring was performed before and 3 months and one year after surgery to evaluate HRT parameters: T onset (TO) and turbulence slope (TS) as well as heart rate variability (HRV) parameters (both time and frequency domain)
Results: Median values of pre- and postoperative HRT and HRV parameters as well as p-values of Wilcoxon's paired test are shown in a table

Pre- and postoperative HRT and HRV value

	A	B	C	p	p	p
	before CABG	3 months after CABG	1 year after CABG	A vs.B	A vs.C	B vs.C
TO (%)	-1.49	-0.64	-1.18	0.005	0.460	0.006
TS (ms/RR)	8.73	6.81	6.82	0.010	0.026	0.810
av RR (ms)	909	843	862	<0.0001	0.020	0.030
SDNN	120	108	130	0.001	0.270	0.0002
rMSSD	32	30	33	0.810	0.620	0.240
LF	640	365	475	<0.0001	0.004	0.380
HF	225	144	182	0.040	0.310	0.140
#VBPs	25	44	39	0.004	0.003	0.080

Conclusions: Significant impairment of HRT parameters in postoperative period in CABG patients suggests that HRT parameters should not be used for stratification purposes in patients up to 1 year after CABG until a firm evidence for their predictive value using newly determined cutoffs is established.

P2088 Heart rate variability, turbulence and dynamics as predictors of sudden cardiac death after myocardial infarction in the beta-blocking era

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Background: Beta-blocking (BB) medication may alter the impact of risk markers of sudden cardiac death (SCD) in patients after an acute myocardial infarction (AMI).
Methods and Results: A consecutive series of 700 patients (mean age 62±10 years) with an AMI was included in this prospective follow-up study. BB-therapy was prescribed for all patients, adherence to its usage being 97% at discharge, and 95% at one after the AMI. The end-points were SCD and non-sudden cardiac death (non-SCD). Standard deviation of N-N intervals (SDNN), postectopic turbulence onset (TO), turbulence slope (TS), short-term fractal scaling exponent (alfa) and power-law slope (beta) were assessed from 24-hour ECG recording at the time from discharge from hospital. During a mean (±SD) follow-up of 43±15 months, 37 non-SCDs (5.3%), and 23 SCDs (3.3%) occurred The hazards ratio (HR) of each measure as a predictor of SCD or non-SCD, respectively, in Cox regression analysis are presented in the table. All measures predicted the occurrence of non-SCD, but only TS and beta predicted SCD. After adjusting for age and ejection fraction, neither TS or beta remained as significant predictors of SCD (NS for both).

HRV indices

	SCD (HR+/-95%CI)	non-SCD (HR+/-95%CI)
SDNN <70 ms	1.6 (0.6-4.2)	2.2 (1.1-4.8)*
TS < 2.55	3.6 (1.2-10.6)*	5.0 (2.0-12.1)***
TO > 0	1.1 (0.4-2.9)	2.3 (1.0-5.6)*
alfa < 0.75	2.6 (0.6-11.2)	10.2 (4.6-22.6)
beta < -1.55	2.9 (1.1-7.4)*	3.7 (1.7-8.0)**

*p<0.05, **p<0.01, ***p<0.001

Conclusions: BB-therapy alters the impact of HR variability, turbulence and dynamics in prediction of SCD. All these measures still provide prognostic information on the risk of non-SCD.

P2089 The sinus nodal tissue arrangement into the musculature of the terminal crest: implications in ablation of inappropriate sinus node tachycardia

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Treatment of inappropriate sinus node tachycardia (IST) with radiofrequency (RF) catheter ablation has lower success rates than those attained in other atrial tachycardias. This anatomical study aims to clarify the morphology of the sinus node (SN) from the perspective of transcatheter nodal modification for IST.
Methods: In 47 normal human heart specimens (49±20 years; 31 male),we examined the shape and dimensions of the SN by histological sections and scanning electron micrographs containing the superior cavo-atrial junction.
Results: The thickness of the terminal crest ranged from 3-10 mm. The node is generally irregular and fusiform in shape with the uppermost portion described as the head, followed by the body and a tapering tail. Table shows the length, width and thickness of the three portions (mean±SD and range in mm)of the SN. In the majority of cases the long axis of the sinus node was parallel to the terminal groove. The nodal cells always within a matrix of connective were arranged as interlacing strands of specialized myocytes that are smaller than working atrial myocytes. The tail of the sinus node in 61% of specimens was separated by fibrous tissue into islands of specialised cells. Short nodal extensions could be traced in most of the hearts passing superiorly (0.5 to 1.5 mm in length) towards the superior vena cava (18 specimens, 38%) and inferiorly (0.3 to 2.3 mm in length) ending in the subepicardium (12 specimens, 25%) or deeper into the ordinary myocardium (26 specimens, 55%).

Dimensions of the sinus node (mm)

	Length	Width	Thickness
Head	2.2 ± 1.2 (1-4)	2.4 ± 0.7 (1-3.5)	1.2 ± 0.3 (0.5-2.2)
Body	9.5 ± 2.3 (6-14)	5.3 ± 1.5 (2.2-8.3)	1.5 ± 0.5 (0.5-3.5)
Tail	1.6 ± 0.5 (1-3.5)	1.1 ± 0.2 (0.4-1.5)	0.4 ± 0.1 (0.1-0.9)

Conclusions: The sinus nodal tissue tends to be non-uniform in shape with irregular extensions and branching into the musculature of the terminal crest. These findings probably accounts for the difficulties during RF ablation of IST.

P2090 Long conduction time in Coumel type accessory pathways: slow conduction or a ventricular insertion away from the ventricular base?

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The reason for the long conduction time of Coumel type accessory pathways (AP) is unknown. A ventricular insertion (VI) close to the ventricular apex and away from the cardiac base, like in the Mahaim syndrome, has been suggested and supported by an anatomic description. The aim of the present study was to localize the VI of Coumel type APs by pacing from different ventricular sites looking for the shortest stimulus to atrial activation interval (SA).

Methods: The study was conducted in two phases. The SA approach for localizing the AP VI was validated in 34 consecutive patients with a single, left free wall, and concealed AP in the first phase of the study. Successful AP localization and ablation with 5 or less radiofrequency pulses (mean 1.6±1.0, median 1) was achieved by the SA interval approach without the guidance of other mapping techniques in 25 of these patients (74%).

Ten consecutive patients (6 male, 49±17 yo) with a Coumel type AP (non apparent anterograde conduction and decremental retrograde conduction with VA interval >150 ms) mediated AV reentrant tachycardia were prospectively included in the second phase of the study. Tachycardia entrainment was attempted in all of them by bipolar pacing with a constant cycle length (10-20 ms shorter than the tachycardia cycle length) from the following sites: right ventricular (RV) apex, RV septal base, RV lateral base, RV perihisian region, left ventricular (LV) apex, LV septal base, LV lateral base, and sites between those with the shortest SA.

Results: Stable tachycardia entrainment was achieved in all patients except the one with tachycardia cycle length oscillations (>20 ms). The AP atrial insertion (AI) was found in the coronary sinus ostium in 7 patients, the mitral annulus in 2 and the inferior tricuspid annulus in 1. The IV (SA 64±18 ms shorter than the SA recorded while pacing from the RV apex) was found in the LV inferoseptal base in 6 patients, the RV perihisian region in 1 and the RV inferoseptal base in 1. The AP conduction was transiently abolished by the first radiofrequency pulse delivered to the LV inferoseptal base in the only 2 patients in whom ablation at the VI was attempted after failure of the attempt at AI ablation.

Conclusions: Long conduction time of Coumel type APs cannot be explained by a VI away from the ventricular base. The LV inferoseptal base appears to be the typical VI, similar to that seen for the AI, which is commonly found in the coronary sinus ostium.

P2091 Conduction across the whole cavo-tricuspideal isthmus or preferential conduction in common atrial flutter?

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Background: The cavo-tricuspideal isthmus (CTI) is often divided in two contiguous structures with different muscular composition and disposition: the vestibule (V), which is adjacent to the tricuspid valve, and the pouch-like recess (R), which is adjacent to the inferior venae cava orifice. Whether the activation front of common atrial flutter (AFT) is preferentially conducted through one or both structures is unknown.

Methods: We prospectively studied 23 consecutive patients with AFT. Entrainment was performed by pacing from the V, the R and the VR junction with a cycle length (CL) 10-30 ms shorter than the AFT CL in all of them. The difference between the first post pacing interval (PPI) and the AFT CL was calculated. Proper mapping catheter positioning in each site was demonstrated by a non-fluoroscopic 3-D navegation system (localisa©;) in all patients. In addition, validation of the VR junction was performed by right atrium angiography while the mapping catheter was positioned in this specific site. Linear radiofrequency application by a 4-mm tip catheter was initiated in the structure showing a shorter PPI. Radiofrequency (RF) application was stopped and the PPI determination protocol repeated whenever a significant AFT CL prolongation (>20 ms) was observed.

Results: The stimulation protocol could not be terminated in 8 patients (recurrent induction of atrial fibrillation, AFT termination, etc). No significant PPI differences across the CTI were found in 4 patients. No AFT CL prolongation during RF application was observed in none of these 4 patients, who required complete CTI RF application for AFT termination. AFT termination (4 patients) or CL prolongation (7 patients) was observed in the 11 remaining patients, in whom RF application was initiated at the segment with the shortest PPI (6 V, 5R). After AFT CL prolongation previous significant differences between AFT CL and PPI were absent in these structures in all the patients. RF application in these structures sites terminated the AFT.

Conclusion: Conduction through the CTI during common AFL is not homogenous in most patients, who may have a segment of preferential impulse conduction.

P2092 Echocardiographic predictors of non-valvular atrial fibrillation

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Background: In patients (pts) with atrial fibrillation (AF) structural heart disease is frequently present, however, some abnormalities may result from AF itself. Limited data exist about echocardiographic precursors of AF.

Aim: To detect echocardiographic predictors of AF in patients (pts) in sinus rhythm.

Methods and Results: Pts submitted to multiple (≥2) echocardiograms (ECOs) in our institution, between 1999 and 2002, were selected. Pts with congenital or valvular heart disease were excluded. Echocardiographic parameters, obtained at the time of the first ECO, were evaluated in order to assess the association to late AF.

693 pts (49% men; mean 58,1±11.2 years; range 25-83 years) were included. These pts have done 1687 ECOS (mean 2.4 ECOs/pt; range 2-7), over a mean period of 26± 9 months.

Forty-two pts (6.1%) developed AF. At the time of the basal ECO, this group was older (64.7 vs 57.7 years, $p<0.001$), had male predominance (74% vs 47%, $p<0.001$, AF hazard ratio (HR) for males =3.2) and more frequent regional wall motion abnormalities (14% vs 4%, $p<0.05$, HR 2.9), when compared with the group of pts maintaining sinus rhythm. LV global systolic function (shortening fraction =35±9 vs 37±9%, ns; ejection fraction =64±17 vs 65±16%, ns), wall tickness (septum 10,6±2,7 vs 10,4±2,5 mm, ns; posterior wall 10,5±2,8 vs 10,3±2,5 mm, ns) and left heart chambers dimensions (parasternal mean diameter: left atrium (LA) =37 vs 39 mm, ns; LV 49 vs 50, ns) were similar, but, in the first ECO with the pt in FA, LA dimensions were already increased (43 mm, $p<0.01$). Pts with posterior AF had lower transmitral E wave and lower E/A ratio in the basal ECO (E/A 1.03 vs 1.25, $p<0.001$, E<A HR=2.2; deceleration time 222 vs 235 ms, ns).

Conclusions: In pts without valvular heart disease, the presence of LV relaxation abnormality and regional wall motion abnormalities were associated with a higher risk of AF, before the occurrence of left atrium or LV dilatation and of LV global systolic impairment.

MANAGEMENT OF ATRIAL FIBRILLATION

P2093 Multisite atrial pacing to facilitate pulmonary veins isolation

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Connections between the left atrium (LA)and the pulmonary veins (PVs)constitutes a complex fiber network. Target of catheter ablation (CA) is to abolish the electrical activity around the PVs' ostia as to achieve effective PVs disconnection in paroxysmal atrial fibrillation (AF). The aim of the study was to investigate whether pacing at multiple atrial sites could facilitate identification of multiple connections between LA and PVs and, thus guiding segmental ablation of PVs'ostia at specific sites.Methods: Fifteen patients(13 males, mean age 51±9 years)with drug-refractory AF entered the study. Complete PVs isolation was achieved by conventional or irrigated tip electrode catheter in 42 PVs:15 left superior PVs(LSPV);12 left inferior PVs(LIPV);15 right superior PVs(RSPV). Recording of local electrical activity around the ostia was obtained by positioning a loop-shaped decapolar catheter; the LA-PV activation pattern for LSPV and LIPV was evaluated during pacing from distal coronary sionus (dCS), right atrial appendage (RAA), and interatrial septum (IAS); for RSPV from paroximal CS;RAA and IAS. Results: The LA-PV pattern of activation for LSPV was better defined during dCS pacing as compared to RAA and IAS (12 vs 3, $p<0.05$; 11 vs 4, $p<0.05$, respectively), while no significant difference was detected among the three pacing sites for LIPV and RSPV. In 9/15 LSPV (60%) and in 8/15 RSPV (53%)the sequence of activation of local PV electrograms was the same regardless the pacing site, suggesting a single, broad connecting fascicle mostly located at the antero-superior aspect of the ostium. This scenario was documented only in 3/12 (25%)LIPV, indicating the presence of multiple connecting fibers with more complex orientation in this vein.A mean number of 5 radiofrequency current (RF) applications (range 2-8) aiming at 30%-50% of ostium's circumference was required to isolate LSPV and RSPV, which showed a single activation sequence of electrograms.A mean number of 17 RF applications (range 15-22) aiming at nearly 90% of PV's ostium was necessary for LIPV, supporting the hypothesis of a complex fiber network. Conclusions: Multisite atrial pacing can identify a single, broad connecting fiber between LA and PV in most of LSPV and RSPV, encompassing nearly 50% of the ostium's circumference. A more complex fiber network is often documented in LIPV, requiring a more extensive CA aimed at about 90% of the ostium.

P2094 Can the pulmonary vein ostium be accurately defined by biplane angiography?

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Radiofrequency (RF) ablation at the ostium of the pulmonary veins (PV) may isolate drug-refractory atrial fibrillation. However, there is still little information on the association of the ostial diameter of the PV and AF. The purpose of this study was to investigate morphology and changes of all PV ostia pre-and post-ablation.

In 75 pts (f 19, m 56; mean 54 $\pm$ 7 years) with recurrent AF after primary catheter ablation aiming at selective PV isolation, a second or third procedure was attempted. A contrast dye injection into all PVs was performed to enable a biplane assessment of the ostial PV diameter pre- & post-ablation in comparison to the previous procedure. Moreover, a classification into different ostium types was made: type A: clear delineated ostium (OS); type B: only unilateral clear delineatable OS; type C: funnel-shaped OS without clear OS, type D: common OS of both superior and inferior PVs.

Type A was found in 34% (24/71) in the right superior PV (RSPV), in the left superior PV (LSPV) in 21% (15/71), in the right inferior (RIPV) in 26% (14/53) and in the left inferior PV (LIPV) in 30% (16/53) (n.s.). Type B occurred in 52% (37/71) in the RSPV, in 65% (46/71) in the LSPV and in 57% (30/53) in the RIPV and in the LIPV (n.s.). Type C was demonstrated in the RSPV in 9% (6/71), in the LSPV in 6% (4/71), in the RIPV in 9% (5/53) and in the LIPV in 9% (5/53) (n.s.). Type D was detected with the same incidence of 9% in the left and right PVs (n.s.). On the other hand the most common type of all PVs was Type B ($p < 0.01$). In comparison to the previous procedure the mean diameter of the RSPV was reduced from 18 $\pm$ 2 mm to 17 $\pm$ 3 mm, the diameter of the RIPV from 15 $\pm$ 3 mm to 14 $\pm$ 3 mm, the diameter of the LSPV from 18 $\pm$ 3 mm to 17 $\pm$ 3 mm and the diameter of LIPV from 17 $\pm$ 5 mm to 16 $\pm$ 4 mm (ns). The number of necessary RFC applications did not correlate with the ostium type. Acute PV stenosis had been demonstrated in 7 pts, while chronic PV stenosis developed during follow-up (after 7, 150 days) in 2 pts (8/9 pts$<$ 70%, in one 85%).

Due to complex anatomy of the pulmonary veins, the PV ostium was clearly determinable in 21-34% using biplane contrast angiography. In 99% of the patients ostial ablation did not induce significant changes in ostial PV diameters.

P2095 Analysis of ventricular rate before spontaneous termination of paroxysmal atrial fibrillation

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In the electrophysiology laboratory, slowing and pseudoregularisation of atrial activity often precede the spontaneous termination of paroxysmal atrial fibrillation (PAF) episodes. To evaluate whether such phenomenon might occur also during clinical PAF episodes, we analysed the ventricular rate during the final minutes of the arrhythmic episode, with the assumption that a less disorganised acivity at atrial level could be reflected by a pseudoregularisation of ventricular rate.

Methods: We studied 28 patients (67$\pm$10 years, 57% male) who presented, during Holter recordings, 42 episodes of PAF lasting 212$\pm$33min. Amiodarone or 1c anti-arrhythmic drugs were used in 12 subjects. For each episode, we measured mean RR interval, standard deviation of RR intervals (SDNN) and coefficient of variation (CV) during 5-minute periods corresponding to the beginning, central and final part of the arrhythmic episode. Sinus rhythm periods before and after PAF were also considered.

Results: Data in the Table are presented as mean $\pm$ SD. PAF episodes were characterised, as expected, by a shorter mean RR interval and a greater RR variability. However, when considering the 3 selected PAF periods, no reduction in either SDNN or CV could be observed before PAF termination. This pattern was also present in patients on antiarrhythmic treatment.

Mean RR interval, SDNN and CV

	Sinus rhythm before PAF	PAF, initial period	PAF, central period	PAF, final period	Sinus rhythm after PAF
RR interval (msec)	901$\pm$168	655$\pm$163	638$\pm$176	628$\pm$172	892$\pm$183
SDNN (msec)	75$\pm$61	142$\pm$42	132$\pm$48	131$\pm$54	65$\pm$37
CV%	8.5$\pm$6.7	12.3$\pm$11.9	10.7$\pm$10.5	11.6$\pm$11.1	7.3$\pm$4.3

Conclusions: Our data indicate that spontaneous recovery of sinus rhythm is not preceded by slowing or psudoregolarisation of ventricular response. Thus, the changes in atrial activity that occur before PAF termination do not seem to have major effects on ventricular response. It is therefore unlikely that improvement in hemodynamic conditions and consequent changes in autonomic activity might play a major role in facilitating arrhythmia termination.

P2096 Fatal and non-fatal complications in chronic permanent atrial fibrillation in 18 months period of observation. Dependency on different drug combinations

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Drug therapy for chronic atrial fibrillation (CAF) as an alternative to cardioversion is still a problem for discussion.

Purpose of the study is to evaluate the frequency of complications and mortality in pts with CAF with different therapeutic combinations for heart failure.

Methods: 74 pts with CAF were included in the study and then observed for 18 months. 50 male (64%) and 24 female (36%). Mean age 62+18,38 yr. Mean duration of CAF 113+134,35 yr (from 18 to 204 months). Diagnoses were CAD with arterial hypertension in 44 pts (59.5%), rheumatic heart disease in 13 pts (17.5%), arterial hypertension in 6 pts (8.1%), CAD in 5 (6.8%), cardiomyopathy in 6 pts (8.1%). All the pts had heart failure at the beginning of the study: 10 pts (13.5%) with the 1st functional class; 33 pts (44.6%) with the 2nd class; 31 pts (41.9%) with the 3d class. Thromboembolic prophylaxis with Warfarin was done in all cases. Patients were randomly divided into three groups of different medical combinations. Group 1 is 27 pts, who were given Digoxin, Metoprolol, and Enalapril. Group 2 is 24 pts on Metoprolol and Enalapril. Group 3 is 23 pts on Digoxin and Enalapril. Doses of the drugs were selected according to the heart rate and adequate BP control.

Results: Total amount of serious complications was: 15% in group 1; 21% in group 2; 39% in group 3. Stoke was the most frequent complication. Worsening of heart failure was observed in group 3 only; mortality also was higher in group 3 (8 pts, 35%), and was significantly higher then in group 1 (p=0.01). Most frequent causes of death were stroke (the most frequent reason in all groups), fatal arrhythmia, and worsening of heart failure.

Conclusions: Fatal complications were mostly observed in patients, who received combination of Digoxin and Enalapril. Few fatal and nonfatal complications were observed in patients, who received combination of Digoxin, Metoprolol, and Enalapril, so it can be recommended for the chronic use in patients with CAF.

P2097 Steroids and verapamil but not allopurinol are effective in preventing late extension of radiofrequency lesions: implications for the characterization of delayed effects of radiofrequency ablation

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Background: Delayed effects of radiofrequency (RF) ablation may occur, particularly as late AV block, but their mechanisms are unknown.

Aim: Lesion extension beyond the area of acute necrosis may be involved in the genesis of delayed RF effects. We explored the impact of anti-inflammatory and antioxidant drugs on the healing of 41 RF lesions (70°C, 60 sec) created on the right ventricular endocardium of 31 dogs.

Methods: Lesion size, histological and ultrastructural (US) characteristics in 3 zones extending from the visible lesion border, namely, A (0-3 mm); B (3-6 mm) and C (6-9 mm), were assessed acutely (n=7), and at follow-up (30 days) in controls (n=7); dogs (n=7) receiving combined therapy with allopurinol (400 mg po 24 and 2 hours before RF); verapamil (200 μg/kg iv 15 min before and after RF); hydrocortisone (10 mg/kg iv after RF) and prednisone (20 mg po for 29 days); dogs (n=3) receiving allopurinol plus verapamil; dogs receiving (n=3) hydrocortisone and prednisone; and dogs receiving verapamil (n=2) or allopurinol (n=2).

Results: Lesion size was similar in all groups, but decreased scar formation was noted in steroids-treated groups. Acutely and at follow-up, significant US abnormalities of the plasma membrane, intercalated discs, mitochondria, sarcomeres and nuclei occurred in zones A and B. Chronic lesions exhibited collagen proliferation either as strands or small foci of fibrils. Zone C was virtually normal in all groups. In zone A, the extent of US injury and collagen proliferation was less in dogs receiving combined therapy compared to groups receiving steroids and verapamil alone. Zone B was normal in the combined treatment group only. In dogs receiving allopurinol alone, US damage was much greater than the other treated groups and similar to controls.

Conclusion: The US injury surrounding acute RF lesions does not resolve over time. Steroids and verapamil are equally effective in limiting US damage surrounding chronic RF lesions and combination therapy with these drugs seems to afford additional protection. Allopurinol, however, is ineffective. Progression of an inflammatory process and cytosolic calcium overload, but not generation of reactive oxygen intermediates, may play a role in the genesis of delayed RF-induced damage to the myocardium.

P2098 Spontaneous onset of atrial fibrillation from the pulmonary vein muscolature: high-resolution activation mapping with a basket catheter

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The pulmonary vein (PV) musculature is the major source of ectopies initiating atrial fibrillation (AF). However, high-resolution (HR) PV activation mapping during the spontaneous onset of AF is not well-described.
Methods: During 24/52 PV electrical isolation procedures performed in 44 pts (34 m, age 56±8 yrs), 96 AF spontaneous onsets (range 1-15 episode/pt) were mapped with a 64-pole basket catheter (Constellation 31 mm, Boston Scientific) positioned within the culprit PV. HR PV mapping was performed combining the electrodes to obtain 3 series (distal, mid, proximal; 6 mm distance between cross-sections) of 8 circumferential bipoles. The selected proximal series of electrodes was that placed at the angiographically defined PV ostium.
Results: AF initiated from 30 PVs (11 left superior, 11 left inferior, 7 right superior, 1 right inferior) with a coupling interval of the earliest PV deflection (EPVD) of 222±88 ms and a PV to left atrial activation delay of 125±55 ms. These intervals did not differ from those measured with PV ectopies not initiating AF (220±84 ms and 116±62 ms, respectively; p: ns). Over the cross-sectional plane, the EPVD was recorded at the superior, inferior, anterior, or posterior segments of the PV in 40%, 49%, 2%, and 8% of the cases, respectively. Longitudinally, EPVD occurred in the distal, mid, or proximal cross-sections in 45%, 24%, and 31%, respectively. Mean PV activation cycle length at the AF onset (first 5 beats) was 135±33 ms (range 104-234 ms). Fractionated electrograms associated with marked conduction delay and complex activation patterns were recorded in 77% of the culprit PVs at the AF onset, in the distal (19%), mid (51%), or proximal (30%) cross-sections. In 63% of the cases, the sites of EPVD and electrogram fragmentation were coincident.
Conclusions: AF episodes are initiated by repetitive, rapid PV discharges, mostly originating from sites with a more complex fiber architecture. In the majority of the cases, activation wavefront degeneration occurs within the vein itself, supporting the hypothesis that PV musculature might represent also the substrate for AF initiation.

P2099 Spontaneus versus post-ablation related conversion rate to sinus rhythm after different cardiosurgical procedures

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Purpose: Microwave ablation (MW) has been established as an efficient and absolut safe procedure for the treatment of permanent atrial fibrillation (pAF) to restore sinus rhythm in patients with the need of further concomitant cardiosurgical therapy.
We performed a retrospective study comparing the follow-up of patients with pAF and cardiosurgical procedures alone with patients receiving MW as a concomitant procedure to a cardiosurgical intervention.
Methods: Group A included 62 patients, age 72 ± 9 years, ejection fraction 25 - 74%, left atrial diameter 53 ± 9 mm suffering from mitral valve disease (MVD), coronary artery disease (CAD) or aortic valve disease (AVD) with pAF documented for 6.9 ± 5.5 years. Cardiosurgical therapy included mitral valve interventions, CABG or biological aortic valve replacement. Group B included 88 patients, age 67 ± 4 years, ejection fraction 26 - 76%, left atrial diameter 52 ± 6 mm with documented pAF for 6.4 ± 4 years suffering from MVD, CAD or AVD. The mean additional ablation time was 13 min.
Results: See table. There were no ablation related complications. The survival rate in group A was 94.2% and in group B 98%.

	Nr. of patients	SR (%)
Group A	62	
MVD	11	6
CAD	35	9
AVD	16	5
Group B	88	
MVD	49	62
CAD	26	72
AVD	8	83

Conclusions: Our results illustrate high effectiveness of MW to restore sinus rhythm in patients with pAF and different concomitant cardiosurgical procedures independently from the nature of cardiac disease in comparison to isolated cardiosurgical procedures. As a consequence of this study we have extended this approach to most patients with pAF and cardiosurgical disease.

P2100 Comparison of multielectrode and electroanatomical mapping of conduction over the right atrial istmhus during radiofrequency ablation of type I atrial flutter

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Background: Achievement of bi-directional conduction block (BCB) over the right atrial isthmus is the endpoint for Type I Atrial Flutter Ablations. Various methods have been used to map conduction over the isthmus. The most accepted one seems to be placement of multielectrode reference catheters. Electroanatomical mapping (CARTO) is a new and effective method for mapping isthmus' conduction, which has been demonstrated to decrease the fluoroscopy time of the procedure. However, it has not been established whether there is agreement concerning the findings of the two methods.
Objective: To investigate the degree of concordance between assessing isthmus conduction using conventional (multielectrode) and CARTO mapping.
Methods: We studied 25 male patients with type I atrial flutter, mean age 58,8 years old (42-80). Nine had been previously submitted to an unsuccessful attempt of RF conventional ablation. In each patient we obtained both multielectrode and electroanatomical maps of the right atrial activation during CS pacing and right inferior wall pacing. This was performed before ablation and after construction of each linear lesion.
Results: BCB detected by both methods was obtained in 19 patients. In 2 patients both methods revealed absence of block despite many attempts of RF ablation. In 4 patients conventional mapping did identify the presence of conduction block and the electroanatomical maps did not. In 3 of these 4 patients, CARTO revealed very slow isthmus conduction. In one patient there was a localized conduction gap.
Conclusions: Electroanatomical and conventional mapping of conduction over the right atrial isthmus with multielectrode reference catheters were concordant in 84% of the patients studied. Probably, the multielectrode mapping was unable to detect slow conduction over the isthmus or localized gaps. False diagnosis of bidirectional isthmus conduction block may explain some of the clinical recurrences observed after conventional atrial flutter ablations.

P2101 Ischaemic complication associated with pulmonary vein ablation in a prospective multicentre study

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The BITMAP Study (Breakthrough and Isolation Trial: Mapping and Ablation of Pulmonary Veins) investigated the safety and efficacy of a new catheter with circumferential mapping and ablation electrodes for pulmonary vein ablation. We report the occurrence of transient ST-Segment-Elevation during catheter placement in the left atrium (LA) and superior pulmonary veins (PV) in this prospective multi-center study.
Methods: 40 patients (57±10 years) with recurrent PAF were prospectively included. RFC ablation supported by the 4F REVELATION Helix©; microcatheter (Cardima Inc., USA) with 8 distal electrodes for bipolar mapping and ablation targeted a total number of 3±1 PV per pt. At the ostial region RFC was applied (max. power 30 W, 45-50°C) with a maximum of 4 RFC per electrode. Continuous ECG-Monitoring was performed and all patients were adequately anticoagulated (ACT>250).
Results: We recorded the occurrence of ST-Segment-Elevation >0.2mV and left thoracic pain in 5 out of 40 patients from three centers after successful transseptal puncture during LA- or PV-Mapping. The symptoms and the ECG changes started abruptly and lasted for 5±4 min. Pericardial effusion was immediately excluded by echocardiography in all cases. Coronary angiograms were performed in three patients with the longest episodes, no thrombotic material or air emboli were present. The symptoms and the ECG-changes resolved completely in all patients.
Conclusions: In this prospective multi-center trial we reported the phenomenon of transient ST-Segment-Elevation during LA- and PV-Mapping. No cardiovascular or cerebral damages were observed during procedure and follow-up. Although the mechanism is still unclear, vasospasm due to autonomic dysregulation seems to contribute to this occurrence, because no evidence for air embolism or embolic material was present.

P2102 Left atrial substrate modification to cure atrial fibrillation: a prospective study on the efficiency of linear and circular non-isolating lesion lines

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The results of intraoperative ablation of atrial fibrillation (AF) using left atrial linear lesions for substrate modification without pulmonary vein (PV) isolation have demonstrated a high efficiency as curative treatment of AF during long-term follow-up. The aim of the present study was the percutaneous application of left atrial linear lesions for substrate modification.
In 65 pts. (39 male; mean age, 53±18 years) with paroxysmal AF for 7±6 years, linear lesions were placed between the right and left PVs and from the left PVs to the mitral annulus guided by the electromagnetic mapping system (Carto). In addition, circular lesions were placed around the left and right PVs, respectively. Pacing inside the circular lesions after ablation tested whether the PVs were completely isolated by the circular lesions. Temperature-guided energy applications were placed with an 8-mm tip electrode (60 °C, 60 watts). Follow-up was performed using serial continuous 7-days-ECGs. The mean procedure times and fluoroscopy times measured 136±29 min. and 26±9 min., respectively. A complete isolation of the right and left PVs was achieved after ablation in 2/65 pts. (3%). Within the first 10 postablation days, recurrent episodes of AF or atypical left atrial flutter were documented in 61% of the pts, and 39% demonstrated stable sinus rhythm directly after ablation. Within the first 3 months, however, 66% of the patients were completely free from AF episodes. For the whole group, analysis of serial digital Holter recordings showed a significant reduction of AF episodes: Pre-ablation 39 hours AF of 152 hours analysed per patient, immediately post ablation 32 h AF of 153 h analysed, at 3 months 11 h AF of 146 h analysed, and at 6 months 7 h AF of 159 h analysed. No PV stenosis was observed in this study.
Conclusions: Circular lesions around the PVs at the atrial level did not completely isolate the PVs using our method, i.e. the lesion lines were nontransmural and/or noncontiguous at some sites. Nevertheless, about 70% of the pts. developed stable sinus rhythm during the first 3 postablation months indicating that the methods of the present study modify the substrate rather than isolate the trigger of AF.

P2103 Hybrid therapy based on radiofrequency catheter ablation combined with pharmacological treatment in patients with refractory atrial fibrillation

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Aim of the study was to evaluate the absolute efficacy of right atrium arrhythmogenic substrate ablation in patients with refractory atrial fibrillation (AF) and to test its adjunctive positive effect to previously Ineffective antiarrhythmic agents (AA).
Methods: 30 consecutive patients (15 m and 15 F, mean age 59.7 years, range 42 – 78 years) with frequent episodes of paroxysmal (24 pts) or persistent (6 pts) AF referred to our EP Lab to undergo radiofrequency catheter ablation (RFCA) were enrolled. Primary AF pts were considered those in whom AF was the only inducible arrhythmia or was already present at the beginning of the procedure. Such pts underwent right atrial compartmentalization (cavo – tricuspid isthmus bidirectional block, intercaval and septal linear lesion). Secondary AF pts were considered those in whom atrioventricular nodal reentrant tachycardia (AVNRT, 4/30 pts), atrial flutter (9/30 pts) or atrial ectopic tachycardia (2/30 pts) were also inducible. In these patients, the substrate responsible for the associated arrhythmia was chosen as the target of RFCA.
Results: After a mean follow up of 13.6 months (range 2 – 28 months), 14 pts (46.6%) were free of arrhythmia recurrence. Among them, 7 pts (23%) did not require any AA, while the remaining 7 pts remained asymptomatic with class III AA. The success rate, however, increased to 63% (19 out of 30 pts) if we include 5 more patients (3 under AA regimen) who exhibited only an isolated AF recurrence and therefore declared to be greatly satisfied of the final result. No complication occurred.
Conclusions: Hybrid therapy based on right atrium arrhythmogenic substrate RFCA associated with class III AA administration may represent a valid option alternative to the left atrium approach in patients with drug refractory AF. Despite a lower success rate, the procedure is definitely safer and requires a lesser exploitment of hospital sources.

ATRIAL FIBRILLATION: MECHANISMS AND MANAGEMENT II

P2104 Effects of a new class III antiarrhythmic drug nibentan in a canine model of spontaneous atrial fibrillation

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Introduction: Nibentan, a new class III antiarrhythmic drug, blocks both delayed rectifier IK and muscarinic IK.ACh potassium currents. High efficacy of nibentan for treatment of paroxysmal and chronic atrial fibrillation (AF) (more than 80%) has been demonstrated by recent clinical studies. However, the mechanism of antiarrhythmic efficiency of nibentan is unknown. The purpose of this study was to investigate the mechanism of nibentan efficacy using a canine model of cholinergic-mediated AF.
Methods: AF was induced in 6 anesthetized open-chest dogs by perfusion into the sinus node artery (SNA) with normal Tyrode's solution containing acetylcholine (ACh; 9 ml/min)) without electrical stimulation of the atria. Pacing and recording bipolar electrodes were sutured on the right atrium for measurements of the atrial effective refractory period (AERP) and conduction velocity at basic cycle lengths (CL) of 200 and 400 ms. Epicardial mapping of the right atrium (112 unipolar electrodes) was used to evaluate activation during AF.
Results: AF was induced by perfusion with ACh (4±2 μM) into the SNA in 100% (18/18, n=3 for each dog) of attempts. After intravenous administration of nibentan (0.25 mg/kg/2min), ACh perfusion (4±2 μM) induced AF in only 6% (1/18, n=3 for each dog) of attempts ($p<0.001$). Nibentan increased the threshold for AF induction to 32±16 μM ACh ($p<0.05$). Nibentan did not change conduction velocity, but increased AERP independent of rate (CL200ms/CL400ms= +63±12%/+67±12%, $p<0.01$ for each CL). Effects of nibentan were stable over 90 minutes without a continuous infusion. Primary antiarrhythmic mechanism of nibentan in this model (14/17 cases, 82%) was related to preventing atrial premature depolarizations (APDs) which triggering reentrant arrhythmias. Secondary mechanism, in cases of APDs and reentrant excitation (3/17 cases, 18%), was related to producing conduction block of reentrant waves, leading to rapid arrhythmia cessation. These changes in activation patterns can be accounted for by nibentan-induced increase of AERP and wavelength for reentry (52±8%, $p<0.01$) at rapid atrial rate (CL200 ms).
Conclusion: . High efficacy of nibentan against spontaneous AF was associated with significant rate-independent increases in AERP and in wavelength, and might be in part explained by blocking both IK and IK.ACh potassium currents.

P2105 Wavelet transform analysis of heart rate variability to assess the autonomic changes associated with the onset of paroxysmal atrial fibrillation

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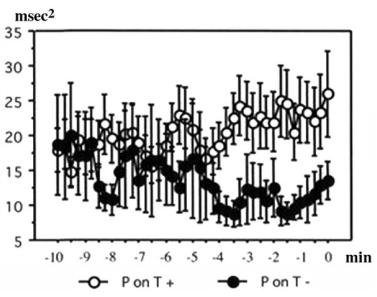
Background: Previous study have suggested that paroxysmal atrial fibrillation (PAF) originating from the pulmonary vein show atrial premature beat with P on T phenomenon and vagal activation increases gradually before onset of PAF in heart rate variability (HRV) using by fast Fourier transform analysis. However autonomic tone has dynamic change, there are limitations to evaluate its changes used by FFT. This study was designed to evaluate change of autonomic tone before onset of AF used by wavelet transform, which can provide a reliable estimation of spectral variables during non-stationary phenomena.
Methods: We analyzed the changes in HRV preceding 48 episodes of PAF detected on Holter monitoring. The R-R intervals during 10 minutes before onset of paroxsmal AF was analyzed by wavelet transform. Before 10minutes to 5 minutes onset of AF, HRV indices were calculated every 30 seconds and last 5 minutes, calculated every 10 seconds.



Variation of HF before onset of PAF.

Results: There were 26 P on T phenomena in 48 episodes. In patients with P on T a significant linear increasing in high frequency components (HF, 0.15-0.4 Hz) was observed during 3 minutes before onset of PAF ($P = 0.003$). On the other hand low frequency components (LF, 0.04-0.15 Hz) and HF ratio was significant change both group just before onset of AF. But it was not significant between 2 groups.
Conclusion: It seems that mechanism of AF initiation related primary increase in vagal tone followed by sudden increase of sympathetic tone just before onset of AF with P on T phenomenon.

P2106 Do patients with recurrent atrial fibrillation benefit from right atrial multilinear ablation?

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Background: A new approach for treating paroxysmal atrial fibrillation is right-atrial compartmentalization using radiofrequency catheter ablation. This study investigated the long-term follow-up of patients treated with this new method.
Patients and methods: 37 patients with symptomatic paroxysmal atrial fibrillation refractory to antiarrhythmic drugs were enrolled in this prospective study irrespective of their underlying heart disease. All patients underwent radiofrequency catheter ablation including right-atrial compartmentalization and ablation of the right atrial isthmus region. 12 patients suffered from coronary heart disease and 5 from myocarditis in the past, 8 had left-ventricular hypertrophy (6 patients due to systemic arterial hypertension, 2 patients due to hypertrophic cardiomyopathy), 2 had dilated cardiomyopathy, 2 had mitral valve prolapse and 8 patients were classified as having "lone atrial fibrillation".
Results: During a mean follow-up period of 2.4 years, 22% of patients were free from relapse, while 78% suffered at least from one relapsing episode of atrial fibrillation. According to the underlying heart disease, patients with "lone atrial fibrillation" and left-ventricular hypertrophy (37% vs. 50% without relapse) appeared to benefit in particular compared to patients with coronary heart disease (8%). In the group of patients suffering a relapse of paroxysmal atrial fibrillation, the mean time of duration of an arrhythmic episode decreased significantly from 10.9 to 2.4 hours under continued administering of antiarrhythmic drugs (p=0.01), as did the number of episodes from 2.3 to 1.9 per week.
Conclusions: Right-atrial radiofrequency catheter ablation is a new approach for treating paroxysmal atrial fibrillation. Despite the high rate of clinical relapse (78%), there is evidence that responsiveness to antiarrhythmic drugs improves following ablation. Right-atrial compartmentalization should not be seen as a causal therapy approach but, rather, as a form of hybrid therapy, i.e. ablative electrophysiological modulation and consecutive antiarrhythmic drug therapy.

P2107 Clinical impact of radiofrequency catheter ablation in focal atrial fibrillation

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The clinical impact of radiofrequency catheter ablation (RCA) in focal atrial fibrillation (AF) is not well defined.
Methods: Patients with focal AF who underwent a RCA in our institution were requested to fulfill a modified Brignole AF symptom checklist at baseline and 6 months after the last RCA procedure. This test quantifies from 0 (never) to 10 (always) several symptoms associated with AF. Additionally, the NYHA functional class and the number of AF-related unscheduled visits in the previous 6 months were also recorded.
Results: Twenty-two consecutive patients aged 48 $\pm$ 14 years with drug-refractory AF who had completed the follow-up were the study population. AF was paroxysmal in 16 patients (13 of them had daily recurrences), and persistent in 6 patients (27%). Spontaneous or induced ectopic activity was used to select the target for ablation. A mean of 1.7 $\pm$ 0.9 potential triggers were ablated per procedure. Empirical isolation of the 4 pulmonary veins was performed only in 2 patients. In case of AF recurrences the procedure was repeated. Fifteen, 6 and 1 patients underwent 1, 2 and 3 ablation procedures respectively. The changes in the symptom status are presented in the Table. The mean number of AF-related unscheduled visits was 4.0 $\pm$ 5.4 before RCA and 0.2 $\pm$ 0.7 after RCA ($p<0.01$). Fourteen patients (64%) did not require any antiarrhythmic drug after RCA.

Changes in symptom status

	Baseline, mean	After ablation, mean	Rsquare	A	B
Palpitations	6.9 (3.1)	1.0 (1.3)	0.85	0 (NS)	-1.02 (0.1)
Symptoms on effort	5.2 (4.2)	0.4 (0.9)	0.95	0 (NS)	-0.91 (0.05)
Symptoms at rest	2.2 (3.5)	0.1 (0.2)			
NYHA class	1.7 (0.8)	1.2 (0.4)	0.76	0.8 (0.19)	-0.79 (0.1)

R square, correlation coefficient between the symptom status at baseline and the change after RCA. A and B, parameters of the linear regression equation (Change in symptom status = A + B·Symptom at baseline). Standard errors of the estimates are presented between parenthesis. All p values are < 0.01 unless otherwise specified.

Conclusions: RCA produces a noteworthy symptomatic improvement in patients with drug-refractory focal AF. The magnitude of this improvement is highly correlated with the symptom severity at baseline.

P2108 Activation of inflammation after direct current cardioversion atrial fibrillation

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Background: The restoration of sinus rhythm in chronic atrial fibrillation is associated with increased risk of embolic events. It is thought that this phenomenon is a consequence of decreased function of the left atrial appendage function compared with the precardioversion state. The injury of the skin, fatty tissue and skeletal muscles as a current-related tissue damage may lead to activation of the inflammatory status which also may predispose to embolic events. C-reactive protein is a marker of inflammation.
The aim of the study was to assess the influence of direct current external cardioversion (DCC) of the chronic atrial fibrillation on the serum concentration of C-reactive protein.
Material and methods: The study group consisted of 17 patients, mean age 69,0 $\pm$ 10,3 years, mean height 162,0 $\pm$ 9,1 cm, mean weight 77,5 $\pm$ 13,6kg (11 women and 6 men) with chronic atrial fibrillation. All patients were anticoagulated with acenocumarol, no one had infectious disease, unstable angina or recent myoracdial infarction, had undergone coronary angioplasty and surgical procedure within the previous six month. The DCC was performed under typical general anesthesia. Two patients had mitral stenosis, eight hypertension with mild ventricular hypertrophy and seven stable coronary artery disease. The serum concentration of C-reactive protein was measured before (CRP before) and 24-hours after (CRP after) DCC.
Results are listed in table as median and mean $\pm$ SD: The serum concentration of C-reactive protein 24 hours after DCC was significantly higher than before this procedure ($p<0,005$). The ratio of CRP before and after negatively correlate with the height ($r=-0,62$, $p<0,05$) and didn't correlate with number and total energy of the shocks or the patients weight and gender.

	CRP before (mg%)	CRP after (mg%)	Number of the shocks	Total energy of shocks (J)
Median	3,17	6,6	1	200
Mean $\pm$ SD	5,4 $\pm$ 6,0	14,0 $\pm$ 24,3	1,6 $\pm$ 0,9	338 $\pm$ 239

Conclusions: 1. The electrical cardioversion lead to increase in serum concentration of C-reactive protein.
2. The activation of inflammation during DCC may predispose the patients to the thrombophilic state and be in part responsible for increased risk of thromboembolic events after DCC.

P2109 Mapping and radiofrequency ablation of atrial tachyarrhythmias in patients after atrial septal defect repairment

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Introduction: It is well established that patients (pts) after atrial septal defect (ASD) repairment are prone to develop atrial tachyarrhythmias. The objective of this study was to analyze the mechanism of atrial tachyarrhythmias in pts after ASD repairment.
Methods: Twenty-eight pts after ASD repairment (9 female, mean age 45 years), who were refered to our center between 1997-2002 for mapping and ablation of their documented atrial tachyarrhythmias, were analyzed. Besides conventional mapping techniques, electroanatomical mapping (Carto Biosense Webster, n=5) or non-contact mapping (NCM, n=5) techniques were used.
Results: Out of 29 atrial tachyarrhythmias mapped, 21 (72%) were identified as intraatrial reentrant tachycardia (IART), 8 (28%) ectopic atrial tachycardia (EAT). Among 21 IARTs, 14 (67%) were isthmus-dependent atrial flutter, 7 (33%) were incisional scar related (n=5) or ASD patch related (n=2) atypical atrial flutter. Out of 8 EATs, 5 (63%) originated from right atrial myocardium adjacent to the ASD patch, 2 (25%) from the left upper pulmonary vein ostium and the remaining one (12%) from the right midseptum. In total 26 (90%) out of 29 mapped atrial tachyarrhythmias were successfully ablated. Of the IARTs, all (100%)isthmus-dependent atrial flutter and 5 (71%) out of 7 atypical atrial flutter were abolished by radiofrequency ablation. Seven (88%) out of 8 EATs were successfully ablated.
Conclusions: 1) Isthmus-dependent atrial flutter is the main type of IARTs which is the most common mechanism of atrial tachyarrhythmias in pts after ASD repairment. 2) Right atrial myocardium adjacent to the ASD patch is the main source of EATs. 3) Atrial tachyarrhythmias are amenable to radiofrequency applications in most pts after ASD repairment.

P2110 Evaluation of sinus and paced P-wave duration and P-wave dispersion as predictors for developing atrial fibrillation during pacemaker treatment in patients with sick sinus syndrome

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Aim: To prospectively evaluate the sinus P wave and the paced P wave duration and dispersion as electrocardiographic predictors for atrial fibrillation (AF) during pacemaker treatment in sick sinus syndrome (SSS).
Methods and Results: Patients with SSS (n=109), mean age 72 ± 11 years, 69 female, 59 with brady-tachy syndrome (BTS), were included. From each patient a 12-lead electrocardiogram (ECG) was recorded before pacemaker implantation and during high right atrial (HRA) and septal right atrial (SRA) pacing (70 + 100 bpm). The ECG's were scanned into a computer and analyzed on screen. The patients were treated with AAIR (n=52) or DDDR pacing. The P wave duration was measured in each lead, mean P wave duration (p-mean) and P wave dispersion (p-disp) were calculated. AF during follow-up (FU) was defined as: AF in an ECG at or in between FU visits, an atrial high rate episode ≥ 220/min. for ≥ 5 min., atrial sensing with a rate of ≥ 170/min. in ≥ 5% of total counted beats, mode-switching (MS) in ≥ 5% of total time or a MS episode of ≥ 5 min. in the pacemaker telemetry. The ECG parameters were correlated to AF during FU. Mean FU was 1.5 ± 0.9 years.

Table 1

	AF	n	no AF	n
p-mean-sinus	107 ± 16 ms	58	105 ± 13 ms	47
p-disp-sinus	67 ± 22 ms	58	64 ± 18 ms	47
p-mean-HRA70	138 ± 19 ms	28	137 ± 20 ms	25
p-disp-HRA70	51 ± 23 ms	28	53 ± 24 ms	25
p-mean-HRA100	155 ± 24 ms	34	149 ± 29 ms	32
p-disp-HRA100	53 ± 27 ms	34	58 ± 28 ms	32
p-mean-SRA70	117 ± 16 ms	28	118 ± 20 ms	24
p-disp-SRA70	45 ± 20 ms	28	42 ± 18 ms	24
p-mean-SRA100	133 ± 25 ms	32	134 ± 16 ms	31
p-disp-SRA100	55 ± 29 ms	32	45 ± 22 ms	31

None of the ECG parameters did differ between patients with and without AF during FU (table 1). Nor was there any difference between groups after correction for BTS and age. BTS was the strongest predictor for AF during FU ($p<0.001$).
Conclusion: P wave duration and dispersion measured before pacemaker implantation and during pacing were not predictive of AF in patients with SSS.

P2111 Prediction of early recurrence of atrial fibrillation in patients with ischaemic heart disease

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Aim of Study: To create an algorithm for prediction of AF recurrence during the first month after cardioversion.
Patients and Methods: Retrospective study of 294 pts. with ischemic heart disease based AF and no treatment with class I and III antiarrhythmic drugs was performed. High-accuracy binary logistic regression model for prediction of early recurrence of AF was created using multivariate analysis. Logistic regression was used to identify predictive factors. Significance of variables was estimated by a backward stepwise method. Odds ratio (OR) and 90% confidence intervals was estimated for each significant variable. The binary logistic regression model for prediction of early recurrence of ischemic AF and estimation of the probability of an event was based on the formula,

$$P(y = 1 \mid x_1, \ldots x_k) = \frac{e^z}{(1 + e^z)}$$

where $Z = b_0 + b_1 x_1 + \ldots + b_k x_k$.
Results: Independent predictive variables in multivariate analysis were age (p=0,01, OR=0,95), number episodes of AF (p<0,00, OR=1,18), ischemic mitral valve incompetence and severity of mitral regurgitation in echocardiography (p=0,007, OR=1,52), left atrial supero-inferior dimension (p=0,001, OR=1,16), pathology of the thyroid (p=0,017, OR=2,10), usage of beta-blockers (p=0,063, OR=2,05), and method of cardioversion (p<0,00, OR=1,63). The optimal breakpoint that best separated high-risk from low-risk patients was 0,31. Model sensitivity was 0,82, specificity 0,79, positive predictive value 0,68, negative predictive value – 0,89.
Conclusion: Easily available clinical, anamnestic and transthoracic echocardiographic data were used to create highly accurate prognostic model, allowing prospective identification of patients at high risk to develop AF recurrence, in whom preventive antiarrhythmic therapy is rationally justified.

P2112 Percutaneous left atrial appendage occlusion: incidence of cerebral embolism after the procedure

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Background: Patients with atrial fibrillation (AF) and contraindications to oral anticoagulation are at high risk to develop cerebral thromboembolism. A new percutaneous left atrial appendage occlusion system (PLAATOtm)has the potential to decrease this risk. The aim of this prospective study was to determine the incidence of cerebral embolism after implantation of the occlusion device by means of serial cerebral magnetic resonance imaging (MRI).
Methods: 9 patients with persistent AF and dense spontaneous echo contrast were included in the study. To evaluate peri-interventional thromboembolism, cerebral MRI was performed 24 hours prior to the procedure, and after 48 hours, at 1 month, at 6 months and at 12 months after the implantation of the device.
Results: In 6 out of 9 patients, former cerebral embolism was documented before the implantation procedure. None of the patients presented clinical signs of cerebral embolism during the evaluation period. Cerebral MRI examinations carried out directly after the procedure and in the follow up period of 7.33 ± 5.85 months after implantation excluded the presence of new cerebral embolism in all patients.
Conclusions: The acute implantation of a new percutaneous left atrial appendage occlusion system in patients with AF and dense spontaneous echo contrast is not associated with acute cerebral embolism. Furthermore, long-term follow up did reveal neither silent nor clinically apparent cerebral thromboembolism.

P2113 Amiodarone-induced atrial flutter with 1:1 atrioventricular nodal conduction

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Introduction: Atrial flutter (Flu) with 1:1 atrioventricular (AV) nodal conduction is a well-known complication of Vaughan-Williams class I antiarrhythmic drugs (AAD). Because of its action on the AV node refractoriness and conduction velocity, class III AAD are not expected to induce such a proarrhythmic effect.
Objective: The goal of this study was to report 7 patients (Pts) who presented atrial Flu with 1:1 AV nodal conduction under oral amiodarone therapy. This amiodarone side-effect has never been reported before. Methods: Seven Pts (6 men), mean age 58 ± 14 years, were included from 1994 to 2001. Four Pts had underlying heart disease: dilated cardiomyopathy in 2 Pts with 22% and 45% left ventricular ejection fraction (LVEF) and ischaemic heart disease in 2 Pts with 52% and 41% LVEF. No Pt had hyperthyroidism while 1:1 Flu occurred. History of atrial Flu or atrial fibrillation was present in 4 Pts.
Results: The initial arrhythmia was 2:1 atrial Flu (n=4), 1:1 atrial Flu (n=2) and atrial fibrillation (n=1). Preventive amiodarone therapy, 200 and 400 mg/day, was running while 1:1 Flu occurred in 2 Pts. High oral dose of amiodarone was given in 5 Pts, 9200 mg ± 2400 mg (range 7800 to 13200 mg) over 10 ± 4 days (range 7 to 17 days). One Pt was under carvedilol 13 mg/day. Symptoms included palpitations in 2 Pts, syncope (1 Pt), near-syncope (1 Pt)and cardiogenic shock (1 Pt). Two Pts were free from symptoms. The atrial and therefore ventricle cycle length during 1:1 Flu was 287 ± 33 ms (range 240 to 330 ms). The QRS complexes were large in 6 Pts (136 ± 35 ms, from 110 to 180 ms) with a V1 to V6 QS morphology in 3 Pts and a left bundle branch block pattern in two. All Pts but 2 had normal QRS morphology and duration during sinus rhythm or 2:1 Flu. Vagal stimulation, intravenous diltiazem, digoxin or 5'-adenosine-triphosphate allowed the diagnosis of 1:1 Flu. Sympathetic activation has been a triggering factor in 5 Pts. One Pt required an emergency cardioversion while three others cardioversion was secondary to amiodarone inefficacy for restoring sinus rhythm.
Conclusion: Despite its action on the AV node, amiodarone can induce 1:1 atrial Flu.

P2114 Clinical value of left atrial appendage flow velocity for prediction of long-term sinus rhythm maintenance in patients with persistent atrial fibrillation

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Background: Echocardiographic parameters for assessing long-term sinus rhythm maintenance after successful electrical cardioversion of persistent atrial fibrillation are not accurately defined.
Aim: To evaluate the role of various clinical and echocardiographic parameters, including the left atrial appendage emptying flow velocity, for prediction of the long term preservation of sinus rhythm in patients underwent successful cardioversion of persistent atrial fibrillation.
Methods: Clinical, transthoracic and transesophageal echocardiographic data measured in 62 patients (38 men, mean age 66±11 years) with persistent atrial fibrillation (arrhythmia duration > 4 weeks and < 12 months) underwent successful electrical cardioversion were analysed for assessment of 1 year maintenance of sinus rhythm.
Results: At 1 year follow-up, 29 patients (46.7%) who underwent successful cardioversion continued to have sinus rhythm. Mean left atrial appendage emptying flow velocity was higher in patients remaining in sinus rhythm for 1 year than in those with atrial fibrillation relapse (42.1±18 cm/sec vs 28.6±16 cm/sec; $p < 0.001$). Other independent predictors of sinus rhythm maintenance at 1 year follow up at univariate analysis were absence of left atrial spontaneous echocardiographic contrast during transesophageal echocardiography ($p < 0.04$), the left atrial parasternal diameter < 45 mm ($p < 0.04$) and the use of antiarrhythmic drugs ($p < 0.03$). At multivariate regression analysis (Cox model) the mean left atrial appendage flow velocity > 41 cm/sec ($p = 0.001$; chi square: 24.4, OR = 5.1, CI 95% = 2.8-9.9) and the use of antiarrhythmic drugs ($p = 0.04$; chi square 4.1, OR = 2.2, CI 95% = 1.2-3.9) predicted the continous preservation of sinus rhythm during 1 year. The overall specificity, sensitivity, positive and negative predictive values of left atrial appendage peak emptying flow velocity > 41 cm/sec were 81% (CI 95% = 70.1-87.2), 58% (CI 95% = 46.1-67.4), 71% (CI 95% = 61.6-84.5) and 68% (CI 95% = 57.2-75.4) respectively for assessment of 1 year sinus rhtythm maintenance.
Conclusions: In patients with persistent atrial fibrillation, left atrial appendage peak emptying flow velocity provides valuable information for prediction of 1 year outcome of successful cardioversion. In transesophageal echocardiography guided management of atrial fibrillation, assessment of left atrial appendage velocity profile can be readily incorporated into pre-cardioversion echocardiographic examination.

RESYNCHRONIZATION THERAPY IN HEART FAILURE I

P2115 Implantable cardioverter-defribrillator treated patients should be screened for eligibility of cardiac resynchronization therapy

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Background: ICD-therapy prevents sudden death in patients at high risk, but incidence of death due to heart failure remains unaltered. Recent data suggest that Cardiac Resynchronization Therapy (CRT) is an useful treatment option in patients with end-stage heart failure. The aim of the study is to evaluate how many ICD patients are eligible for CRT and if the combined therapy (CRT-ICD) has improved clinical outcome compared to ICD treatment only.
Methods: all patients who received an ICD were analyzed for eligibility of CRT using the following criteria: NYHA class III or IV, QRS duration >120 ms, depressed LVEF. The patients eligible were evaluated for their clinical parameters, hospitalisation and survival after implantation of the ICD with CRT or ICD only.
Results: 390 consecutive patients received an ICD from June 1996 till March 2001. Underlying disease was ischemic in 66%. The mean LVEF was 36±17%, 20% were in NYHA class III-IV and 16% were in NYHA class II with an LVEF <30%. Of these 140 patients, 79 (20%) had a QRS duration >120 ms. Of the 79 (20%) eligible patients, the most recent 20 received CRT with an ICD. During 1y follow-up, hospitalization rate for congestive heart failure was 2.9±4.1days/year for ICD patients (n=59), compared to 0.5±1.5 d/y ($P<0.05$) in the ICD-CRT treated patients (n=20). One year mortality was 20% in the ICD patients, compared to 10% in the ICD with CRT treated patients. NYHA class did not improve in the patients receiving an ICD only (2.6±0.6 to 2.8±0.8, NS), whereas the patients who received an ICD with CRT improved significantly in NYHA class (3.2±0.6 to 2.1±0.6, $P<0.05$).
Conclusion: 20% of patients with an ICD indication may also benefit from CRT. Since clinical outcome, hospitalization rate and survival is superior in patients treated with a combined device, screening for eligibility of CRT should be performed in patients sceduled for ICD implantation.

P2116 Inducibility of ventricular arrhythmia in congestive heart failure patients is reduced after long-term cardiac resynchronization therapy

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Background: Cardiac Resynchronization Therapy (CRT) may improve systolic left ventricular function, functional status and well-being of patients with depressed left ventricular function and interventricular conduction delay. These patients with congestive heart failure often have an indication for ICD implantation as well. The aim of the present study was to evaluate whether long term CRT decreases inducibility of ventricular arrhythmias in these patients.
Methods: 12 patients treated with a combined CRT-ICD device for dilated cardiomyopathy and at risk for ventricular arrhythmia were included. All patients underwent an electrophysiological (EP) study with ventricular programmed electrical stimulation (PES), both before implantation of the BV-ICD device and after a period of at least 6 months of CRT. PES protocol was 8 beat drive train with basic cycle length of 600, 500 and 400 ms and up to 3 extrastimuli with minimal cycle length of 200 ms.
Results: The patients included (10 M, age 61±14y) had dilated cardiomyopathy (7 ischemic, 5 idiopathic) and interventricular conduction disturbances. Indications for ICD device were out of hospital cardiac arrest (n=7) or ventricular tachyarrhythmia (n=5). Prescription of antiarrhythmic drugs before CRT-ICD (sotalol n=5, amiodarone n=7) was not significantly changed at long term follow-up (sotalol n=7, amiodarone n=5). Before CRT-ICD implantation, sustained VT could be induced in 10 patients and nonsustained VT in one. After a period of 8.7 ± 5.3 months of CRT, VT was inducible in only 4 patients.
Conclusion: Long term CRT decreases the inducibility of VT from 92% to 33% ($p<0.05$). CRT may have an antiarrhythmic effect after long term CRT.

P2117 Is there a difference in response to cardiac resynchronization therapy in patients with sinus rhythm or chronic atrial fibrillation?

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Background: Cardiac resynchronization therapy (CRT) is a new therapeutic option for patients with drug-refractory end-stage heart failure. CRT is used in patients with sinus rhythm (SR) and patients with chronic atrial fibrillation (AF) who require permanent pacing. Accordingly, clinical response and long-term survival after CRT were compared between patients with SR versus patients with chronic AF.
Methods: 40 patients with end-stage heart failure, NYHA class III-IV, LVEF<35%, QRS>120ms and LBBB received a biventricular pacemaker. At baseline and after 6 months CRT NYHA class, Minnesota Quality of life score, and 6-minute walking distance were evaluated. Long-term follow-up was obtained up to 2 years.
Results: 50% (n=20) were in stable sinus rhythm and 50% (n=20) in chronic atrial fibrillation. The 6-months follow-up data are summarized in the table.

	Sinus Rhytm	Atrial Fibrillation	P-value
NYHA class			
– baseline	3.3 ± 0.5	3.1 ± 0.6	0.302
– 6 months	1.9 ± 0.9	2.3 ± 0.7	0.132
Minnesota Score			
– baseline	44 ± 11	37 ± 15	0.091
– 6 months	32 ± 14	25 ± 12	0.054
6 min walking distance (m)			
– baseline	256 ± 88	307 ± 109	0.181
– 6 months	375 ± 125	424 ± 123	0.292

Follow-up data SR and AF group

Of note, 85% of patients with SR as compared to 80% AF improved >1 in NYHA class. Long-term follow-up (22±8months) showed a superior survival rate for the SR group as compared to the AF group (85% vs 65%, $p<0.05$).
Conclusion: Clinical response after 6 months CRT was similar in patients with SR and AF. Long-term survival rates however were superior in the SR group, compared to the AF group.

P2118 Assessment of resynchronisation therapy based on dynamic three-dimensional echocardiography and semi-automated border detection

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Background: Biventricular pacing provides the most hemodynamic benefit when it is applied to the most delayed left ventricular (LV) site. Currently, the ideal LV pacing site is selected according to acute invasive hemodynamic study and/or Doppler myocardial imaging. The aim of the present study was to develop a new approach for guiding and evaluating resynchronization therapy. Our proposed method is based on three-dimensional (3D) transthoracic echocardiography.
Methods: A total of 11 patients with advanced heart failure and previously implanted biventricular pacemaker/ICD were included in this feasibility study. Transthoracic, apical left ventricular images were obtained using a self-developed, fast rotating second harmonic transducer. Acquisitions were performed in sinus rhythm (SR), right ventricular (RV) apical and biventricular pacing modes. 3D reconstruction of the LV was performed using semi-automated contour analysis (4D LV analysis, TomTec, Germany). Using 3D echocardiographic images, segmental wall motion characteristics, including determination of the most delayed part of the LV, were assessed. The global LV function was evaluated by calculation of the end-systolic and end-diastolic LV volumes and ejection fraction (EF).
Results: Optimal images were obtained from 8 patients. Using this transducer the duration of data acquisition was 10 sec. The greatest delay in SR was found in the anterior/anterior-septal segments in most of the patients (3 pts/60%). Biventricular pacing resulted in reduction of the intraventricular conduction delay as compared to SR and RV pacing in 3/5 (60%) and 3/7 pts (43%), respectively. The global LV function did not change significantly.
Conclusions: 1, 3D real time echocardiography is a feasible approach to assess the most delayed LV site. 2, Our data suggest that 3D echocardiography can be used for selection of the optimal pacing site during resynchronization device implantation.

P2119 Comparison of tissue Doppler echocardiography and strain rate imaging in the prediction reverse remodelling response after cardiac resynchronization therapy

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Background: A number of non-invasive techniques have been employed to predict the effectiveness of cardiac resynchronization therapy (CRT) in heart failure patients, in particular LV reverse remodeling. Tissue Doppler (TDI) and strain rate imaging (SRI) have been the focus of interest in the past 2 years. It has been claimed that SRI is superior to TDI to assess regional cardiac function due to the virtual elimination of passive systolic movement. However, it is not clear if SRI is superior in the assessment of cardiac synchronicity.
Methods: 31 patients (mean age: 68±12 years, 23 male) who received CRT were studied by echocardiography with TDI and SRI at baseline and 3-month follow up. The long-axis function was studied by the 6-basal and 6-mid segmental model. In TDI, the time to peak systolic contraction (Ts) was measured and asynchrony index was derived by the standard deviation of Ts of 12 segments (Ts-SD). Similarly, in SRI, the time to peak strain rate (Tsr) and Tsr-SD were measured. The number of segment with true post-systolic shortening (PSS) which was confirmed by SRI with a negative peak was calculated. The septal-lateral difference of Ts and Tsr was also calculated.
Results: There was significant reverse remodeling with reduction of LV end-dastolic and end-systolic volumes, and gain in ejection fraction (all $p<0.001$). There was improvement of septal-lateral difference of Ts by TDI, but not septal-lateral difference of Tsr by SRI. The table shows that Ts-SD is the strongest predictor of the degree of reverse remodeling (by the change of LV end-systolic volume), followed by septal-lateral difference of Ts by TDI and number of PSS segments.

Systolic asynchrony & reverse remodeling

	Correlation coefficient	P value
Ts-SD	-0.80	<0.001
Septal-lateral difference in Ts	-0.46	0.015
Tsr-SD	0.08	NS
Septal-lateral difference in Tsr	-0.11	NS
No. of segments with PSS	-0.46	0.018

Conclusions: TDI is superior to SRI to assess systolic asynchrony and to predict LV reverse remodeling. The Ts-SD is a reliable index of systolic asynchrony which predicted reverse remodeling the best.

P2120 Non-responders and biventricular stimulation: impact of alternative left and right-ventricular pacing sites

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Introduction: Biventricular stimulation has emerged as an important treatment for patients with advanced heart failure and prolonged QRS duration. However, a substantial numer of patients appears to have litte or no benefit from this treatment (non-responders).
Method: A group of 68 patients with congestive heart failure class III-IV with QRS>120 msec were studied. Acute hemodynamic response was assessed with pacing leads in thr right ventricular apex (RVAP), right ventricular outflow tract (RVOT) and from a postero-lateral (LVPL) or anterior (LVA) position in the coronary sinus. An increase in cardiac index $\geq$ 10% on echo Doppler measurement was used as cut-off value for responders. Cardiac index during RVAP-LVPL was compared with four alternative pacing configurations: RVAP-LVA, RVOT-LVA, RVOT-LVPL and RVOT-RVAP. Pacing was performed in the VDD mode with the AV delay set at the longest delay with full ventricular capture.
Results: From the group of 68 patients, 49 (72%) were responders during RVAP-LVPL pacing with a mean increase in cardiac index of 18.8 $\pm$ 7.8%. In only 23 of this 49 patients (47%) the RVAP-LVPL was the best pacing position. Moreover, 5 patients in the non-responder group (26%) demonstrated a response at alternative pacing sites (1 patient during RVOT-LVPL, 2 patients during RVA-LVA pacing and 2 patients during RVOT-RVAP pacing).
Conclusion: In a substantial number the RVAP-LVPL position shows a response, but is not the most optimal position for the patient with the highest hemodynamic respons. Moreover, non-responders can convert to a responder group by using altenative pacing sites.

P2121 Cardiac resyncronization therapy: what effects on left and right-ventricular ejection fraction during exercise?

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In patients with heart failure and wide QRS complex, cardiac resyncronization therapy (CRT) is associated with improvement, at medium term, of left ventricular (LV) ejection fraction (EF) at rest. Aim of the present study was to assess the effects of CRT on both right ventricular (RV) and LV EF, both at rest and during exercise.
Patients and methods: Fourteen patients (pts) (age 60±6 yrs) with severe heart failure (due to dilated cardiomyopathy in 7 pts and ischemic cardiomyopathy in 7 pts) and wide QRS complex (mean 169±6 ms) underwent implant of a system for CRT (pacemaker or defibrillator). Before the implant and 4 months after the implant all the patients underwent assessment of cardiac performance with equilibrium radionuclide angiocardiography (Tc 99) with imaging in left anterior oblique view (best septal). Exercise was performed at bicycle ergometer (load = 25 watt).
Results: During follow up a significant improvement in NYHA functional class was observed (from 2.92±0.47 to 2.36±0.63, $p<0.01$). The effects on LV and RV function are shown in the Table.

Radionuclide angiocardiography

	Baseline, , at rest	F-up, at rest	P value	Baseline, exercise	F-up, exercise	P value
LV EF (%)	22.2 ± 8.4	29.3 ± 13.7	<0.01	24.1 ± 10.6	29.5 ± 16.0	<0.05
LV EDV (ml)	277 ± 86	232 ± 95	<0.01	292 ± 91	258 ± 87	0.12
LV ESV (ml)	219 ± 78	167 ± 71	<0.05	224 ± 81	188 ± 87	<0.05
RV EF (%)	35.7 ± 14.6	37.4 ± 9.1	0.73	30.7 ± 15.5	36.5 ± 13.1	0.25

F-up = follow up; EDV = end-diastolic volume; ESV = end-systolic volume.

Conclusions: In conclusion, assessment of cardiac function during exercise by radionuclide angiography shows that CRT leads to an improvement of LV EF not only at rest but also during exercise. The improvement in LV EF during exercise is associated with a significant reduction of LV end-diastolic volumes. Moreover, the improvement in exercise capacity associated with CRT seems mainly dependant on significant changes in LV volumes and EF, although we found a trend towards an improvement also of RV EF during exercise.

P2122 Biventricular pacing and Cheyne-Stokes respiration in heart failure

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Background and Methods: Cheyne-Stokes respiration (CSR) is an independent marker of death in heart failure. Interest has therefore been aroused in therapies that might attenuate CSR and reduce heart failure mortality. Biventricular pacing (BVP) improves cardiac output and reduces wedge pressure. We hypothesised that BVP would therefore reduce CSR. We investigated this using single-blind cross-over design; one month each in BVP and DDI-40 pacing modes. CSR was documented and respiratory variables assessed using overnight polysomnography. Daytime sleepiness was assessed using the Epworth sleepiness score (ESS).
Results: We report provisional results for our first 7 subjects Demographic characteristics: mean (SD) age – 60 years (10), ejection fraction – 29% (8), QRSD – 168msec (8). 5 subjects had ischaemic heart disease, 2 dilated cardiomyopathy. All were NYHA class 3.
All values are means (SEM). Over 80% of measured respiratory variables were central in origin. BVP was associated with reductions in apnoea index (13.7(6.3) v 7.7(3.8) v 16.6(7.3) per hour for baseline, BVP and DDI respectively; p=0.07), apnoea-hypopnoea index (26.3(5.4) v 16.9(6.9) v 27.1(6.1); p=0.07) and periodic breathing time (43(11) v 26(10) v 43(13); p=0.02). There was an associated trend towards reduced daytime sleepiness assessed by ESS scores (9.9(0.8) v 6(2) v 9(1.6); p=0.13).
Conclusion: The significant reductions in respiratory events suggest that BVP may exert a beneficial effect on Cheyne-Stokkes respiration. This was associated with a trend towards improved patient symptoms.

P2123 Transthoracic high-resolution real-time three-dimensional echocardiography for the analysis of regional left-ventricular wall motion patterns in patients with cardiac resynchronization therapy

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Cardiac resynchronization therapy (CRT) improves left ventricular (LV) function in patients (pts) with heart failure and left bundle branch block (LBBB). Echocardiography allows direct evaluation of the mechanical dyssynchrony. We evaluated the recently developed transthoracic high-resolution real-time 3D echocardiography (rt3DE) in combination with semi-automated contour tracing algorithms for the analysis of global function and regional LV wall motion in CRT patients.
Methods: In 12 pts (68±6 years) with sufficient transthoracic image quality two rt3DE data sets (Live3D, Philips; acquisition time 8±4 s) were acquired: the first one during intrinsic rhythm (sinus rhythm; QRS duration 190±20ms), and a second during CRT. 3D data were analysed off-line using a semi-automated contour tracing algorithm (LVAnalysis 1.1RT, TomTec) under both conditions. Global LV volumes were determined at each time point every 40 ms over a complete heart cycle as well as regional volumes and regional ejection fraction (= EF) for all 16 LV segments separately. Time differences between maximal LV wall in- and outward motion were evaluated as well as its velocities.
Results: Global LV EF improved from 29±11% (IR) to 36±12% (CRT; $p<0.01$). During IR septal wall motion amplitude was reduced compared to both lateral and posterior segments and increased by 55±26% during CRT ($p<0.001$). The time difference of maximal inward wall motion between lateral and septal segments decreased from 96±22 (IR) to 28±25ms (CRT; $p<0.001$). However, there were no significant differences in regional wall motion patterns (amplitude and time point) or velocities between anterior, inferior and lateral LV segments.
Conclusion: High-resolution rt3DE allows a comprehensive analysis of global LV function and regional wall motion before and during CRT. In contrast to conventional 2D echo (where not all LV segments can be acquired simultaneously) rt3D allows a comparison of all LV segments at the same time point. During IR septal and lateral wall showed a significant time difference of contraction and differences in wall motion amplitude which were reduced during CRT. Whether these parameters can be used for preoperative patient selection or postoperative monitoring needs further evaluation.

P2124 Autonomic changes induced by cardiac resynchronization therapy in patients with congestive heart failure

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Cardiac resynchronization therapy (CRT) is now widely used as an additional treatment for patients with congestive heart failure (CHF) and already in optimal drug therapy. The heart rate variability (HRV) parameter is an index of autonomic function and can be of prognostic value for both arrhythmic and total mortality depending on the selected cut off. Limitations bounded to this methodology are mainly related to the quality of the recorded surface ECG and to the premature contractions that could occur in atrium or ventricle forging the analysis. The aim of our study was to record the HRV modifications at predischarge and at 6 months follow up in patients with CHF, undergoing CRT and having conventional indication to implantable cardioverter defibrillators (ICD), using an automatic analysis function of the device.
Methodology: the HRV parameters were calculated by an automatic algorithm implemented in the diagnostic of the implanted device (Contak Renewal ICD, Guidant), which only computed ventricular beats triggered by spontaneous atrial activity that needed to be evident for at least 67% of the total time of 24 hours. The SDNN, the Median of the heart rate and the Footprint values were automatically calculated every day and stored into the device memory. The Footprint calculated percentage value represents the ratio of the area of the variability graph of the heart rate and the total area of the graph, the greater is the ratio the bigger is the increase in HRV.
Study population: 10 pts (9 males, mean age 69,7±5) with cardiomyopathy of any etiology and wide QRS duration (left bundle branch block with more than 150 ms) underwent CRT. The functional NYHA class at baseline were III/IV (one in class II) with low ejection fraction (EF) and Minnesota Quality of Life (MQOL) score of 54,5±7.
Results: a statistical significant decrease ($p<0.005$) of the SDNN (67,1±25 vs. 109±46, 36% increase), and increase of the footprint (35,9±16 vs. 47,9±19, 33% increase) were found from predischarge to 6 months follow up, whereas no statistical difference was shown by the median heart rate. Similarly the EF increment was 31% (26±4 vs. 35±4) while the MQOL reduced of 45% being both values statistically significant ($p<0.005$).
Conclusions: The CRT favorably affects SDNN and Footprint values in this patient population suggesting a reverse remodeling effect for both cardiac geometry function and the autonomic function. The patient well being status reported in the MQOL is an additional confirmation of this improvement. Further studies on larger population are needed to confirm these results.

RESYNCHRONIZATION THERAPY IN HEART FAILURE II

P2125 Characterisation of left-ventricular activation in left bundle branch block; implications for cardiac resynchronisation therapy

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Up to 30% of patients with heart failure and left bundle branch block (LBBB) treated with biventricular pacemakers (BVP) fail to show any clinical improvement and the reasons for this remain unclear. Left ventricular (LV) endocardial activation was characterised using non-contact mapping in 41 patients (mean age 66.0±7.4, 6 female) with impaired LV function, 36 with ischaemic heart disease, 4 with dilated cardiomyopathy and 1 with cardiac sarcoidosis. 20 patients had normal QRS duration (NQRS) (mean 107.3±10.1ms) and 21 had LBBB (QRS 163.5±30.6ms). RVA depolarisation occurred 21.4±15.4ms after QRS onset in the NQRS group and 21.2±18.4ms in the LBBB group (p=NS). Earliest LV activation occurred 0.42±13.5ms (range -26 to +28ms) after QRS onset in the NQRS group and 21.2±18.4ms (range -10 to +80ms, p=0.002) in the LBBB group and earliest LV activation occurred prior to RVA depolarisation in 11 of 21 patients with LBBB (52%). Latest activation (the latest measurable depolarisation), however, occurred 47.6±12.4ms after QRS onset in the NQRS group and 105.7±38.6ms in the LBBB group (p=<0.001). Therefore, total LV activation time (from earliest to latest depolarisation) was 47.2±16.2ms in the NQRS group and 89.5±33.5ms in the LBBB group (p=<0.001), but as a proportion of QRS duration was similar between the two groups, 45.2±14.6% in the NQRS group and 53.2±16.0% in the LBBB group (p=NS). Conclusions- Earliest LV endocardial activation occurs prior to RVA depolarisation in >50% of patients with LBBB. Although there is a relatively small delay in onset of LV activation in LBBB (~20ms), the principal cause of QRS prolongation is due to increased left ventricular activation time (by ~40ms). This factor, which is not addressed with current resynchronisation therapy, may explain the lack of benefit in some patients and has major implications for the further development of both location and time interval selection of LV pacing in patients requring BVP.

P2126 Intrinsic and paced QRS duration are predictive of the global clinical response to cardiac resynchronization therapy in patients with severe heart failure

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The aim of this study was to assess the value of intrinsic and paced QRS duration to predict the clinical response to permanent biventricular pacing. 139 consecutive patients under optimized drug treatment, 77% males, mean age 68 years, were implanted with a biventricular pacemaker for severe heart failure (HF) between 1994 and 2000. 96 pts were in NYHA class III and 43 in class IV. The mean LV ejection fraction (LVEF) was 21 $\pm$ 6% and the mean baseline QRS duration: 188 $\pm$ 28 ms. The right and left ventricular lead positions were optimized in each patient to achieve the shortest biventricularly paced QRS duration. The clinical response at 6-months was assessed with a composite endpoint. Responder pts (R) had to be alive, without any new heart failure hospitalization and functionally improved with a decrease $>$1 NHYA class and/or a $>$10% increase in peak VO2. All other pts were classified as non responders (NR). There was no statistically significant difference between R and NR for all baseline parameters except baseline QRS duration (192 $\pm$ 27 ms vs 180 $\pm$ 29 ms, p=0.02).

Results at 6-months follow-up

	R (101)	NR (38)	
NYHA Class	1.9 $\pm$ 0.8	2.9 $\pm$ 0.4	$<$ 0.001
6 min walk (m)	395 $\pm$ 84	266 $\pm$105	$<$ 0.001
VO2 peak (ml/min/kg)	15.5 $\pm$ 4	13.6 $\pm$ 3.8	0.003
LVEF (%)	29 $\pm$ 6	22 $\pm$ 7	$<$ 0.001
QRS Biv. paced (ms)	155 $\pm$ 20	168 $\pm$ 20	$<$ 0.001
Delta based/paced QRS (ms)	37 $\pm$ 23	11 $\pm$ 27	$<$ 0.001

In conclusion: 73% pts respond positively to CRT. Wider baseline QRS duration and greater QRS shortening after biventricular pacing were associated with significantly better clinical outcome.

P2127 Comparison of unipolar and true bipolar left-ventricular pacing in patients undergoing cardiac resynchronization therapy

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Background: High pacing thresholds and inadvertent phrenic stimulation are limitations for effective left ventricular (LV) pacing. The aim of the study was to compare at implantation of a new bipolar coronary sinus lead bipolar and unipolar pacing and sensing characteristics to each other. **Methods:** The study included 35 patients with advanced heart failure and bundle branch block who received for cardiac resynchronization therapy the bipolar coronary sinus lead model 1055 T (St. Jude Medical). The lead was implanted in a side branch of the coronary sinus. After lead fixation pacing thresholds at 0.5 ms pulse duration, pacing impedance, R-wave amplitude, and the pacing output for inadvertent phrenic stimulation were determined with a pacing system analyzer. Unipolar measurements were performed with the tip (UTIP) or ring (URING) as cathode and the bipolar measurements with the ring as anode (BI).
Results: Unipolar pacing threshold was in the regular configuration 1.2 $\pm$ 1.0 V (UTIP) and increased to 2.7 $\pm$ 2.3 V in the URING configuration ($p<0.05$). Bipolar threshold was with 1.2 $\pm$ 0.8 V not significantly different to UTIP pacing. Unipolar pacing impedance was 1041 $\pm$ 362 ohms for UTIP and 705 $\pm$ 317 ohms for URING ($p<0.05$). The bipolar pacing impedance was with 1121 $\pm$ 460 ohms not different from UTIP. Stimulation of the phrenic nerve was observed during UTIP pacing at 8.9 $\pm$ 2.2 V, during URING at 7.7 $\pm$ 2.9 V, and during BI pacing at 8.9 $\pm$ 2.3 V. R-wave amplitude was not statistically significant different with 19.5 $\pm$ 8.6 mV (UTIP), 16.5 $\pm$ 8.7 mV (URING), and 16.2 $\pm$ 8.9 mV (BI).
Conclusions: The bipolar LV pacing threshold of the new bipolar coronary sinus lead was not increased and bipolar pacing impedance not decreased compared to unipolar pacing. Inadvertent stimulation of the phrenic nerve was observed in most patients only at very high outputs. High R-wave amplitude were measured in both sensing modes. The bipolar coronary sinus lead for cardiac resynchronization therapy had an excellent acute pacing and sensing performance. Current delivery from the ring seems to deteriorate LV pacing characteristics.

P2128 Left-ventricular pacing alone has acute haemodynamic benefits similar to those of biventricular pacing in patients with severe heart failure

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Major mechanisms of cardiac resynchronisation therapy in patients with advanced heart failure are improvement of intra- and inter- ventricular synchrony, and decrease of secondary mitral regurgitation (MR). We compared the effects of left ventricular (LV) and biventricular (BiV) pacing on these mechanisms, using conventional and tissue Doppler echocardiography.
Methods: One to six months after their pacemaker implantation, 16 patients (64$\pm$8 years, EF = 31$\pm$8%) underwent a crossover comparison during sinus rhythm (unpaced), LV pacing, and BiV pacing. Tissue Doppler velocities and timings (from the onset of the QRS complex to peak systole) were measured off-line, in six LV basal segments for longitudinal function (apical views), and one right ventricular (RV) segment (free wall, A4C view). The velocities of the basal segments were averaged. LV longitudinal synchrony was defined as the standard deviation of the myocardial timings. Interventricular synchrony was defined as the difference between RV and mean LV longitudinal timings. The severity of MR was assessed from the regurgitant orifice area (PISA method). Global systolic and diastolic function were assessed using ejection fraction and transmitral flow propagation velocity.
Results: We calculated and compared the changes from baseline for both pacing modalities (table). Intraventricular synchrony, regional and global systolic function, diastolic function, and degree of MR were similar between LV and BiV pacing. LV pacing was more effective than BiV pacing in coordinating onset of regional contraction between LV and RV; in some patients (62%), LV pacing caused LV to contract before RV.

Comparison between LV and BiV pacing

	LV pacing vs baseline	BiV pacing vs baseline	p
Intraventricular synchrony (ms)	-17 (19)	-20 (18)	0.16
Longitudinal velocity (cm/s)	+0.25 (0.46)	+0.19 (0.32)	0.32
Interventricular synchronicity (ms)	-77 (65)	-51 (39)	0.02
Regurgitant orifice area (mm^2)	-0.04 (0.07)	-0.04 (0.09)	0.71
Ejection fraction (%)	+2 (2)	+3 (2)	0.29
Flow propagation velocity (cm/s)	+6(5)	+5(7)	0.55

Conclusion: LV and BiV pacing have similar acute haemodynamic effects, suggesting that in some patients LV pacing alone may be sufficient for clinical benefit. This should be tested in long-term studies.

RESYNCHRONIZATION THERAPY IN HEART FAILURE III

P2129 Assessment of ventricular asynchrony in severe heart failure: comparison between patients with advanced ischaemic and non-ischaemic cardiomyopathy

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Biventricular stimulation (BVS) has shown efficiency in terms of functional improvement in chronic heart failure (CHF). Correction of intra-ventricular asynchrony is well correlated with these results. The stimulation site is usually lateral. Ischemia is the most important etiology of CHF but asynchrony has never been evaluated in this population. The aim of our study was to assess left ventricular asynchrony parameters in a population of 100 consecutive severe CHF patients, with or without evident delayed electrical conduction, and to compare ischemic (50 pts) and non ischemic (50 pts) patients.
Method: In 100 consecutive CHF patients with depressed systolic function (LV ejection fraction (LVEF)$<$35%), we assessed QRS duration on surface ECG, and with echocardiography: LVEF, LV diastolic (LVTD) volume and Aorto-pulmonary (AoP) delay. Intra-ventricular delay (LV delay) and last activated wall were assessed using Doppler Tissue Imaging (DTI).
Results: Results are summarized in the following table. LV delay was significantly correlated with QRS duration (r=0.47, p=0.001) and LVTD volume (r=0.47, p=0.001) for non-ischemic patients. This was not significant in ischemic patients.

	n	Ischemic			Non-ischemic			p
		QRS $<$120ms	QRS: 120-150ms	QRS $>$150ms	QRS $<$120ms	QRS: 120-150ms	QRS $>$150ms	
n	100	23	14	13	25	7	18	ns
LV delay $>$40ms	65	12	7	11	14	5	16	ns
Last wall activated= lateral	44/65	8	5	9	10	4	8	ns
Last wall activated= anterior or septal	21/65	4	2	2	4	1	8	ns
AoP delay$>$40ms	31	3	3	9	2	1	13	ns

Conclusion: ECG is insufficient to detect intra-ventricular asynchrony particularly for ischemic patients. Last activated wall is not lateral for 32% of patients even with a large left bundle branch block. Thus, echocardiography should be made whatever the QRS duration to select patients for BVS, to assess intra-ventricular asynchrony and to define the last activated wall for an optimal LV lead location.

P2130 Electroanatomical mapping of left-ventricular endocardial activation and acute haemodynamic effect of left-ventricular stimulation in patients with dilated cardiomyopathy and left bundle branch block

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Left ventricular (LV) stimulation improves systolic LV function in patients (pts) with heart failure and left bundle branch block (LBBB). Whether the site of LV endocardial breakthrough affects the site of latest LV activation, and the relationship between the acute hemodynamic benefit and conduction delay (CD) are unclear.
Methods: We performed 1) 3D electroanatomical mapping of LV endocardial activation during sinus rhythm and 2) LV stimulation in VDD mode at 5 different sites (at 4 AV delay) at anterior and lateral branches of coronary sinus (from earliest to latest CD, as measured from the onset of QRS to local activation time) using two 2.5F 16 poles mapping catheter in 12 pts (9 males, age: 67±10 yrs) with dilated cardiomyopathy and LBBB (ejection fraction: 27±7%; QRS duration: 165±17 ms). LV +dP/dtmax and aortic pulse pressure changes from baseline during LV pacing were measured at LV sites with different CD.
Results: The mean LV endocardial activation time was 98±22ms (47±10 ms after onset of QRS complex). There is a significant correlation between the QRS duration and endocardial activation time ($r=0.6$, $p<0.01$). 9 pts had 1 site of LV endocardial breakthrough (mid septum=6, apical septum=2, mid anterior=1) and 3 pts had 2 sites of breakthrough (mid septum + mid anterior=2, apical septum +basal septum=1). All pts had only 1 latest LV site (basal posterior=4, mid posterior=2, basal lateral=5, mid lateral=1). No consistent relationship between the sites of endocardial breakthrough and the sites of latest LV endocardial activation was observed. LV stimulation protocol was completed in 10 pts. LV pacing at sites with latest CD yielded significantly larger +dP/dtmax (19.5±13.6% vs. 4.6±8.6%, $p<0.01$) and aortic pressure (8.3±6% vs. 3±5.8%, $p<0.001$) compared with sites with earliest CD. 8/10 pts showed a strong and significant individual correlation between CD and %+dP/dtmax (all $r>0.7$ and $p<0.05$).
Conclusions: In pts with dilated cardiomyopathy and LBBB, LV endocardial activation sequence is heterogeneous and no discrete pattern of LV endocardial breakthrough site is observed. However, independent of the sites of endocardial breakthrough, the latest LV endocardial activation was frequently observed at the posterior or lateral basal sites of LV. LV stimulation at sites with latest CD produced a significantly better systolic performance compared with at sites with earliest CD. Our data suggest that the LV stimulation sites for cardiac resynchronization therapy should be selected the posterior or lateral basal sites of LV with longest CD for optimal hemodynamic benefit.

P2131 Long-term comparison of coronary venous leads versus epicardial leads for left-ventricular pacing in patients receiving cardiac resynchronization therapy

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Purpose: Currently the coronary venous (CV) approach is preferred to the epicardial (EC) approach for left ventricular (LV) pacing in patients receiving cardiac resynchronization therapy (CRT). The purpose of this study is to compare both approaches in the long-term follow-up.
Methods: We evaluated 81 patients (pts) receiving a CRT-system (age 65±12 years, 52men, 38 pts with ischemic cardiomyopathy (ICM), 43 pts with non-ischemic cardiomyopathy (NICM), NYHA class 3,0±0,4, EF 24±6%, QRS duration 166±21msec) retrospectively: 25 pts received EC leads, in 56 pts CV leads were placed. Data from the 6- and 12-months follow-up were analysed.
Results: After CV lead implantation we observed a shorter postoperative hospitalisation (8±4 vs. 12±5 days, $p<0,01$). LV pacing thresholds (see table). There was no significant change of LV sensing in both groups during follow-up. After CV implantation reinterventions were necessary in 7 cases (12.5%): because of increased LV thresholds (n=2), LV lead dislodgment (n=3) and phrenic nerve stimulation (n=2). After EC implantation only 1 reintervention (4%) because of increased LV threshold was needed. Postoperative chest radiographs revealed an anterior lead position in the EC group in 44% vs 5.4% in the CV group ($p<0,01$), whereas more leads in the CV group were placed in a posterolateral or posterior position (55% vs 4%, $p<0,01$). Cardiopulmonary exercise test (n=37) showed a significant increase in peak oxygen consumption (VO2max) in the CV group (n=24) at 6 and 12 months in contrast to the EC group (15,5±3,1 vs. 12,7±1,5 at 12 months, $p<0,01$). At 1-year follow-up mortality rate was 24% (6/25) after EC lead implantation versus 12,5% (7/56) after CV implantation.
Conclusion: EC leads have the advantage of lower pacing thresholds and a lower incidence of reinterventions. In contrast hospitalisation after EC implantation is longer, increase in functional capacity is lower and mortality rate at 1-year follow-up tends to be higher, potentially related to a more anterior lead position. Therefore CV leads seem to be preferable to EC leads.

LV pacing thresholds

Pacing threshold (V/0,5msec)	Implant	6 months	12 months
CV	1,14	1,80#	1,91#
EC	0,82*	1,51#	1,61+

*$p<0,05$ vs. CV; #$p<0,05$ vs. implant; +p=non significant vs. CV

P2132 Acute effect of biventricular pacing on mitral regurgitation in patients with severe chronic heart failure: a quantitative echocardiographic study

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Background: Resynchronization of the lateral and septal wall contraction of the left ventricle (LV)with biventricular pacing (BiP) may lead to an increased stroke volume in patients with advanced heart failure and delayed intraventricular conduction due to left bundle branch block (LBBB). However, improving the synchronization of the LV segmental contraction may also have an impact on mitral annulus and subvalvular apparatus motion, reducing mitral regurgitation (MR). We sought to analyze the effect of BiP on MR, using validated quantitative echocardiographic methods.
Methods: Twenty-two patients (17 (77%) men, age 70±7 y.o.) with heart failure, NYHA functional class III-IV, LV ejection fraction < 35% and LBBB and some degree of MR were studied with color-Doppler echo before and after activation of BiP. MR was quantified according to the flow convergence method with a hemispherical assumption so that regurgitant orifice area (ROA= 2*3.14*r2*V/Vmax, where r is the radius of the flow convergence area, V equals to the Nyquist velocity and Vmax to the peak regurgitant velocity. Regurgitant volume (RV) was calculated as RV = ROA* VTI, where VTI is the velocity-time integral of the regurgitant flow as determined by CW Doppler. LV dimensions (by M-Mode) and ejection fraction (by the biplane Simpson's method) were also determined. Cardiac output was estimated with quantitative Doppler.
Results: Table shows quantitative data of MR and LV dimensions without pacing (OFF) and with activated BiP (ON). With BiP, MR was significantly reduced with a significant decrease in LV end-systolic dimension and a slight increase in LV EF.

Quantitative data of MR and LV

PACING	ROA (mm^2)	RV (ml/beat	LVEDD (mm)	LVESD (mm)	LV EF(%)	CO (L/Min)
OFF	0.18±0.23	26.9±32.6	74.8±7.2	62.5±8.6	21.9±4.2	3.6±1.2
ON	0.07±0.09*	11.1±13.7*	74.0±6.7	59.4±8.6*	25.1±5.0*	3.8±.08

ROA= mitral regurgitant orifice area; RV= mitral regurgitant volume; LVEDD= LV end-diastolic diameter; LVESD=LV end-systolic diameter; LV EF= LV ejection fraction; CO= cardiac output;* $p<0.01$.

Conclusions: Resynchronization therapy with biventricular pacing acutely reduces MR in patients with advanced heart failure and delayed intraventricular conduction due to LBBB. Reduction of the LV end-systolic dimension may cause MR reduction that in turn, may contribute to clinical improvement of these patients.

P2133 Cardiac resynchronization is associated with a lower incidence of implantable cardioverter-defribrillator therapy in a case control study

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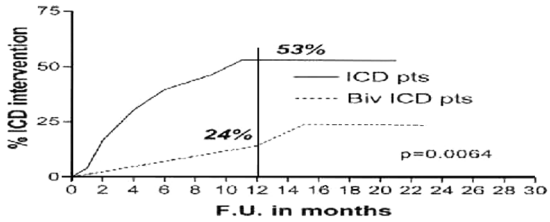
Cardiac resynchronization by biventricular pacing improves subjective well-being and exercise tolerance in patients (pts) with end-stage heart failure. Controversy exists about the possible antiarrhythmic effects of cardiac resynchronization in heart failure pts. The aim of this study therefore was to compare the incidence of ICD therapy during follow-up in recipients of a biventricular ICD to a case control population of pts with a regular ICD.

Methods: Thirty-nine pts with severe heart failure and cardiac asynchrony (LVEF 22±7%) due to congestive (59%) or ischemic cardiomyopathy (41%) who received a biventricular ICD because of monomorphic ventricular tachycardia (69%), ventricular fibrillation (21%) or prophylactically (10%) were studied. The study pts were compared to control pts out of our database of 350 ICD pts who received a regular ICD because of a comparable arrhythmia and who were further matched with respect to underlying pathology, LVEF and drug treatment. The cumulative occurrence of ICD intervention was calculated using the Kaplan-Meier method.

Results: Matching of pts and controls was complete except that controls had a significantly higher baseline LVEF of 27±8% (p=0.008). Cumulative occurrence of ICD intervention at 12 months was significantly higher in control pts (53%) compared to biventricular ICD pts (24%) (see figure). Biventricular ICD pts showed an increase in LVEF from 22±7 to 32±11% (p=0.0001) during follow-up.



Conclusions: Congestive heart failure pts with a biventricular ICD have a lower incidence of ICD intervention than control pts with a regular ICD. Reversed left ventricular remodeling associated with cardiac resynchronization therapy may explain part of the difference.

P2134 Supraventricular arrhythmia can be reduced by cardiac resynchronisation therapy

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Patients (pts.) with heart failure (HF) and left bundle branch block (LBBB) frequently suffer from supraventricular (SV) and ventricular (V) arrhythmias (A). Cardiac resynchronisation therapy (CRT) has been shown to improve hemodynamics and autonomic balance of pts. with HF and LBBB and may thus exert antiarrhythmic effects. We investigated the effects of CRT on the incidence of SVA in Holter ECG (HOL) and compared these results to echocardiographic parameters, brain natriuretic peptide (BNP) and norepinephrine (NEP) levels.

Methods: We included 23 pts (14 m, 66±11y) with ischemic (11 pts) and non-ischemic (12 pts) cardiomyopathy. The functional class of heart failure was 3.0±0.6, QRS duration was 162±16ms and left ventricular (LV) ejection fraction was 26±7%. Pts. with a change of antiarrhythmic medication within the observed period were excluded. Before implantation (pre) of a CRT device and after 3 months of therapy (VDD mode), left atrial diameter (LAD), biplane LV enddiastolic (LVEDV) and endsystolic volume (LVESV) were measured by echocardiography. BNP and NEP blood samples were collected and frequency of supraventricular extrasystoles (ES) and SV tachycardia (SVT) was assessed from HOL.

Results (see table): A significant reduction of non-sustained VT or ventricular extrasystoles in Holter could not be observed.

Results (Mean ± SD):

	SVT [/24h]	SVES [/24h]	LAD [mm]	LVESV [ml]	LVEDV [ml]	BNP [pg/ml]	NEP [nmol/l]
Pre	0.27 ± 0.86	131 ± 356	43.8 ± 7.9	185 ± 63	251 ± 70	471 ± 380	3.8 ± 1.5
CRT	0.14 ± 0.64	9 ± 24	43.5 ± 8.7	133 ± 71	192 ± 74	195 ± 230	2.7 ± 1.5
p	<0.001	<0.001	n.s.	<0.001	<0.001	<0.001	<0.05

Conclusion: CRT reduce significantly SVA and SVT. Decreased LV volumes and BNP indicate reduced wall tension and decreased NEP levels a reduction of sympathetic tone. These may be the underlying mechanisms for the antiarrhythmic effect of CRT. However, reduction in VA could not be demonstrated suggesting other involved mechanisms responsible for VA.

P2135 Septal to posterior wall motion delay predicts long-term reverse remodelling after cardiac resynchronization therapy

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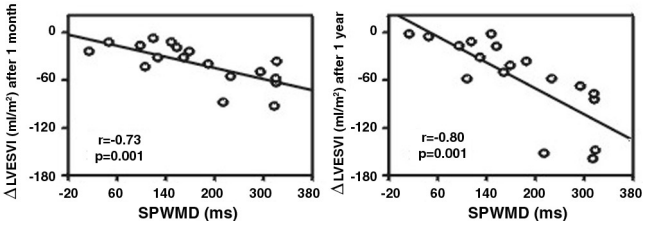
The characteristics of patients who most benefit from cardiac resynchronization therapy (CRT) are not well clarified. The aim of this study was to investigate the value of an echocardiographic intraventricular asynchrony parameter in predicting short- and long-term hemodynamic effects of CRT. We studied 18 patients (64±11 years, 9 male) with heart failure (HF), NYHA class III and left bundle branch block (LBBB), in optimal medical therapy. Intraventricular asynchrony was assessed as the shortest interval between the maximum posterior displacement of the septum and the maximum displacement of the left posterior wall during systole (septal to posterior wall motion delay, SPWMD, ms). Left ventricular end-diastolic (LVEDVI, ml/m^2) and end-systolic (LVESVI, ml/m^2) volumes indexed for body surface area as well as left ventricular ejection fraction (LVEF, %) were analyzed. Measures were taken at baseline, 1 month and 1 year after CRT. At 1 month, LVEDVI (from 149±55 to 118±40 ml/m^2, p<0.001), LVESVI (from 117±44 to 86±30 ml/m^2, p<0.0001) and LVEF (from 23±4 to 29±6%, p<0.05) improved. A further improvement was observed after 1 year: LVEDVI= 89±40 ml/m^2, p<0.001; LVESVI= 60±33 ml/m^2, p<0.001; LVEF= 35±10%, p<0.001. Baseline SPWMD was significantly related to 1 month and 1 year improvements of both LVESVI (Figure) and LVEDVI (r=-0.71, <0.05; and r=-0.73, p<0.05, respectively) as well as to 1 year improvement of LVEF (r=0.48, <0.05).



In conclusion, in patients with advanced HF and LBBB, baseline SPWMD is a strong predictor of short- and long-term occurrence of hemodynamic improvement after CRT, thus suggesting its usefulness in identifying patients who most benefit from biventricular pacing.

DIASTOLIC FUNCTION

P2136 Developmental changes in diastolic behaviour from fetal period to first year of life: an echocardiographic colour-Doppler study

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Background: There are few observations on the diastolic heart function during fetal and/or first life periods; compared to adult heart, a reduction in ventricular compliance indexes seems to be present in fetuses, perhaps due to ultrastructural variations of myocardium. Ultrasounds may be a suitable method to provide further information about these developmental changes. **Purpose:** To evaluate right ventricular (RV) and left ventricular (LV) diastolic properties at different gestational ages and during first year of life. **Methods:** Echocardiographic Color-Doppler examinations were performed in 91 normal subjects: 66 fetuses (22 at the 20th week of gestational age, 27 at the 30th week and 17 at the 36th week, respectively), 15 newborns, and 10 one-year old children. Peak E (pE), peak A (pA), E/A ratio, deceleration time (DT), time-velocity integral (TVI), nPeak Filling Rate (nPFR) were derived from PW Doppler flow contours across atrio-ventricular valves; chamber stiffness was evaluated as K ventricle = 0.08/DT. **Results:** Similar values in heart rate were observed during gestational ages and at birth, whereas a significant (p<0.05) decrease was present at one-year of life. In fetal stages pE, pA and TVI were significantly greater in RV rather than in LV (p<0.05); both E/A ratios were <1. With advancing gestational age progressive increases in pE, pA, E/A ratio, TVI, DT, with parallel decreases in both chamber stiffness were observed; conversely, no changes in nPFR in both ventricles were found. At birth significant changes of transmitral flow pattern were present, resulting in profound effects on E/A ratio (>1), increases in TVI, K ventricle and nPFR respectively, and DT reduction. Tricuspid inflow analysis showed no change in E/A ratio (still <1), TVI increase (p<0.01), nPFR decrease (p<0.01). At one year-age further TVI increases were observed in both ventricles; the rise in RV (p<0.01) pE shifted E/A ratio to > 1. **Conclusions:** Ultrasounds carefully describe developmental changes in heart diastolic properties, encompassing right-sided dominance (fetal period) and progressive biventricular compliance increments (advancing gestational age). Physiological changes in loading conditions yield suddenly at the birth, leading to transmitral flow "adult" pattern, while a "fetal" flow pattern may persist at tricuspidal level until one-year of life.

P2137 Left-ventricular diastolic dysfunction as early manifestation of adriamycin (doxorubucin) cardiotoxicity

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Background: Adriamycin is well known to cause dose-dependent cardiotoxicity. This is manifested as left ventricular (LV) systolic dysfunction and congestive heart failure, the clinical presentation of which may be delayed for years after completion of chemotherapy. There is limited data regarding early manifestation of cardiotoxicity as LV diastolic dysfunction detectable in asymptomatic stage after initial doses of the chemotherapeutic agent.
Aim: To evaluate the early effect of adriamycin in left ventricular (LV) diastolic function.
Method: 105 consecutive oncology patients who were referred for echocardiography during the course of adriamycin therapy (adriamycin group) or before commencement of chemotherapy (control group) were assessed for LV diastolic dysfunction.
Results: There were 72 patients in adriamycin group (Group A) (F:M=70:2) and 33 patients in control group (Group C) (F:M=30:3). There was no difference in age between the two groups (48 $\pm$ 7.3 yrs for Group A, 47 $\pm$ 8.4 yrs for Group C, p=0.17). In Group A, echocardiogram was performed 16 $\pm$ 8 days after last dose of adriamycin, after a mean of 1.8 doses (range 1-6 doses), with a mean accumulated dosage of 107mg/sq m (range: 40-300mg/sq m). There was a significant higher incidence of diastolic dysfunction ("impaired relaxation") in Group A than in Group C (47% Vs 24%, p=0.026). As compared to Group C, Group A showed a lower mitral E velocity (0.69 Vs 0.78 m/s, p=0.01), a lower mitral E/A ratio (1.1 Vs 1.3, p=0.03), a longer isovolumetric relaxation time (IVRT) (91 Vs 80 ms, p=0.001), and a lower mitral septal annular early diastolic velocity (Ea) (0.106 Vs 0.120 m/s, p=0.04).
Conclusion: Left ventricular diastolic dysfunction occurred early after initiation of adriamycin therapy, suggesting that this is an early marker of adriamycin cardiotoxicity. The clinical implication of this finding, especially in predicting patients at risk for developing clinically significant cardiomyopathy, deserves further study.

P2138 Age and diastolic function. Which parameters are more useful in ageing subjects?

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Background: Diastolic function could be a cause of cardiac heart failure (CHF), and left ventricular diastolic parameters can measure its impairment. Nevertheless, some of those parameters change with age, making diastolic dysfunction measurement more difficult, when comparing young, old and very old subjects or during long-term clinical follow-up. Recently a new index, the ratio of early to late transmitral flow propagation velocity, Vp/Vpa, has been reported as a promising parameter of diastolic function that provides us with additional information about the late filling period. In a multicenter population study we compared E/A, IVRT, tau, deceleration time (DT), Vp and Vp/Vpa in healthy subjects from 50-80 years old to assess their variation with age.
Methods: We studied 215 subjects (119 F, 96 M), age 66$\pm$9, (45-86), obtained from a random sample of 432 people from the Valencian Community, Spain (Alicante, Castellon, Valencia), which in a previous questionnaire had declared to suffer from some degree of dyspnea. These 432 subjects were referred to their local hospital (10 hospitals involved in the study) where blood samples were taken, an echo-Doppler study was performed and a specific questionnaire was completed. Tapes were all measured independently at the same hospital. Out of the 432 subjects we got a positive answer from 215. From this population, we identified subjects in sinus rhythm without cardiovascular (CV), renal or pulmonary disease or diabetes, they were not on any CV medications, and they all had a normal systolic, diastolic and valvular function on echo-Doppler (n=88). IVRT, tau and DT are in ms and Vp in cm/s.
Results: For the overall population E/A was 0.91$\pm$0.22, IVRT 91$\pm$10, tau 35$\pm$4, DT 197$\pm$37, Vp 67$\pm$15 and Vp/Vpa 0.98$\pm$0.37. When we compared age groups (50-60, AI; 60-70, AII and 70-80, AIII) we found for E/A (1$\pm$0.26, 0.86$\pm$0.17, 0.77$\pm$0.13), p$<$0.0001; IVRT was (93$\pm$10, 87$\pm$10, 94$\pm$11), NS; tau was (36$\pm$4, 33$\pm$4, 36$\pm$5), NS; DT was (188$\pm$34, 196$\pm$32, 220$\pm$43), p$<$0.05; Vp was (66$\pm$13, 71$\pm$17, 62$\pm$11), NS and Vp/Vpa was (0.93$\pm$0.45, 1$\pm$0.37, 0.96$\pm$0.22), NS.
Conclusion: This multicenter population study shows that IVRT, tau, Vp and Vp/Vpa did not change in AI, AII and AIII groups. DT increased and E/A decreased progressively. This could be of potential diagnostic and prognostic importance when comparing left ventricular diastolic function in old and very old subjects or during long-term clinical follow-up.

P2139 Assessment of left atrial input impedance in normal subjects and in hypertensive patients

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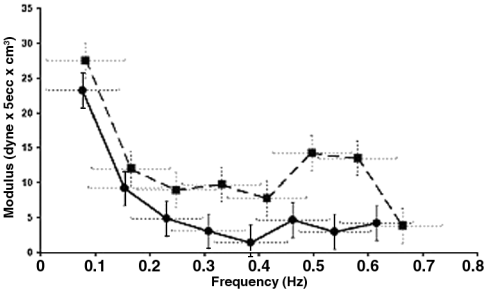
Background: To assess left atrial (LA) input impedance in patients with diastolic heart dysfunction due to essential hypertension, the transesophageal Doppler pulmonary venous (PV) flow velocity and the pulmonary capillary wedge (PCW) pressure were studied in 20 such patients and compared to 20 matched normal controls. **Methods:** The LA impedance was calculated as the ratio of harmonic terms of the PCW pressure (measured by right heart catheterization) to the corresponding harmonic terms of PV flow (measured by transesophageal Doppler echocardiography). Eight harmonics were analyzed (figure: squares represent patients and circles controls). **Results:** Left ventricular mass index (LVMI, p$<$0.001), heart rate (HR, p$<$0.05), systoloic and diastolic blood pressure (p$<$0.001), isovolumic relaxation time (IVRT, p$<$0.001), peak A transmitral flow velocity (p$<$0.001), peak reversal atrial PV flow velocity (pAR, p$<$0.001) and LA diameter (p$<$0.001) were increased in patients compared to controls. Spectra of impedance moduli were displaced upwards and to the right. The increase in the impedance moduli was observed at all frequencies of all harmonic components (p$<$0.001). In multivariate test LVMI (p=0.003), IVRT (p=0.001), and LA diameter (p=0.007) had significant effect on all harmonic components of the impedance moduli (adjusted R2= 0.970 to 0.999, p$<$0.001).



Conclusions: The LA input impedance may be a sensitive index of diastolic function and it expresses resistance to heart filling. Spectra of impedance moduli are displaced upward and to the right in hypertensive patients.

P2140 Low prevalence of isolated diastolic dysfunction in a cohort of suspected heart failure patients and its relationship to brain natriuretic peptide

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Estimates of the prevalence of heart failure due to isolated LV diastolic dysfunction (DD) vary widely. We report the prevalence of DD in a cohort of 331 patients with suspected heart failure and the corresponding levels of BNP. LV systolic dysfunction (LVSD) was defined as wall motion score $<$ 1.4. Transmitral doppler was used to assess diastolic function: an E:A ratio $<$1.0 and deceleration time (DT) $>$220ms (for age $<$50) or E:A ratio $<$0.5 and DT $>$280ms (for age $>$50) defined DD. A restrictive filling pattern (RFP) was defined as E:A ratio $>$2 or E:A ratio 1-2 with DT $<$130ms. AF patients were assessed on the basis of the DT. Patients were defined as 'normal' if there was no significant echocardiographic abnormality present. BNP was measured using a direct immunoradiometric assay (shionoria).
Results: 103 patients met the criteria for LVSD. 11 patients met the criteria for DD. 11 patients also met the criteria for RFP. Thus the prevalence of DD and RFP in this cohort of suspected heart failure patients was 3.3% in each case. 95 patients had an entirely normal echo. 111 patients had other echo abnormalities.

Total no = 331	LVSD n-103	RFP n=11	DD n=11	normal n=95
Median BNP pg/ml	230.5	148	24	30
IQR	87.3-532.5	60-289	11-45	14-61

IQR = inter quartile range

The BNP levels in the DD group were no different to the 'normals'. The BNP levels in the RFP and LVSD groups were significantly higher than both the normals and the DD group. We have previously reported a useful cut-off of BNP for excluding LVSD is 50pg/ml. Only 3 of the 11 DD patients had a BNP level $>$ 50pg/ml. 9 of the 11 with RFP had a BNP $>$50pg/ml.
Conclusions: Both isolated DD and RFP, as defined by transmitral doppler, had a low prevalence in this cohort of patients, especially when compared with definite LV systolic dysfunction. The low BNP in the reversed E:A ratio group (DD) suggests this may not be an important 'abnormality'. The high BNP levels in the RFP group suggests this pattern of transmitral flow does indicate significant cardiac pathology.

P2141 Ageing of left-ventricular diastolic function affects the subendocardium and first involves the septum

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Background: Global left ventricular diastolic function measured by Doppler mitral inflow shows an age-related decrease in E/A ratio, due to progressive stiffening of the myocardium. Understanding the relative contribution in normals of segmental myocardial relaxation is necessary to assess pathophysiologal changes. Methods: 151 normal subjects with normal exercise ECG (young healthy volunteers with low 10-year risk of coronary disease, 11.9%) and patients with no significant coronary artery disease (<50% diameter stenosis on angiogram, no previous MI or revascularisation) underwent tissue Doppler echocardiography (Vingmed system 5) with off-line analysis (Echopac). Diastolic relaxation was assessed by the ratio of diastolic E to A myocardial tissue Doppler velocities: for long axis function basal segments in apical views, for short axis function the basal posterior segment in parasternal long axis view.
Results: Myocardial E/A<1 indicating impairment of relaxation is detected earliest in the ventricular septum, affecting long axis function in a majority of a normal population from the 5th decade onwards. This is followed by E/A<1 in >50% of normals in the inferior (6th) and anterior/lateral walls (7th decade). For short axis function, although altered by age, the proportion of E/A<1 never exceeded 38% (table).

Prevalence of E/A <1, by segment and age

Segment	20-30 years	30-39 years	40-49 years	50-59 years	60-69 years	70-79 years	p
n	10	16	28	48	30	19	<0.001
basal septal	0%	31%	56%	68%	90%	88%	<0.001
basal inferior	0%	13%	39%	66%	76%	88%	<0.001
basal lateral	0%	0%	22%	48%	64%	63%	<0.001
basal anterior	0%	7%	31%	44%	67%	56%	<0.001
mean basal	0%	6%	19%	53%	70%	71%	<0.001
basal posterior	0%	7%	15%	33%	38%	11%	<0.001

Conclusion: Diastolic ageing of the left ventricular myocardium affects subendocardial long axis function, more than radial function. The heterogeneity of the onset of age-related decline of long axis relaxation needs to be considered when using regional myocardial velocities to unmask a pseudonormal global mitral inflow pattern or when using algorithms incorporating regional myocardial velocities to diagnose increased left atrial pressures.

P2142 Decreased diastolic tolerance to afterload and impaired systolic function after 6 hours of volume overload

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Introduction: Diastolic tolerance to afterload refers to the ability of the left ventricle to respond to an afterload elevation without slowing of relaxation. The level above which an afterload elevation slows relaxation becomes smaller and the magnitude of such slowing becomes greater as systolic function deteriorates. Recent evidences suggest that acute myocardial overload induces precocious alterations in expression of various genes including those coding calcium-regulating proteins, but the functional counterpart was not yet established. The present study investigated to what extent acute volume overload could lead to functional hemodynamic abnormalities.
Methods: Open-chest adult Wistar rats (n=6, 350-400 mg) were instrumented with a tip micromanometer to record left ventricular pressures (LVP) and its first derivative dP/dt. Single beat afterload elevations were performed by clamping the ascending aorta before and 6 hours after a perfusion of dextran70 (5 ml/h) that raised end-diastolic LVP from 2.1±0.9 to 6.2±1.9 mmHg. Significant results presented as mean±SEM; $p<0.01$.
Results: There was a significant deterioration of systolic function after 6 hours of volume overload: systolic LVP (94±7 vs. 63±3 mmHg), dP/dtmax (4273±458 vs. 2512±201 mmHg/s) and peak isovolumetric LVP (183±10 vs. 134±13 mmHg). The time constant of relaxation Tau was similar, at baseline, before and after volume overload (17.9±2.3 vs. 19.2±1.8 ms, p=ns). However the response to afterload was markedly altered, with an increase in systolic LVP of 75±6 mmHg being necessary to slow relaxation (increase Tau) before and just 19±5 mmHg after volume overload. Additionally, the magnitude of such slowing was altered: in response to an isovolumetric beat Tau increased only 8±3% before and 69±12% after volume overload.
Conclusion: This study demonstrated that 6 hours of ventricular overload induce precocious impairment of systolic function and diastolic intolerance to afterload. This intolerance is such that even a small elevation in systolic LVP was enough to significantly decrease relaxation rate.

P2143 Reversibility of pulmonary hypertension in patients with heart failure is associated with mitral flow velocity changes

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Background: Pulmonary artery hypertension (PAH) has been widely recognized to be a factor affecting prognosis in heart failure. Since increased left ventricular (LV) filling pressure is a major determinant of PAH, reversal of diastolic dysfunction at Doppler echocardiography may predict the reversibility of increased pulmonary artery pressure.
Objectives: This study sought to assess reversibility of PAH in patients with heart failure and whether left-sided Doppler and echocardiographic variables were predictors of pulmonary artery systolic pressure (PASP) before and after medical treatment.
Methods: Doppler-echocardiographic examinations were performed in patients (n=100) with LV ejection fraction (EF) <45% and sinus rhythm recruited after hospital admission or from a specialist cardiology outpatient ambulatory. Patients were divided according to mitral flow pattern into impaired relaxation (n=43) and restrictive/pseudonormal (n=57). Restrictive filling was defined by a E wave deceleration time <140 msec. Pseudonormal pattern was defined by a positive response to Valsalva maneuver and/or by a pulmonary vein flow (PVF) reversal wave exceeding by more than 30 msec mitral A wave. A follow-up echo-Doppler study was recorded after 6±2 months during which patients were stabilized with optimized medical treatment.
Results: At baseline, LV EF was 30%±7% and PASP was 48±14 mmHg. At the follow-up study, only patients (n=25) who had reversible restrictive/pseudonormal filling showed a significant decrease of PASP: 38±8 mmHg versus 53±7 mmHg ($p<0.0001$). The closest correlations were found with E wave deceleration rate (EDR) (r=0.73) at baseline and with the systolic fraction of PVF forward peak velocities (SF) (r=-0.67) at follow-up. The stepwise regression model showed that EDR and the degree of mitral regurgitation were the strongest independent predictors of PAH at baseline, while the ratio between PVF reverse and mitral wave velocities at atrial systole and LV EF added minor contributions leading to cumulative r value of 0.81. The SF was the strongest at the follow-up study with minor contributions provided by EDR and the left atrial dimension index leading to cumulative r value of 0.71.
Conclusions: In our series of patients with heart failure due to LV systolic dysfunction, reversibility of PAH with optimized medical therapy was associated with favorable changes in mitral flow patterns. Mitral and PVF variables were strong predictors of PASP either before or after treatment.

EXPERIMENTAL HEART FAILURE III

P2144 Inducible nitric oxide synthase expression and mitochondrial function in pacing-induced heart failure in rabbits

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Inducible nitric oxide synthase (iNOS) and NADPH oxidase expression are increased in patients with left ventricular (LV) dysfunction. Increased concentrations of nitric oxide and free radicals are associated with LV dysfunction. Furthermore, nitrotyrosylation of proteins, such as the mitochondrial respiratory chain complex I, can occur and, indeed, the complex I activity is reduced in patients with LV dysfunction.
Our aim was to study the protein expression of iNOS and activities of complex I and cytochrome oxidase in the myocardium of rabbits with pacing-induced heart failure (HF).
Echocardiography revealed an increase in LV end-diastolic diameter (14.6 ± 0.6 to 18.2 ± 0.6mm) and a reduction in shortening fraction (32.8 ± 1.4 to 10.0 ± 0.7%, both $p<0.05$) after 3 weeks of pacing. Sham-operated rabbits served as controls.
Morphologically, in HF rabbits the extent of fibrosis (31.1 ± 1.9 vs. 7.1 ± 1.0% of analyzed area) and the number of TUNEL-positive cardiomyocytes (0.097 ± 0.011 vs. 0.008 ± 0.004 per mm^2) were significantly increased compared to sham rabbits. The myocardial iNOS protein expression was increased in HF rabbits (178,960 ± 46,012 vs. 63,083 ± 25,596 AU, $p<0.05$, densitometry) compared to sham rabbits. Whereas complex I activity was reduced in HF rabbits compared to sham rabbits (13.17 ± 1,68 vs. 18.46 ± 1.93 U/g, $p<0.05$), cytochrome oxidase activity did not differ between HF and sham rabbits (11.77 ± 1.15 vs. 10.85 ± 0.88 U/g).
In this non-ischemic HF model, iNOS protein expression is increased, whereas complex I activity is reduced. Further studies will have to define whether or not these entities are causally related and whether or not chronic blockade of iNOS can attenuate the progression of HF.

P2145 The anti-oxidant probucol and chronic ischaemic heart failure of the rat

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Recently it was reported, that oral application of the anti-oxidant probucol reduces the short term mortality of rats after experimental myocardial infarction. The beneficial effect should be due to reduction of interstitial cardiac fibrosis in the remote non infarcted area by reduction of oxidative stress. Timely parallel we applicated probucol (60 mg/kg/day, BID by gavage) over a period of 182 days to Lewis rats after experimental myocardial infarction. This was induced by ligation of the left anterior descending artery. Rats, fed with placebo after myocardial infarction or after sham operation served as controls. Rats, dying in the experimental period, were autopsied. At day 182 surviving rats were killed and organs removed for further analysis. Only animals with large myocardial infarction were included into the analysis (Pro: n=47; Pla: n=36; Sham: n=45).
Results (data in Mean): The weight of the left ventricles after myocardial infarction increased compared to that of sham-operated rats (Sham 834 mg). Treatment with probucol resulted in a significantly lower weight of the left ventricles, compared to placebo (Pla 1056; Pro 967 mg; $p < 0.05$). The infarct related dilatation of the left ventricle was reduced by probucol, as assessed by pressure volume measurements in the isolated left ventricle. Additionally the pressure-volume relation in between 0-30 mmHg was attenuated by probucol, both not significantly. Interstitial cardiac fibrosis, as measured as hydroxyprolin content in the remote non infarcted area via HPLC and then corrected to μg collagen per mg dry-weight showed an increase to the same extent in both groups with myocardial infarction (Pro 111; Pla 108; Sham 41). Most important, there was no significant difference in the Kaplan-Meier survival curves of the rats, fed with probucol or Placebo after myocardial infarction (Exp (B)=0.868; p=0.671). The mortality rates after 182 days were: Sham 0%; Pla 47.2%; Pro 40.4%.
Conclusion: Chronic treatment of rats after myocardial infarction with probucol attenuates the cardiac remodelling, but does not have an effect on the long term mortality.

P2146 Changes in myocardial 1,2-diacylglycerol levels during transition from cardiac hypertrophy to heart failure in murine model of systemic carnitine deficiency

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Background: The juvenile visceral steatosis (JVS) mouse, a murine model of systemic carnitine deficiency, develops cardiac hypertrophy with lipid accumulation and shows transition to heart failure characterized by left ventricular dilatation and global hypokinesis. We have reported that the increased level of myocardial 1,2-diacylglycerol (DAG), a lipid second messenger, was associated with the development of cardiac hypertrophy and the maintenance of cardiac function in the JVS mice. However, the serial change in myocardial DAG during transition from cardiac hypertrophy to heart failure is not known.
Methods: The myocardial DAG level and fatty acid composition were measured in both JVS and control mice at the cardiac hypertrophy stage (8 weeks of age) and at the heart failure stage (24 weeks of age). Echocardiographic analysis was also performed.
Results: JVS mice showed marked deterioration of fractional shortening and increased left ventricular end-diastolic dimension at the heart failure stage compared with that at the cardiac hypertrophy stage (10.6 ± 1.2 vs 44.4 ± 3.6%; $P<0.01$, 6.4 ± 0.2 vs 3.0 ± 0.1mm; $P<0.01$, respectively). At the cardiac hypertrophy stage, the myocardial DAG level in JVS mice was 2.6-fold higher than that in controls (1585 ± 84 vs 607 ± 90 ng/mg dry wt; $P<0.01$). Fatty acid composition of myocardial DAG in JVS mice showed an increase in 18:1(n-7,9) and 18:2(n-6) fatty acids ($P<0.01$ vs controls). At the heart failure stage, the myocardial DAG level in JVS mice decreased compared with that at the cardiac hypertrophy stage (950 ± 102 vs 1585 ± 84 ng/mg dry wt; $P<0.01$). However, no difference was seen in the fatty acid composition of myocardial DAG in JVS mice between the cardiac hypertrophy stage and the heart failure stage.
Conclusions: The increased myocardial DAG level at the cardiac hypertrophy stage was followed by a decrease at the heart failure stage in JVS mice. The decrease in myocardial DAG may be implicated in the detrimental progression to heart failure in JVS mice.

P2147 In vivo effects of myocardial creatine depletion on left-ventricular function, morphology and energy metabolism during resting and stress conditions

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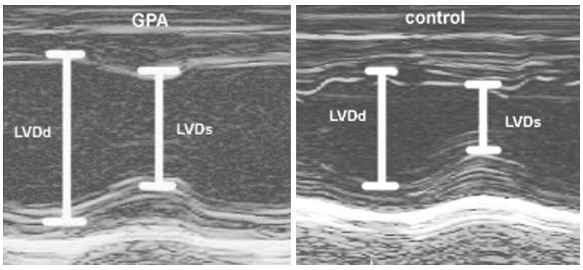
Background The failing heart is characterised by disturbed myocardial energy metabolism and creatine depletion. The aims of this study were to evaluate in vivo the effects of creatine depletion on: 1) left ventricular (LV) function and morphology during rest and stress, 2) LV energy reserve during rest and stress, 3) myocardial and plasma catecholamines, 4) myocardial adrenergic and cholinergic receptors.
Methods Male rats body weight (BW) $\sim$ 200g was used. Two groups were studied: the rats treated with creatine analogue beta-guanidinopropionic acid (GPA) (n = 10) and controls (n = 6). GPA (1 M) was administered by subcutaneously implanted osmotic minipumps during 4 weeks. The rats were examined in vivo by echocardiography and 31P magnetic resonance spectroscopy (MRS) at basal and at stress conditions induced by transesophageal pacing and dobutamin. HPLC and receptor-binding assays were used for measurements of catecholamines and adrenergic/cholinergic receptors.
Results BW was lower ($p< 0.01$) wile LV/BW was higher ($p<0.01$) in the GPA group indicating myocardial hypertrophy. In the GPA treated rats, total myocardial creatine pool was $\sim$ 40% lower ($p < 0.01$) wile total nucleotide pool was 30% lower ($p < 0.01$) compared to the controls. LV systolic function (ejection fraction, fractional shortening) was decreased during rest and deteriorated further during stress (all $p < 0.05$). Similary, LV dimensions were increased in the GPA group ($p < 0.05$).



M-mode echocardiography.

Conclusions Creatine depletion results in functional and structural LV alterations. Intact myocardial creatine metabolism is important for normal LV function during resting and stress conditions. This simple model may be valuable for studies of myocardial energy metabolism in small animal models of heart diseases.

P2148 Cardiac output distribution and cytokine expression in lipopolysaccharides-induced septic shock in rats

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Septic shock (SS) is a frequent, serious and cost intensive clinical picture. The underling pathophysiologic changes are not well understood. The aim of this study was to investigate hemodynamic alterations and expression of cytokines in a rat model. Method: In anaesthetized Lewis rats SS was induced by i.p. application of E.-coli lipopolysaccharides (20mg/kg b.w.). Controls were injected with NaCl 0,9%. Cardiac output distribution (CO) was estimated by the fluorescence-labelled-microsphere-method five times in 2 hour intervals. Serum levels of IL-1β, IL-6, IL-10, TNF-[alpha] were measured at the beginning after 2 and 8 hours of SS. Results: Whereas organ blood flow rates (BF) and cytokines remained nearly unchanged in control animals, organ BF in SS significantly increased to cerebrum (0,44 to 0,81ml/min/g) heart (3,2 to 5,0), spleen (1,6 to 2,1) and liver (0,40 to 0,49) but decreased to kidney (6,1 to 4,8), lung (3,7 to 1,5), colon (0,91 to 0,65) and skin (0,102 to 0,054). TNF-[alpha] first increased to 2. hour but decreased again to 8. hour (1,38 pg/ml to 30,3 ng/ml to 2,1 ng/ml), IL-10 (112 pg/ml to 40,6 ng/ml to 138 ng/ml) and IL-6 (74 pg/ml to 33,8 ng/ml to 61,2 ng/ml) increased to the 2. and 8. hour. Conclusion: These results demonstrate a complex redistribution of cardiac output in septic shock in favour of heart, cerebrum, liver and spleen but to the disadvantage of especially lung, colon and skin. A massive expression of measured cytokines in septic shock appears.

P2149 Metabolic phenotype in moderate severity heart failure includes reductions in pyruvate dehydrogenase activity and malonyl CoA

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Recent human and animal studies have demonstrated that in severely decompensated heart failure (HF), the cardiac muscle switches to a more fetal metabolic phenotype, characterized by down regulation of free fatty acid oxidation and an enhancement of glucose oxidation. The goal of this study was to examine myocardial substrate metabolism in a model of moderately severe coronary microembolism-induced HF. We hypothesized that during well-compensated HF, free fatty acid oxidation would predominate as opposed to a more fetal metabolic phenotype of greater glucose oxidation. Myocardial free fatty acid and glucose oxidation was measured in normal dogs (n=8) and dogs with microembolism-induced HF (n=12, LV ejection fraction = 28%) by infusing isotopic tracers (3H-oleate and 14C-glucose) in anesthetized open-chest animals. Dogs with HF had significantly reduced peak dP/dt, peak LV pressure, and rate-pressure product. There were no significant differences between normal and HF dogs in the rate of myocardial oxygen consumption (3.19±0.34 vs 2.70±0.39 μmols/g/min, respectively), fatty acid oxidation (39±6 vs 44±8 nmols/g/min, respectively), or glucose oxidation (0.17 ± 0.03 vs 0.13 ± 0.02 μmols/g/min, respectively). The total activity of pyruvate dehydrogenase, the key enzyme regulating myocardial pyruvate oxidation (and hence glucose and lactate oxidation) was not affected by HF, however the activation state was significantly reduced (from 51% active in normal dogs to 39% in HF; $p<0.05$). We did not observe any difference in the activity of carnitine palmitoyl transferase-I (CPT-I; a key enzyme regulating long-chain fatty acid oxidation in mitochondria) between groups nor in the ability of malonyl-CoA (an endogenous inhibitor of CPT-I) to inhibit CPT-I activity in isolated mitochondria. On the other hand, myocardial malonyl-CoA content was significantly decreased in the HF group (0.81±0.05 vs. 1.05±0.06 nmols/g; $p<0.05$), suggesting less in vivo inhibition of CPT-I activity. These results support the concept that there is not a decrease in fatty acid oxidation early in HF, and that the dramatic down-regulation of fatty acid oxidation enzymes and the switch to greater glucose oxidation observed in severely decompensated HF is a late-stage phenomemon.

P2150 Right-ventricular pressure load in pigs: progressive loss of regional myocardial function without ischaemia

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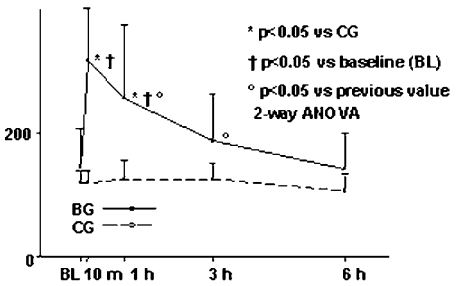
Purpose: Right ventricular (RV) pressure load (RVPL) frequently leads to RV failure, the mechanisms remain unclear. We tested whether myocardial dysfunction induced by RVPL is associated with ischemia.
Methods: Pigs were randomised to control group (CG, n=7) or banding group (BG, n=6). Baseline measurements of RV pressure and systemic hemodynamics (micromanometry), regional RV function (sonomicrometry) and right coronary flow (ultrasonic flow probe) were performed. RV oxygen consumption (RVOC) and regional RV work index (RVWI: pressure-segment length area, mm*mmHg) were calculated. RV pressure was increased from 28±5 to 67±11 mmHg by pulmonary artery constriction (PAC). The degree of PAC remained unchanged throughout the protocol. Measurements were repeated at 10 min, 1, 3 and 6 h after PAC. Transmural RV biopsies were obtained at baseline and at 6 h after PAC for ultrastructural analysis.
Results: Heart rate and mean arterial pressure were not different between groups throughout the protocol. Right coronary inflow remained constant in CG and increased at 6 hours after PAC compared to baseline in BG (99±22 vs 66±21 ml/min; $p<0.05$). After initial increase, RVWI declined progressively in BG, but remained unchanged in CG (see figure). Regional RVOC at 6 h after PAC was 182%±39% of baseline in BG. In BG cellular edema index increased at 6 h after PAC (0.43±0.04 vs 0.36±0.04; $p<0.05$) but mitochondrial surface to volume ratio remained unchanged (6.36±0.19 vs 6.32±0.34; n.s.). Ultrastructure did not changed by time in CG.
Conclusion: RVPL in pigs results in progressive RV dysfunction in spite of maintained oxygen supply and preserved mitochondrial integrity. Thus, RV dysfunction induced by RVPL is mediated by an event cascade distinct from ischemia.



Regional RV work index [mm∗mmHg].

P2151 Changes in epicardial activation patterns and conduction velocity in isolated rabbit hearts with chronic apical myocardial infarction

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Introduction: Myocardial infarction is a common cause of left ventricular dysfunction. The mode of death in heart failure is usually either pump failure or arrhythmia - frequently a ventricular tachyarrhythmia. The mechanisms of arrhythmogenesis continue to be studied in order to identify potentially modifiable features.
Methods: Chronic (8 weeks) coronary artery ligation (INFARCT) caused marked left-ventricular dysfunction compared with sham-operated (SHAM) rabbits. Left ventricular ejection fraction as assessed by echocardiography was 43 ± 2% in INFARCT (n=8) and 74 ± 1% in SHAM ($p<0.0001$) (n=8) (mean ± SEM throughout). Langendorff-perfused hearts were loaded with the voltage-sensitive dye RH 237 and action potentials recorded at 254 sites simultaneously from a 2cm x 2cm area on the basal, anterior surface of the left ventricular epicardium. In the INFARCT hearts, the area studied did not include infarcted tissue. Right atrial and left ventricular epicardial pacing were performed with bipolar electrodes at a cycle length of 250ms. Epicardial activation patterns were analysed off-line to obtain conduction velocity (CV) profiles. Local conduction inhomogeneity was assessed using the method of Lammers et al. (1).
Results: Activation patterns in atrial pacing from sham hearts and those with an apical infarct were significantly different. Mean time to earliest activation was greater in INFARCT (100.6 ± 3.7ms) compared to SHAM (86.2 ± 2.3ms, $p < 0.01$). This delay, combined with a non-significantly greater dispersion (21.4 ± 4.1ms vs. 15.5 ± 1.8ms), resulted in higher maximum activation times (122.0 ± 6.9 vs. 101.8 ± 6.9, $p < 0.01$).
On epicardial pacing, the orientation of anisotropy was the same in INFARCT and SHAM. Longitudinal CV was higher in INFARCT (76.7 ± 3.4cm/s vs. 65.7 ± 3.4cm/s, $p < 0.05$). Transverse CV was not significantly different (44.6 ± 3.2cm/s vs. 43.4 ± 3.3cm/s). The difference in the Lammers inhomogeneity index (2.1 ± 0.3 vs. 1.7 ± 0.2) was not significant.
Conclusion: This study of activation and CV has revealed increased conduction delay and higher longitudinal velocities. The delay in epicardial activation is not the consequence of altered epicardial conduction parameters, therefore it must originate earlier in the activation pathway.
Reference: 1. Lammers WJEP, Schalij MJ, Kirchhof CJHJ, Allessie MA. Quantification of spatial inhomogeneity in conduction and initiation of reentrant atrial arrhythmias. Am J Physiol 1990;259:H1254-H1263

P2152 Selective beta1-blockade attenuates post-infarct remodelling without improvement in myocardial energy metabolism and function in rats with heart failure

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Objective To investigate in vivo the effects of long-term selective beta1-blockade on cardiac energy metabolism, remodelling, function and plasma cytokines in rat model of post-infarct congestive heart failure (CHF).
Methods Myocardial infarction (MI) was induced in male rats by ligation of left coronary artery. Only rats with large (> 35% of left ventricle)were included. Three different groups of rats were studied, MI rats treated with metoprolol (n = 17), MI rats treated with saline (n = 14) and sham operated rats (n = 12). The treatment with metoprolol 1mg/kg/h was initiated the 3rd week post-infarct for a period of 6 weeks. All rats were investigated non-invasively with volume-selective 31P magnetic resonance spectroscopy and echocardiography for evaluation of left ventricular (LV) energy metabolism, morphology and function. Plasma concentration of IL-1 beta (IL-1) and IL-6 and density of beta-adrenergic receptors were analyzed.
Results Metoprolol attenuated increase in LV dimensions and volumes (all $p<0.05$). Treatment with metoprolol had no effect neither on PCr/ATP nor LV function. Plasma level of IL-1 was higher ($p<0.05$) and IL-6 was lower ($p<0.05$) in the metoprolol group. Density of beta-adrenergic receptors was similar in all three groups.

Beta blockade in rats with heart failure

	delta LVDd (mm)	delta LVVd (ml)	delta SV (ml)	PCr/ATP
metoprolol	1 ± 0.3#	0,12 ± 0.03#	0,08 ± 0.01	2.2 ± 0.04*
saline	3 ± 0.3*	0,27 ± 0.06*	0.14 ± 0.02	2.1 ± 0.02*
sham	0.9 ± 0.1	0,09 ± 0.02	0.1 ± 0.02	3.2 ± 0.06

# $p<0.05$ v. saline, * $p<0.05$ v.shamLVDd = left ventricular diameter in diastole, LVVd = left ventricular volume in diastole, SV = stroke volume, PCr/ATP = phosphocreatine/adenosine-triphosphate ratio

Conclusion Selective beta1-blockade in rats with chronic CHF attenuates post-infarct structural remodelling without concomitant improvement in myocardial energy metabolism and function. This dichotomy in response to beta-blockade was not previously reported. Improvements in myocardial energy metabolism and function do not precede and are not a prerequisite for anti-remodelling effect of beta1-blockade in the setting of chronic CHF.

P2153 The intrinsic mitochondrial maximal oxidative capacity of the failing heart is depressed and relates to disease severity but keeps normal regulatory properties

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Energetic imbalance is suspected to affect the failing heart(FH) but the intrinsic mitochondrial properties are incompletely known and their relations to severity of left ventricular(LV) failure have not been assessed.
Methods: We determined in LV samples from 16 explanted FH (LVEF: 23±2%) during transplantation, the basal (V0) and maximal ADP-stimulated respiration (Vmax, μmol O2/min/g) in an oxygraphic cell after saponin-skinning, and compared it to V0 and Vmax of unfailing control LV(C), obtained during open-heart surgery (LVEF: 69±3%). The Michaelis constant for ADP(Km, μM) was calculated by stepwise ADP increase as an index of sensitivity to ADP. The effect of disease severity was assessed by comparisons between Vmax and Km of patients with brain natriuretic peptide blood levels(BNP, pg/ml) above and below 300.
Results: (means±SEM) Oxidative capacity of LV(Vmax) was lower but Km was normal in FH (figure). The high BNP patients had lower peakVO2 (ml/min/kg) V0 and Vmax (table), whereas their hemodynamics, catecholamines and Minnesota scale were similar.

*p<0.05	V0	Vmax	Km	peak VO2	BNP
high BNP (n=8)	1.9±0.1	10.3±0.7	439±71	10.7±0.8	615±127
Low BNP (n=8)	2.8±0.5*	13.9±1.4*	502±60	13.2±0.4*	182±25*

Conclusion: The energetic imbalance of FH not only results from defective O2 supply and remodelling but also from intrinsic defects in oxidative capacity that relate to disease severity. However mitochondria keep the normal regulatory properties of a highly oxidative muscle.

EXPANDING THE ROLE OF RENIN-ANGIOTENSIN SYSTEM AS A TARGET TO THERAPY IN HEART FAILURE

P2154 Renal effects of different doses of acetylsalicylic acid in overhydrated elderly with activated renin-angiotensin system

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Background: High doses of acetylsalicylic acid (ASA) can counteract the beneficial effects of angiotensin-converting enzyme (ACE) inhibitors and exert detrimental effects on renal function in patients with congestive heart failure. The highest dose not causing negative renal effects is not known.
Aim: The objective was to study the negative effects on renal function, measured as urine flow and excretion rates of electrolytes, from different doses of ASA in elderly healthy volunteers with activated renin angiotensin system from pre-treatment with diuretics, treated with ACE-inhibitors.
Methods: 16 subjects were divided into two groups and each received two different doses of ASA (0-160 mg or 80-320 mg), in a randomised double-blind, cross-over fashion. Before the doses of acetylsalicylic acid the subjects received pre-treatment with bendroflumethiazide 5 mg daily for 6 days but not in the morning of study days, and enalapril titrated to 10 mg daily. To ensure urine production the subjects were slightly over-hydrated: a loading volume of 500 ml water was given one hour prior to dose. Water volumes corresponding to voided urine, +40 ml/h for perspiratio, were given during study days.
Results: The lowest mean values were reached after 75 minutes. Urine flow, excretion rates of sodium, osmolality clearance and free water clearance decreased significantly in a dose dependent manner (table).

	0	80	160	320
Urine flow (ml/min)	5.5	4.9	4.0	2.8
Sodium excretion (umol/min)	108.8	82.9	58.1	33.3
Potassium excretion (umol/min)	53.0	72.4	44.0	55.9
Osmolality clearance (ml/min)	2.1	2.1	1.7	1.5
Free water clearance (ml/min)	3.4	2.8	2.0	1.4

Observations after 75 minutes in urine flow, excretion rates of electrolytes, osmolality clearance and free water clearance from different ASA-doses (0, 80, 160 and 320 mg) in elderly healthy volunteers with activated renin angiotensin system and treated with ACE-inhibitors.

Conclusion: The renal effects of ASA are clearly dose dependent. The negative influence of higher doses of ASA must be taken into consideration in patients with congestive heart failure.

P2155 Bradykinin mediates systemic vasodilatation associated with long-term angiotensin-converting enzyme inhibition in patients with congestive heart failure

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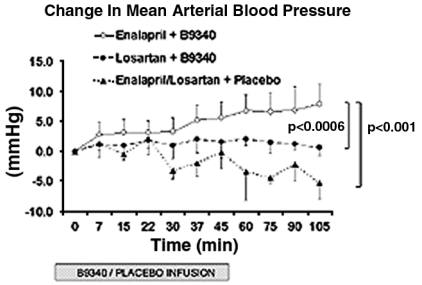
Background: Inhibition of angiotensin converting enzyme (ACE) reduces blood pressure, increases cardiac output and improves morbidity and mortality in patients with chronic heart failure (CHF). It remains unclear whether bradykinin contributes to the systemic haemodynamic changes associated with chronic ACE inhibition.
Aims: To investigate whether inhibition of bradykinin activity with the bradykinin receptor antagonist, B9340, attenuates the haemodynamic effects of chronic ACE inhibition.
Methods: 10 patients with CHF (NYHA II-IV, EF<40%), who were maintained on chronic (>6 months) ACE inhibitor therapy, were randomised to receive enalapril (10 mg twice daily) or losartan (50 mg twice daily) in a randomised, double-blind crossover trial. After 6 weeks of each treatment, patients underwent right heart catheterisation and were randomised to receive a systemic infusion of either B9340 (2, 6 and 20 μg/kg/min for 15 min at each dose) or saline placebo.
Results: In patients treated with enalapril, mean arterial pressure (+7.3 mmHg), systemic vascular resistance (+224 dynes s/cm^5), pulmonary artery wedge pressure (+1.0 mmHg) and heart rate (+3 bpm) were greater after B9340 infusion when compared to placebo ($p<0.0001$, $p<0.05$, $p<0.0001$ and $p<0.005$ respectively) or losartan therapy ($p<0.0005$, $p=0.17$, $p<0.0001$ and $p<0.01$ respectively). There were trends towards reductions in cardiac output with B9340 during enalapril therapy when compared to placebo infusion or losartan ($p=0.08$ and $p=0.18$ respectively).



Conclusions: Bradykinin contributes to the systemic haemodynamic effects of long-term ACE inhibition in patients with CHF. This mechanism may help explain the apparent clinical superiority of ACE inhibitors over angiotensin receptor antagonists in the treatment of CHF.

P2156 Platelet inhibition by valsartan and valeryl 4-hydroxy valsartan: a possible missing link to explain benefits of angiotensin II receptor blockers in patients after acute vascular events

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Background: Valsartan (V) selectively blocks the binding of angiotensin II to the AT1 receptor benefiting patients after acute vascular events. Considering that platelet activation plays a key role in such events, and that AT1 receptors are present on the platelet surface we assessed the in vitro effects of V and its major liver metabolite, valeryl 4-hydroxy valsartan (V4HV), on platelets in subjects with multiple risk factors for vascular disease.
Methods: Data from 20 subjects were analyzed. Blood samples were pretreated with 10nM, 100nM, 1μM, 10μM, and 100μM of V and V4HV, and then incubated for 1 hour at 370C. Platelet characteristics were assessed by conventional (5μM epinephrine, and 5μM ADP), and whole blood (1mg/ml collagen) aggregometry; closure time with epinephrine/collagen cartridge by PFA-100 (Dade-Behring, Inc), and platelet activation units with Ultegra (Accumetrics, Inc.) analyzers. The expression of platelet receptors was determined by using the following monoclonal antibodies: CD31, CD41, CD42b, CD51/CD61, CD62p, CD107a, CD107b and CD151. PAC-1 was used to measure fibrinogen-platelet binding. Platelet–leukocyte formation was detected utilizing dual antibodies for a pan-platelet marker CD151, and CD14, a universal monocyte/macrophage marker.
Results: Pretreatment of blood with V and V4HV resulted in an inhibition of ADP - (p=0.0002; V), epinephrine - (p=0.0001; 4VHV), and collagen-induced (p=0.02; V, and p=0.0001 4VHV) aggregation. Expression of CD41 (p=0.03; V, and p=0.02 4VHV), CD51/CD61 (p=0.01; V, and p=0.02 4VHV), CD62p (p=0.03 for both V and 4VHV), CD107a (p=0.04 for both V and 4VHV), and PAC-1 (p=0.03; V, and p=0.02; 4VHV) was significantly reduced in V and V4HV containing samples as compared to autologous baseline activity. Closure time was delayed (p=0.02; V, and p=0.03; 4VHV) indicating platelet inhibition in whole blood under high shear conditions. Surface expression of CD31, CD42b, CD107b, CD151, intensity of platelet-leukocyte formation, and Ultegra? analyzer readings remained unchanged. Platelet inhibition was not dose-dependent, and was more potent for 4VHV than for V in the therapeutic range.
Conclusions: Both valsartan and valeryl 4-hydroxy valsartan exhibited significant in vitro inhibition of human platelets. Antiplatelet properties of V and 4VHV are mild, but trigger alternative mechanism(s) than those of aspirin, dipyridomole, thienopyridines, selective serotonin reuptake inhibitors, and glycoprotein IIb/IIIa inhibitors.

P2157 Losartan reduces hospitalizations for heart failure in patients with diabetes with no prior history of heart failure

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Introduction: The high incidence of congestive heart failure (CHF) in diabetic patients raises major public health concerns. Two large, randomized, double-blind, outcomes trials enrolling substantial numbers of diabetic patients and using the angiotensin II antagonist losartan were recently completed.
Methods: The Reduction in ENdpoints with the Angiotensin II Antagonist Losartan (RENAAL) study recruited 1513 patients with type 2 diabetes and nephropathy, while the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study recruited 9193 patients with essential hypertension, of which 1195 had diabetes at the start of the study. In both studies patients were treated with losartan 50mg titrated to 100mg if the goal blood pressure of 140mmHg systolic and 90mmHg diastolic was not met. Patients could receive additional antihypertensive medications if goal blood pressure was not achieved. The control in RENAAL was placebo (with conventional therapy), while in LIFE patients were randomized to losartan or atenolol. Followup in RENAAL was a mean of 3.4 years, while in LIFE patients were followed for a minimum of 4 years (mean 4.7 years). Events of hospitalization for CHF were adjudicated by an independent committee in both trials. Patients with a prior history of CHF were excluded from this analysis.
Results: In both studies, blood pressure was reduced equivalently in both treatment groups. Although all of the patients in this post hoc analysis were diabetic, patients enrolled into the RENAAL study were at higher risk of developing CHF (HR for RENAAL versus LIFE 3.0 $p<0.0001$). Losartan was effective in significantly reducing hospitalizations for CHF versus placebo in RENAAL, and versus the beta-blocker atenolol in LIFE.

Study	Losartan	Control	HR(95% CI)	p value
RENAAL	82/710 (11.6%)	109/721 (15.1%)	0.737 (0.553-0.981)	0.037
LIFE	28/565 (5.0%)	48/582 (8.2%)	.573 (0.360-0.914)	0.019
Combined	10/1270 (8.7%)	157/1303 (12.0%)	.687 (0.538-0.877)	0.0025

Conclusions: In diabetic patients without a prior history of CHF, losartan was associated with a significant reduction in the risk of hospitalization for CHF. This effect was demonstrated both in patients who were at high cardiovascular or renal risk.

P2158 Estimation of myocardial perfusion relative to the presence of myocardial viability in patients with left-ventricular dysfunction during 3 months therapy with captopril or eprosartan

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The aim of this study was to estimate myocardial perfusion (MP) relative to the presence of myocardial viability in patients (pts) with left ventricular (LV) dysfunction during 3 month therapy with angiotensin-converting enzyme inhibitor captopril (CAPT) and an angiotensin II AT-1 receptor blockers eprosartan (EPRO). **Methods:** Total 34 pts (30 men, mean age 53.6±8: range 37-66, mean EF 39.6±3.6%, NYHA II-III - 94.1%) with LV dysfunction (EF<45% on day 5-7 of acute myocardial infarction) were included. Myocardial perfusion scintigraphy (MPS) with 99mTc-MIBI was performed between 5-7 days after myocardial infarction. The evaluations of MP and detection of signs of viability of the dyssynergic myocardium were performed twice - at baseline and after sublingual nitroglycerine. MP was calculated for each analysed segment (1-perfusion defect (PD)< 25%; 2- PD - 25-50%; 3 - PD - 50-75%; 4 - PD > 75%). For evaluation of dynamic changes the myocardial perfusion violation index (MPVI - defined as the ratio the total score/number of analyzed segments) was used. During 3 next months, all pts have baseline therapy in combination with CAPT (16 pts - 1 group) and with EPRO (18 pts - 2 group). MPS were repeated after 3 months. For the statistical analysis Wilcoxon test was used.
Results: The analysis of dynamics of values showed that significant improvement of MP has occurred only in patient with signs of viable myocardium(VM)(MPVI 2.86±0.6 and 1.94±0.7,p=0.00008 vs 2.5±0.3 and 2.2±0.6,p=0.82). Analysis of MP relative to the presence of myocardial viability in groups 1 and 2 showed comparable increasing of coronary flow in both treatment groups in pts with viable myocardium (see table).

	MPVI baseline	MPVI after 3 months	p- value
Group 1 - pts with VM (n=11)	2.8± 0.4	1.9± 0.3	0.004
Group 1 - pts without VM (n=5)	2.6± 0.5	2.2± 0.8	0.34
Group 2 - pts with VM(n=11)	2.9± 0.7	2.0± 0.9	0.013
Group 2 - pts without VM (n=7)	2.4± 0.6	2.2± 1.1	0.68

Conclusion: Thus, the evaluation of MP in pts with postinfarction LV dysfunction after 3 months of drug therapy showed that: 1) the significant improvement of MP has occurred only in pts with the signs of VM at baseline 2) CAPT and EPRO demonstrated comparable efficiency in influence on MP in pts with signs of VM.

P2159 Relation of arterial-ventricular coupling changes to left-ventricular geometric patterns in hypertensive adults after antihypertensive therapy with angiotensin converting enzyme inhibitors

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Background: We sought to determine the relation of arterial-ventricular coupling (AVC) changes to left ventricular geometric patterns in hypertensive adults after antihypertensive therapy with angiotensin converting enzyme inhibitors (ACEI).
Methods: A total of 2268 patients with essential arterial hypertension, were studied echocardiographically at baseline, and after 6 months of antihypertensive monotherapy with ACE inhibitors. Patients were divided according to the geometric patterns of left ventricular hypertrophy into four groups: (a) normal geometry (n=394), (b) concentric remodeling, (c) concentric hypertrophy (n=870), and eccentric hypertrophy (n=546). The AVC was calculated by echocardiographic measurements based on the equation: AVC= Ea/Emax = ESP/SV/ESP/ESV= ESV/SV (ESP, End-Systolic Pressure; SV, Stroke Volume; ESV, End Systolic Volume).
Results: There no significant differences in baseline characteristics between the groups. ACEI significantly decreased the LV mass index, and AVC values in the whole patient population. However, the decrease was more prevalent in patients with eccentric and concentric hypertrophy compared to the other three groups (p<0.0001). Patients with eccentric hypertrophy had significantly higher percentage change in AVC compared to concentric hypertrophy group (p<0.0001).
Conclusions: ACEI have the most favorable impact on patients with eccentric and secondary on patients with concentric hypertrophy. These findings may help in the optimization of antihypertensive treatment.

Hemodynamic data of the patient populati

	Normal Geometry, n=394	Concentric Remodelling, n=458	Concentric Hypertrophy, n=870	Eccentric Hypertrophy, n=546
DSBP, mm Hg	-29 ± 9.5	-29 ± 8.5	-35 ± 12*	-34 ± 12*
DDBP, mm Hg	-18 ± 6.2	-18 ± 5	-19 ± 6	-18 ± 6
% Heart Rate	-1.9 ± 3.9	-2.4 ± 4.6	-2.2 ± 4.5	-1.7 ± 5.6
% LV mass index	-10 ± 4	-11 ± 4	-15 ± 5.1*	13 ± 4*
% AVC	-4.3 ± 4.4	-3.3 ± 5.1	-4.7 ± 5.5	-5.3 ± 5.8*

All values are mean ± SD or percentages. BMI, Body Mass Index;D, Difference; DBP, Diastolic Blood Pressure; LV, Left Ventricular; SBP, Systolic Blood Pressure; %, Percentage Change.

P2160 Delayed development of angiotensin-converting enzyme-inhibitor-induced angioedema: association with acute phase proteins

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Acute angioedema, a nonitchy pale swelling of subcutaneous and submucosal tissue can become life-threatening if it occurs in the upper airways. Urticaria and C1 esterase inhibitor deficiency are typical conditions associated with this type of edema. Similarly, angioedema is a well known serious side effect of ACE-inhibitors such as captopril, with an incidence of 0.1-0.7%. The aim of this study was to determine the existence of certain predispositions such as prior allergic reactions and the time interval between initiation of ACE-inhibitor treatment for the occurrence of angioedema. A total of 21 patients presenting with acute angioedema and ACE-inhibitor treatment but no apparent C1 esterase inhibitor deficiency were included (ACE) and 11 patients with oropharyngeal edema of unknown cause served as a control group (CON). All patients were checked for duration of treatment, co-medication, accompanying diseases, prior allergic reactions, changes of C-reactive protein (CRP) and fibrinogen, efficacy of treatment and recurrent episodes. The mean intervall between initiation of ACE-inhibitor therapy and angioedema was 29.5 months (1 week - 96 months). Only 19% of these cases had an allergic predisposition but there was no direct association to the occurrence of angioedema. However, there were only 9% of cases with prior allergic reactions in CON. CRP (mg/dl) was strongly enhanced in ACE (3.97±0.9) as compared to CON (0.62±0.2, p=0.002). ACE-patients also showed slightly higher fibrinogen (475±34 mg/dl) than CON-patients (304±17.3 mg/dl, p=0.0001). Two patients of ACE who continued with an ACE-inhibitor showed a relapse, while patients without further ACE-inhibitor therapy did not. These data suggest that the ACE-inhibitor induced angioedema can occur after several years of event-free treatment and is associated with a strong increase of plasma acute phase proteins, while idiopathic angioedemas are not.

P2161 Long-term irbesartan treatment preserves renal function and increases survival in fatty Zucker rats

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Background: Angiotensin receptor antagonists have been used for the treatment of hypertension, heart failure and renal disease. A recent clinical study has demonstrated a renoprotective effect of irbesartan in patients with diabetic nephropathy (Lewis et al., 2001). The purpose of our study was to determine the effects of long-term (12 months) irbesartan administration in the fatty Zucker rat, a strain characterised by obesity and type 2 diabetes resulting in the development of progressive nephropathy.
Methods: Male 12 week-old fatty fa/fa Zucker rats received during 12 months either standard laboratory diet (n=25) or standard diet containing irbesartan at a daily dose of 30 mg/kg (n=25). A group of untreated age-matched lean fa/+ Zucker rats (n=25) was included as a control. Renal function and blood biochemistry were measured after 3, 6, and 9 months of the study. At 12 months a haemodynamic evaluation was performed in all remaining animals and heart weights were determined to measure the development of cardiac hypertrophy.
Results: Placebo-treated fatty fa/fa Zucker rats exhibited an important mortality during the study period (26%, 35% and 72% at 6, 9 and 12 months, respectively) which was markedly reduced in the group treated with irbesartan (9%, 13% and 22% at 6, 9 and 12 months, p<0.05 versus placebo). Mortality in lean fa/+ rats attained 12% at 12 months. Irbesartan treatment significantly reduced the large increases in urinary protein excretion observed in fa/fa animals. Values (mg/day) were 8 ± 2, 67 ± 15 and 149 ± 23 (irbesartan) versus 152 ± 20, 276 ± 24 and 290 ± 90 (fa/fa placebo) at 3, 6 and 9 months, respectively (p<0.05). Plasma creatinine levels measured after 9 months were significantly lower in the irbesartan group (0.53 ± 0.02 mg/dl) than in placebo fa/fa animals (0.86 ± 0.13 mg/dl, p<0.05) and similar to the fa/+ group (0.58 ± 0.02 mg/dl). Mean arterial blood pressure was lower in the irbesartan-treated animals (86 ± 4 mmHg versus 103 ± 7 mmHg in the placebo fa/fa group, p<0.05) but not different from fa/+ animals (97 ± 3 mmHg). Heart rate values did not differ significantly between the three groups. Heart weight measured as a function of body weight was reduced by 23% in the irbesartan-treated group (3.13 ± 0.17 g/kg compared with 4.08 ± 0.29 g/kg in placebo fa/fa animals).
Conclusions: Prolonged irbesartan treatment preserves renal function, lowers blood pressure, reduces heart weight and substantially increases survival in fatty fa/fa Zucker rats.

P2162 Angiotensin-converting enzyme inhibition with trandolapril prevents recurrences of paroxysmal lone atrial fibrillation in normotensive patients

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Background: In hypertensive patients, ACE inhibition has been shown to induce regression of left ventricular hypertrophy, to improve myocardial systolic function, to reduce the incidence of ventricular arrhythmyas and to prevent atrial fibrillation (AF) recurrences. It is still unclear whether the latter effects are due to a direct antiarrhythmic action as opposed to the elimination of the "anatomical" arrhythmogenic substrate present in hypertensive heart disease.
Methods: The effects of ACE inhibition in preventing AF recurrences in the absence of hypertensive heart disease, i.e. in patients with AF unrelated to cardiac or extracardiac causes and with normal blood pressure values ("lone atrial fibrillation") were assessed in 35 consecutive normotensive subjects (16 males and 19 females, mean age 57 $\pm$ 5 years) presenting a first episode of atrial fibrillation. Concomitant cardiac, thyroid, or renal disease were excluded relying upon medical hystory, echocardiogram, routine blood tests and thyroid hormones. After acute cardioversion to sinus rhythm with propafenone (2 mg/kg e.v. in 10 min, followed by infusion at 0,007 mg/kg/min) was obtained within 6 hours, patients were treated with either Trandolapril (2 mg/die, group A, n=18) or no adjunctive therapy. After 1 and 2 years, patients were re-evaluated to assess the incidence of new AF episodes, and a complete echocardiographic study was repeated.
Results: During the 2-year follow-up the incidence of new AF episodes was higher in group B (8/17 patients: 47%) than in group A (2/18 patients, 11%, $p< 0.01$ vs group B). No difference in echocardiographic parameters was observed. In particular, left atrial size remained in the normal range throughout the study in both groups (14 $\pm$ 2 vs. 14 $\pm$ 2 cm^2 in group A, p= ns; and 15 $\pm$ 2 to 17 $\pm$ 2 cm^2, p=ns in group B).
Conclusions: These data show that Trandolapril may have an important role in preventing recurrences of lone AF not only in hypertensive patients, but also in normotensive subjects, possibly via an ACE inhibition-related antiarrhythmic effect.

P2163 Angiotensin-converting enzyme genotype influences the response to an angiotensin II receptor antagonist, losartan in patients with hypertension

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We prospectively studied whether the response to an angiotensin II receptor antagonist losartan varied depending on the ACE genotype in 42 hypertensive patients (22 men, 20 women, mean age: 60.4 y.o.). After 4-week observation period, losartan 50 mg/day was administered and blood pressure was measured every 2 to 4 weeks for 12 weeks. Among the 42 patients, 19, 11, 12, respectively, had the II, ID and DD ACE genotypes. The baseline plasma ACE activity in patients with the ID or DD was significantly higher than that in patients with the II genotype (13.8$\pm$4.2 vs 9.6$\pm$2.3 IU/L; P=0.0002). However, age, gender, baseline systolic and diastolic blood pressure (BP), BMI was not different among the groups. After 12 weeks of treatment with losartan alone, diastolic BP in the ID or DD group was significantly higher than that in the II group (85.0$\pm$9.0 vs 77.8$\pm$9.6 mmHg, P=0.018), and also the percent reduction in diastolic BP in the ID or DD group was significantly smaller than that in the II group (7.9$\pm$8.8 vs 14.3$\pm$10.1%, P=0.035). Multiple regression analysis showed that the significant predictors of the diastolic BP at 12 week were the age (P=0.030), the ACE genotype (P=0.029) and the baseline diastolic BP (P=0.0001). In conclusion, the ACE genotype is a determinant of the response to losartan in hypertensive patients.

P2164 Twice-a-day regimen of long-acting angiotensin converting enzyme inhibitor has better effects on neurohumoral factors compared with once-a-day administration in patients with chronic heart failure

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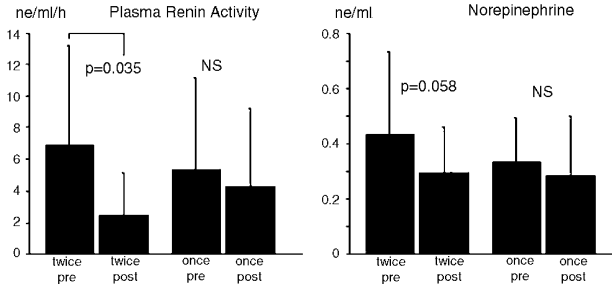
Although an abundance of clinical trials has evaluated the use of long-acting angiotensin converting enzyme inhibitors (ACE-I) in patients with chronic heart failure (CHF), there are no data regarding whether a once or twice daily administrating schedule is preferable on neurohumoral effects. To address this issue, we evaluated the comparative effects of the administration of long-acting ACE-I once daily and twice daily on neurohumoral factors and autonomic nerve activity in patients with CHF. Twenty-nine stable patients with mild CHF who had been administered lisinopril (5-20mg/day) orally once a day (n = 14) or twice a day (n = 15) for more than 3 months were studied. We changed once daily administration to twice daily or twice daily administration to once daily, and followed for 3 months. We measured neurohumoral factors and cyclic variation of R-R interval (CVRR) from ECG. Blood pressure, heart rate and renal function were not significantly changed during the administration once daily and twice daily. Plasma levels of brain natriuretic peptide were not different between the two treatments. However, plasma renin activity was significantly decreased and norepinephrine was tended to decrease in the group of the administration twice daily (figure).



Comparisons of neurohumoral factors.

CVRR was unchanged during the two treatments. These findings suggest that twice daily administration of long-acting ACE-I may have better effects on the neuroendocrine system than once daily in patients with mild CHF.

MISCELLANEOUS THERAPY IN HEART FAILURE

P2165 Levosimendan is beneficial in diabetics with acute heart failure

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In patients with diabetes, heart failure is more common and is associated with a more severe prognosis compared with the normal population. Diabetics have a greater burden of diagnosed and undiagnosed myocardial ischaemic disease, as well as renal insufficiency. Agents, including beta-blockers and ACE inhibitors, are effective in patients with heart failure and concomitant diabetes. Levosimendan is a novel calcium sensitising agent with vasodilatory properties for the treatment of acutely decompensated heart failure, which improves short- and long-term prognosis. This study investigated the efficacy of levosimendan in diabetic patients with decompensated heart failure.
Patients admitted to the cardiology department with NYHA Class IV heart failure were treated with levosimendan, 3-12 μg/kg loading dose over 10 minutes, followed by a continuous infusion of 0.1 or 0.2 μg/kg/minute for 24 hours. Patients were monitored non-invasively for blood pressure (BP), heart rate, urinary output and clinical chemistry. Concomitant diabetes was being treated with either insulin (n=7) or metformin (n=5). Levosimendan decreased heart rate and increased diastolic and systolic blood pressure in patients with (n=12) and without (n=29) diabetes, and at discharge all patients were improved to NYHA Class II-III. In both groups, there was a large increase in net diuresis, and a large decrease in plasma brain natriuretic peptide (BNP) concentration, which has been proposed as a marker for heart failure severity.

Effects of levosimendan treatment

Variable*	Diabetics**	Non-diabetics**	p value
Heart rate (beats/minute)	-9.5 (9.8) [12]	-11.8 (8.6) [29]	0.461
Diastolic BP (mmHg)	+6.3 (11.3) [12]	+6.1 (10.2) [29]	0.957
Systolic BP (mmHg)	+10.0 (9.1) [12]	+10.5 (14.2) [29]	0.914
Diuresis (mL)	+2174 (698) [12]	+2176 (1525) [28]	0.996
Plasma BNP (pg/mL)	-469 (476) [8]	-522 (380) [19]	0.761

*Mean change from baseline to 24 hours, except BNP, which was from baseline to discharge; **Mean (standard deviation) [n]

Levosimendan improved haemodynamic and renal function in patients with severely decompensated heart failure and concomitant diabetes, and no differences in the effects of levosimendan were observed between patients with or without diabetes.

P2166 Levosimendan is efficacious in acute heart failure independent of renal function

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Levosimendan, a novel calcium sensitising agent, is indicated for acutely decompensated heart failure (ADHF). However, it is unclear whether this agent is effective in patients with ADHF and impaired renal function. This retrospective analysis of our clinical experience assessed levosimendan in patients with ADHF and normal (n=35) or impaired (n=6) renal function.
Patients received intravenous levosimendan, 3-12 μg/kg loading dose over 10 minutes, then a continuous infusion of 0.1 or 0.2 μg/kg/minute for 24 hours. Haemodynamic and safety parameters, including heart rate (HR), diastolic and systolic blood pressure (BP), diuresis, creatinine clearance, K^+ and Na^+ were measured at baseline, at 24 hours and at discharge from hospital.
All patients had NYHA class IV heart failure at admission, which improved to Class II-III at discharge. Improvements in haemodynamic parameters were similar in both groups (see table below). Baseline creatinine clearance was 54 ± 26 mg/dL and 13 ± 4 mg/dL in normal and renal impairment patients, respectively. Renal impairment was very severe and necessitated haemodialysis. Additionally, the baseline diuresis in patients with renal impairment was 15% of patients with normal renal function. After levosimendan, the increase in diuresis and creatinine clearance was significantly greater in patients with normal renal function, reflecting the differences in baseline values of both parameters.

Effects of levosimendan

Variable* Mean (SD)	Normal renal function (n=35)	Impaired renal function (n=6)	p value
HR (beats/minute)	-11.0 (9.3)	-12.0 (7.3)	0.798
Systolic BP (mmHg)	+11.5 (12.2)	+3.5 (15.2)	0.158
Diastolic BP (mmHg)	+5.9 (9.5)	+7.7 (16.8)	0.071
Diuresis (mL)	+2406 (1209)	+562 (945)	0.002
Creatinine clearance (mg/dL)**	+5.02	+1.23	0.420
Serum K^+ (mM)	-0.22 (0.60)	-0.22 (0.75)	0.999
Serum Na^+ (mM)	-0.20 (3.30)	+2.83 (4.45)	0.056

*Mean change from baseline at 24 hours; **Calculated by the formula of Cockroft and Gault; SD, standard deviation

Levosimendan may be a useful treatment for ADHF in patients with severely impaired renal function, though more patients are required to confirm these findings. In summary, levosimendan is efficacious in patients with acute heart failure independent of renal function.

P2167 Prognostic markers of levosimendan treatment efficacy in severe congestive heart failure: a prospective multicentre study

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Purpose: Levosimendan(LEVO) is emerging as a new intravenous inotropic drug with advantages compared to dobutamine in CHF patients(pts). We evaluated the hypothesis that the initial clinical status can be a determinant in obtaining beneficial LEVO effects on CHF treatment.
Methods: In the BELIEF study, we assessed effects of LEVO in 115 consecutive pts, (54±15 years old), who were admitted to the hospital requiring intravenous support under optimized CHF treatment, and systolic blood pressure >85 mmHg. The iv LEVO loading dose was 1.11±0.24 followed by 0.11-0.12±0.05 mcg/kg/min over 24 hours. The CHF etiology was ischemic in 28,7% pts, chagasic in 21%, and other in 50,3%. The race was caucasian in 61,5%, and African Brazilian in 38,5%. Prior to LEVO infusion 50% of pts appeared as warm and wet profile,34% as cold and wet, and 19% pts as cold and dry. The primary endpoint was survival assessment up to hospital discharge after LEVO without any additional iv inotropic drug usage as a "rescue" therapy.
Results: 78,6% patients achieved the primary endpoint and were considered as responders(R). Comparing R versus NR(non-responders) pts we observed differences concerning: etiology (R = hypertensive 100%, ischemic 82%, chagasic 61%), race (R=African-Brazilian 7%, NR=African-Brazilian,p=0.015), body mass index (R=24.5.1±0.7, NR 21.6±1.3, p=0.015); basal systolic SBP (mmHg) (R=111±2 x NR=98±4,p=0.005); 24-hour diuresis after LEVO (R=2789±365 x NR=1365±212, p=0.05);previous 48 hours iv dobutamine use (R=19% x NR=50%,p=0.026);initial clinical profile (R=warm/wet 64%,cold/wet 24%,cold/dry 12% x NR=5%,64%, and 29% respectively,p<0.001).In multivariate analysis the basal low SBP(p=0.002) and hypotension after LEVO(p=0.03) were inversely associated with achieved end-point. Hypotension was significantly more frequent in the NR group (NR=71% versus R=14%,p<0.001).We have not seen any differences concerning: last-year hospital admissions; time of cardiac disease; etiology; atrial fibrillation, left branch block, pacemaker; basal heart rate; serum sodium; previous 48 hours iv furosemide; beta-blockers use; serum creatinine; hemoglobin; serum potassium. Obseved events were: headache(7%);sustained ventricular tachycardia(2%); dizziness(2%);fever(2%);thoracic pain(2%); unstable angina(2%); hemoptysis(2%) and phlebitis(4%).
Conclusion: Our findings demonstrating that most patients achieved the primary endpoint, make LEVO an attractive option to treat decompensated CHF patients. The clinical status, etiology and race are prognostic markers of the LEVO treatment efficacy.

P2168 Effect of ALT-711, a novel glucose cross-link breaker, in the treatment of diastolic heart failure

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Background: Despite its high prevalence, optimal therapy for diastolic heart failure (DHF) has not been determined. LV hypertrophy, diastolic dysfunction, and vascular stiffness contribute to the pathophysiology of this disorder. ALT-711 is a novel compound that breaks glucose cross-links and has been shown to improve ventricular and arterial compliance.
Methods: 23 patients, mean age 71 years, with DHF (EF> 50% and no valvular or pulmonary disease) were enrolled in a 16 week, open-label trial of ALT-711 420 mg per day. Assessments included: peak exercise oxygen consumption (VO2) by expired gas analysis, aortic distensibility and LV volumes and mass by magnetic resonance imaging (MRI), Doppler diastolic filling, and quality of life by the Minnesota Living with HF (MLHF) questionnaire.
Results: 17 patients have completed follow-up testing. All had stable New York Heart Association (NYHA) class II-III symptoms. Baseline medications included: ACE inhibitors or angiotensin II antagonists (12 subjects), beta-blockers (10 subjects), and diuretics (12 subjects). At baseline, peak exercise VO2 (12.9 ± 3.5 ml/kg/min) and aortic distensibility (1.5 ± 0.09 10-3 mmHg-1) were markedly reduced. LV mass was 125 ± 36 gm at baseline and decreased to 119 ± 35 gm at follow-up (p = 0.04). This was accompanied by a decrease in the ratio of Doppler early diastolic flow velocity (E) to Doppler early diastolic mitral annulus velocity (Ea) from 10.9 ± 2.1 to 9.6 ± 1.8 (p = 0.02) and an increase in Ea from 7.0 ± 2.0 to 7.9 ± 1.4 cm/s (p = 0.07). The MLHF total score improved from 36.8 ± 18.1 to 31.2 ± 15.5 (p = 0.06) and the physical score improved from 18.4 ± 8.8 to 15.3 ± 8.6 (p = 0.053). There was no change in EF (64 ± 4% at baseline) or LV volumes. Blood pressure was unchanged (142/78 mmHg at baseline versus 143/79 mmHg at follow-up). Changes in peak exercise VO2 and aortic distensibility were not evident.
Conclusion: 16 weeks of treatment with the novel glucose cross-link breaker ALT-711 resulted in a decrease in LV mass and an improvement in LV diastolic filling in patients with diastolic heart failure. This suggests that ALT-711 may be useful in this disorder.

P2169 Effects of digoxin on left atrial function in heart failure

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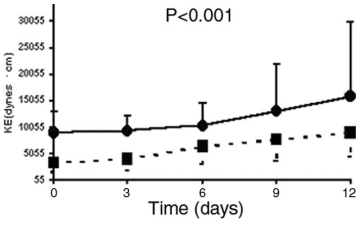
Background: Effects of digoxin, a commonly used drug in cardiology, on the left ventricle are well established. However, little is known about the effects of digoxin on the left atrial (LA) function.
Methods: Thirty patients with enlarged left atrium (maximal LA diameter > 4 mm) due to heart failure (New York Heart Association functional class III or IV) were studied before and after treatment with digoxin (0.25 mg per os for 12 days). Digoxin was also administered to thirty normal subjects who served as controls. LA active and passive emptying fraction (AEF and PEF), reservoir fraction (RF), kinetic energy (KE), and mean velocity of circumferential atrial fiber shortening (Vcf) were calculated using echocardiographic measurements of LA volumes and transmitral Doppler flow velocities at baseline and at the 3rd, 6th, 8th, and 12th day after digoxin administration.



Results: LA AEF, PEF, RF, KE, and Vcf were significantly lower in patients than in controls (P < 0.001). LA AEF, PEF, RF, KE, and Vcf increased significantly both in patients and controls after digoxin administration (P < 0.001). This increase was greater in patients than in controls (P < 0.001, figure). KE was linearly correlated with LA volume at the onset of atrial systole in all subjects. The slope and the intercept of this relation were significantly increased after digoxin both in patients and in controls (P < 0.001).
Conclusions: LA performance is impaired in patients with heart failure. Dilated atria manifest atrial failure. Digoxin improves LA performance and LA contractility both in dilated and in normal atria. The effects of digoxin on LA contractility are augmented in the failing atria than in the normal atria.

P2170 Direct, dose-dependent anti-fibrotic effects of atorvastatin in rat and human cardiac fibroblast cell culture

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HMGcoA reductase inhibitors (statins) may have favourable effects on cardiac remodelling post-MI. Whilst this may be predominantly due to their known anti-ischaemic actions, these drugs also possess additional properties that may be of benefit in this setting, such as anti-cytokine effects. Additionally, as pathological deposition of extracellular matrix (fibrosis) is a key component of remodelling post-MI, we sought to determine whether these agents could directly inhibit matrix production in-vitro. To do so, the effect of atorvastatin (ATV, 10-8M-10-5M) was examined in neonatal rat cardiac fibroblast cell culture after stimulation with the known pro-fibrotic factors angiotensin II (AII, 10-7 M) and transforming growth factor-beta (TGF-beta), n=4. Non-stimulated, non-treated wells served as controls. Collagen production was estimated by [3H]-proline incorporation (P). AII and TGF-beta increased [3H]-P by 38±17% and 90±34% respectively. ATV caused a dose-dependent reduction in [3H]-P (% decrease as c/f AII alone: 10-8M, -44+19%; 10-7M, -44+14%; 10-6M, -55+14%; 10-5M, -78+13%; $p<0.05$; % decrease as c/f TGF-beta alone: 10-8M, -9+4%; 10-7M, -20+12%; 10-6M, -46+6%; 10-5M, -67+15%; $p<0.05$). We also repeated these experiments in human cardiac fibroblasts (n=4). ATV similarly reduced AII- and TGF-beta-induced [3H]-P in a dose-dependent manner, $p<0.05$. Both AII and TGF-beta significantly increased alpha-(1) pro-collagen mRNA by 22 and 300% respectively; an effect that was blocked by ATV (% decrease as c/f. AII alone: 10-5M: -54+23%; % decrease as c/f TGF-beta alone: 10-5M:-33±9.5%). To determine whether these effects were mediated by alterations in connective tissue growth factor (CTGF), we measured CTGF mRNA in these studies. Both AII and TGF-beta increased CTGF mRNA by 86±18% and 98±19% respectively; this was significantly reduced by ATV (% decrease as c/f. AII alone: 10-5M: -67%±18%; as c/f TGF-beta alone 10-5M: -44±13%) We have demonstrated for the first time an anti-fibrotic effect of statins in cardiac fibroblast cell culture, following stimulation with pro-fibrotic factors known to be important in cardiac remodelling post-MI. These actions may contribute to the potential favourable effects of statins on cardiac remodelling.

P2171 Lipid lowering and change of antioxidative potential of plasma by long-term pentaerithrityltetranitrate administration associated with suppression of excessive O_2^- production in hypercholesterolaemia

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Introduction: Recently we have shown that metabolism of pentaerithrityltetranitrate (PETN) is reductive in contrast to oxidative catabolism of other nitro vasodilators. This are associated with additional co-production of reactive oxygen species (ROS) e.g. by hypercholesterolemia during using of nitro vasodilators like nitroglycerin. We analyzed the effects of PETN given for 8 weeks along with an atherogenic cholesterol diet (0.5%) on ROS production in the vascular bed and blood cells and on oxidation of SH-groups in plasma of hypercholesterolemic guinea pigs. **Methods:** Diet was given with and without PETN (3 mg/kg/day). Langendorff hearts were prepared before and after 8 weeks of treatment. ROS were analyzed in perfusate and blood samples. Concentrations of SH-groups were analyzed using ESR and biradical. **Results:** ROS production in blood samples and in perfusates of isolated hearts of cholesterol-treated animals increased from 0.237±0.033μM/min to 0.364±0.024μM/min and from 1.73±0.06 μM/min to 2.73±0.029μM/min (n=12). This excessive production was significantly lower amounting only to 0.294±0.012μM/min in ex vivo blood samples of animals treated additionally with PETN and in heart perfusates amounting only to 2.29±0.044μM/min. Likewise, concentrations of reduced SH-groups were increased after 8 weeks cholesterol diet and were even more augmented when additional PETN was given daily. **Conclusions:** Long-term administrations of appropriate dosages of PETN effectively reduce excessive production of reactive oxygen species during experimental hypercholesterolemia. This may be explained by its metabolism in contrast to other nitrates by reducing of SH-groups and neutralization of formed reactive oxygen species. This effect of PETN can be compared to the effects of lipid lowering drugs.

P2172 Irbesartan, an angiotensin type 1 receptor antagonist, attenuates progression of monocrotaline-induced pulmonary hypertension in rats

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Pulmonary hypertension (PH) is a severe and progressive disease associated with structural changes in the pulmonary vasculature leading to elevation of pulmonary arterial pressure and compensatory right ventricular hypertrophy. A useful experimental model for understanding the pathophysiology of PH is the administration of the pyrrolizidine alkaloid monocrotaline (MCT) to rats. In this animal model, various drugs have been shown to attenuate the development of PH. However, contrasting results have been reported following the use of renin angiotensin system inhibitors. Thus, the aim of our study was to investigate first, the efficacy of irbesartan (IRBE), an AT1 receptor antagonist, alone or in association with a diuretic, hydrochlorothiazide (HCTZ), in the progressive mortality of rats with severe PH, and, then, in the prevention of right ventricular and pulmonary hypertrophies.
Methods: 1) Fifteen days post MCT injection (80 mg/kg, s.c.), SD rats were daily treated with IRBE (30 and 300mg/kg), HCTZ (10mg/kg) and IRBE + HCTZ (30 + 10 mg/kg, respectively) until spontaneous death (n=23 to 24 per group). This first study was stopped at 85 days leading to total mortality of vehicle-treated rats. 2) In a second study, all rats were sacrificed at five weeks post MCT injection (50% survival in untreated group) and cardiac and pulmonary hypertrophies were evaluated (n = 9 to 16 per group).
Results: 1) The 50-day survival rates were 48%, 67%, 25% and 61% for IRBE 30mg/kg, IRBE 300mg/kg, HCTZ and IRBE + HCTZ, respectively, compared to 17% in untreated rats. The median survival time was significantly increased only for IRBE 300 mg/kg (77.5 days, p=0.0003) and IRBE + HCTZ (70 days, p=0.0008) compared to the vehicle group (39 days). 2) Lung weight to body weight ratio (LW/BW) and heart weight to body weight ratio (HW/BW) were significantly increased in MCT rats: 130% and 44%, respectively. IRBE (30 and 300 mg/kg) and IRBE + HCTZ reduced LW/BW by about 20% ($p<0.05$) whereas HCTZ was totally ineffective. HW/BW was significantly decreased only with IRBE 300 mg/kg and IRBE + HCTZ (-12 and -15%, respectively, $p<0.05$). In conclusion, this study clearly shows the beneficial effects of the blockade of AT1 receptors with IRBE on progressive mortality and cardiac and pulmonary remodeling after PH induced by MCT in rats. Moreover, these effects were further potentiated by concurrent administration of a diuretic, HCTZ. Taken together these results raise the clinical potential for AT1 receptor antagonists in the treatment of PH.

P2173 Anti-remodelling effects of growth hormone administration are associated with the reduction of abnormal peripheral immune responses in dilated cardiomyopathy patients

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Background: Experimental studies have demonstrated that growth hormone (GH) administration can influence left ventricular (LV) myocardial growth and geometry in the setting of chronic heart failure (CHF). This study investigates whether the effects of GH administration on LV geometry are associated with the respective modulation of circulating pro-inflammatory/anti-inflammatory cytokine balance in patients with CHF secondary to idiopathic dilated cardiomyopathy (IDC).
Methods: Plasma pro-inflammatory cytokines TNF-a, IL-6, GM-CSF, MCP-1, and anti-inflammatory molecules IL-10, TGF-b2 were measured (ELISA) in 12 IDC patients (NYHA class III; LVEF: 23.6±1.7%) before and after a 3-month subcutaneous administration of GH 4IU every other day (randomized crossover design). Peak oxygen consumption (VO2max) was determined by cardiorespiratory stress test, while LV dimensions, volumes and mass index (LVMI) were calculated by echocardiography at the same period.
Results: A significant decrease of plasma pro-inflammatory cytokines TNF-a (7.8±1.1 vs 5.5±0.9 pg/ml, $p<0.02$), IL-6 (5.6±0.5 vs 4.6±0.3 pg/ml, $p<0.05$), GM-CSF (27.3±1.7 vs 23.3±1.8 pg/ml, $p<0.05$) and MCP-1 (199±5 vs 184±6 pg/ml, $p<0.05$), as well as a significant increase in ratio IL-10/TNF-a (1.9±0.3 vs 3.5±0.9, $p<0.05$), IL-10/IL-6 (2.6±0.6 vs 3.2±0.5, $p<0.05$) and TGF-b2/TNF-a (3.1±0.6 vs 4.4±0.6, p=0.05) were observed in IDC patients after GH treatment. Furthermore, a significant reduction in LV end-systolic volume index (LVESVI, 128±12 vs 102±12 ml/m^2, $p<0.01$) and LV end-diastolic volume index (LVEDVI, 228±16 vs 200±ml/m^2, $p<0.05$), as well as a significant increase in posterior wall thickness (PWTH, 9.2±0.5 vs 10.3±0.6 mm, $p<0.05$) and VO2max (15.3±0.7 vs 17.1±0.9 ml/kg/min, $p<0.05$) were found in patient population after GH administration. A good correlation was found between GH-induced reverse LV remodeling expressed by the percentage reduction of LVESVI and percentage increase in exercise tolerance expressed by VO2max (r= -0.53, p=0.05). Finally, GH-induced reduction in LVESVI was significantly correlated with respective increase of plasma IL-10/TNF-a ratio (r=-0.62, $p<0.01$) in IDC patients.
Conclusions: GH administration reduces abnormal peripheral immune responses and causes reverse LV remodeling in patients with CHF secondary to IDC. Immunomodulatory effects of GH may be associated with the improvement of exercise capacity and LV geometry of IDC patients.

P2174 Are cycloxygenase-2 inhibitors safe in congestive heart failure?

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Background: Congestive heart failure (CHF) is a well known complication associated with nonselective anti-inflammatory drugs (NSAIDS). No literature to date, however, addresses the safety of COX-2 inhibitors in patients with CHF.
Objective: We sought to examine the association between COX-2 inhibitor use and outcomes in individuals hospitalized with CHF.
Methods: We used the population based disease-specific registry of the Improving Cardiovascular Outcomes in Nova Scotia (ICONS) study, and identified all 7350 Nova Scotians consecutively hospitalized with a discharge diagnosis of CHF between January 1, 1999 and December 31, 2001. We compared 282 patients admitted but not discharged on COX-2 inhibitors, 152 individuals admitted and discharged on COX-2 inhibitors, and 6916 patients not on COX-2 inhibitors with respect to traditional outcome measures (See table 1)

Table 1: COX-2 Inhibitors and CHF

Baseline Characteristics	COX-2 Admission	COX-2 Admission/Discharge	No COX-2	P value
Age (Mean)	77.2	76.7	75.7	NS
Females (%)	55.7	58.1	55.2	NS
IHD (%)	29.0	28.0	31.0	NS
DM (%)	35.9	37.8	35.1	NS
ACE I (%)	40.6	39.5	41.1	NS
B Blocker (%)	36.8	37.1	38.6	NS
Outcome Measures				
In Hospital LOS (%)	11.6	11.5	11.6	NS
In Hospital Death (%)	17.5	17.2	16.8	NS
Readmission CHF (%)	27.0	32.6	22.3	<0.05
Nonfatal 1 Yr MI (%)	5.2	5.0	4.6	NS
1 Year Mortality (%)	32.2	33.1	34.6	NS

Conclusion: Although preliminary and observational, our results suggest that COX-2 inhibitors are associated with a higher rehospitalization rate for CHF, but no difference in death or nonfatal MI. These findings may further help to inform the ongoing debate regarding the safety of COX-2 inhibitors, especially among individuals with cardiovascular disease.

ECHOCARDIOGRAPHY: A USEFUL TOOL FOR THE ASSESSMENT OF DIFFERENT PATIENTS WITH HEART FAILURE

P2175 Alteration of the left-ventricular contractile reserve in heart transplant patients: a dobutamine stress strain rate imaging study

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Strain rate imaging (SRI), a recent Doppler derived process allows myocardial systolic function quantification. We sought to investigate whether SRI can quantify the contractile reserve during dobutamine stress tests in heart transplant patients (HT) with respect to normal individuals.
Methods: An incremental dobutamine test (5 to 40 μg/kg/min) was performed in 10 HT (4 to 17 years following HT) and 15 controls, all with normal coronary angiography. Grey-scale and color myocardial Doppler data were acquired in standard B-mode views at baseline, low-dose, peak and recovery. Longitudinal SRI was processed from myocardial velocities for each segment. The changes in maximal systolic SR were used to quantify the myocardial contractile reserve.
Results: Dobutamine infusion failed to induce any clinical symptoms or ECG changes in both groups. Visually determined wall motion score was considered as normal in all analyzed segments for each stage of dobutamine stress.
Heart rate augmented similarly in both groups during dobutamine infusion. In controls, systolic SR increased gradually with incremental dobutamine dose and returned to baseline values upon recovery. In contrast, in HT patients, the increase in systolic SR was blunted at peak dobutamine and differed significantly when compared to controls (Table).

Peak systolic strain rate (s-1) (SD)

	Baseline	Low dose	Peak	Recovery
HT	-1.2 (0.04)	-1.9(0.09)	2.0(0.11)	-1.3(0.05)
Controls	-1.3 (0.03)	-1.9(0.04)	-2.9(0.07)*	-1.5(0.03)

*: $p<0.05$ vs HT

Conclusion: The quantitative assessment of myocardial function using strain rate imaging during dobutamine stress revealed an impaired contractile reserve in long term HT patients with normal coronary angiography. These subtle changes in regional myocardial function could not be identified using visual wall motion scoring. Whether this abnormality reflects endothelial dysfunction in normal coronary arteries needs to be further investigated.

P2176 Non-invasive cardiac rejection surveillance during the late post-transplant periods: reliability of tissue Doppler wall motion assessment

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Routine endomyocardial biopsies (EMBs) continue to detect acute rejections (ARs) beyond the first post-transplant year but their need for late AR surveillance is controversial due to their reduced diagnostic efficiency. However, late ARs are linked to both graft failure and transplant coronary disease (TxCD).
Aim: To provide appropriate AR surveillance during late post-transplant periods, we assessed the value of non-invasive screening by pulsed wave tissue Doppler imaging (PW-TDI) for AR diagnosis.
Methods: In 141 patients (post-transplant times: 2-15 years) monitored routinely by PW-TDI, we compared the diagnostic efficacy of routine EMBs (performed at predefined time intervals, unrelated to PW-TD results) with that of diagnostic EMBs (timed by PW-TDI). Routine EMBs were performed during annual follow-up catheterizations. Diagnostic EMBs were carried out whenever PW-TDI detected left ventricular wall motion alterations. The reduction of early diastolic peak velocity Em and/or prolongation of relaxation time TEm (from onset of second heart sound to Em) and/or reduction of systolic peak velocity Sm were considered indicative for the need of diagnostic EMBs, if these changes exceeded the threshold of 15% in comparison to the previous values.
Results: Among the 102 routine EMBs (102 different patients), 86.3% were ISHLT grade 0 and PW-TDI performed before EMB showed no relevant changes. Mild ARs of grade 1A and 1B were shown in 11.7% of routine EMBs. Only 2 routine EMBs (2%) showed ARs of grade 3A (asymptomatic patients, but with relevant PW-TDI changes). Among the 39 diagnostic EMBs performed in 33 patients because of PW-TDI alterations, only 8 (20.5%) were ISHLT grade 0, but in 6 cases coronary angiograms performed subsequently showed either new appearance or aggravation of TxCAD. The other 31 diagnostic EMBs showed cellular ARs of different degrees (32.3% grade 1A and 1B, 9.8% grade 2, 57.9% 3A and 3B). Vascular reactions were also shown in 71.0% of these EMBs. Systolic velocity (Sm) reductions of $>15\%$ were evident in 81.8% of all patients with AR and were shown in all patients with clinically relevant ARs (ISHLT equal or higher than grade 2, plus 1A and 1B with hemodynamic deterioration and/or vascular rejection).
Conclusions: Routine annual EMBs detect only a fraction of relevant late post-transplant ARs. Serial PW-TDI screenings followed by diagnostic EMBs whenever relevant wall motion alterations are detected increase the efficacy of AR diagnosis and provide an efficient strategy for late post-transplant AR surveillance.

P2177 Improvement of left-ventricular function after cardiac resynchronization therapy is predicted by tissue Doppler imaging

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Background: Cardiac resynchronization therapy was shown to reverse left ventricular (LV) remodeling in patients with congestive heart failure (CHF). However, the prediction of benefit is controversial. We aimed to investigate predictive factors of LV functional recovery and reversed remodeling after biventricular pacing.
Methods and Results: Fourty-four consecutive patients with CHF and a wide QRS complex (181 ± 42 ms) were studied by echocardiography prior to resynchronization. Intra- and interventricular asynchrony and their combination were assessed by pulsed-wave tissue Doppler from measurements of regional electromechanical coupling times in basal segments of the right and left ventricle. At 6-months follow-up, responders were defined by a relative increase in LV ejection fraction $>$ 25% or a decrease in LV end-diastolic diameter $>$ 10 mm as compared to baseline (n=25). The ROC analysis revealed the degree of intra- (AUC=0.80), interventricular asynchrony (AUC=0.74) and their combination (AUC=0.87) as the best predictors of the functional recovery after resynchronization. In addition, the degree of intra and interventricular asynchrony correlated significantly with the improvement of LV ejection fraction ($r=0.73$, $p<0.0001$) and end-diastolic diameter ($r=-0.59$, $p<0.0001$) at follow-up. The QRS duration and conventional echo-Doppler indices were not predictive of reversed LV remodeling.
Conclusions: In patients with CHF, the degree of intra– and interventricular asynchrony and their combination are the best predictive factors of LV functional recovery and reversed remodeling after cardiac resynchronization therapy.

P2178 Echocardiographic predictors of outcome in patients with mild left-ventricular systolic dysfunction

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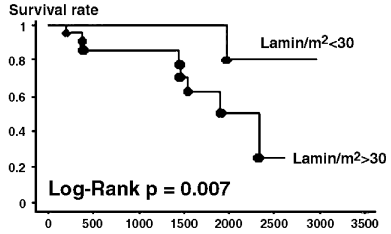
Although many parameters have been accepted as prognostic markers in patients with dilated cardiomyopathy (DCM), little is known about predictors of outcome in presence of only mild left ventricular (LV) systolic dysfunction.
Methods: Out of 264 pts with stable DCM (ejection fraction [EF] < 50% LV diastolic volume > 100 mL/m^2) followed in our out-patients clinic, 54 pts had LV EF > 40% and represent the study population. LV diastolic (LVD), systolic (LVS) volumes and EF were measured by means of monoplane area-lenght method. Left atrial end-systolic (LAmax) and end-diastolic (LAmin) volumes were measured from apical four-chamber view (area-lenght method). Mitral E, A waves velocities, their ratio (E/A) and E deceleration time (DTe) were measured. Mitral regurgitation (MR) was assessed semiquantitatively using a 5-point scale. End points were survival free of cardiac transplantation.
Results: 54 pts (61±11 years; 78% male) had NYHA class 2.3±0.8 and 4% was in atrial fibrillation. LVD/m^2 125±33 mL, EF 44±3%, LAmax/m^2 60±34 mL, LAmin/m^2 35±28 mL, E 0.6±0.2 m/sec, E/A 0.9±0.2, DTe 224±72 msec, MR 1.2±1.5, Univariate Cox analysis showed that the only predictors of outcome were: LAmin/m^2 (OR 2.8; 95% C.I. 2.74-2.85; p=0.005), LVD/m^2 (OR 2.79; 95% C.I. 2.72-2.88; p=0.04), even after adjustment for age.



Conclusion In patients with mild LV systolic dysfunction, survival is predicted by the volume of left atrial and ventricular chambers.

P2179 Role of the Tei index as an early echocardiographic marker of carvedilol-induced left-ventricular function improvement in patients with heart failure

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Background: The Tei index is a new echocardiographic/Doppler index of combined systolic and diastolic function, calculated as isovolumic relaxation time plus isovolumic contraction time divided by ejection time. It has been shown that the Tei index is effective for analysis of global cardiac function. The purpose of our study was to monitor the response of heart failure patients to carvedilol.
Methods: 22 patients (pts) (19 males) with dilated cardiomiopathy (16 ischemic, 6 idiopathic), age 67±6 yrs (range 56-77), NYHA class I 2 pts, class II 18pts and class III 2 pts, under optimal therapy with ACE-inhibitor, diuretics, aldosterone antagonists and digoxin when necessary, were studied. All pts underwent transthoracic Doppler echocardiography, 6 min walking test, NYHA classification and quality of life (QOL/0-100) assessment at baseline and after 3 months of maximal tolerated carvedilol treatment (31.3±15.6 mg).
Results: After 3 months of therapy NYHA class decreased of at least 1 degree in 14 pts, no worsening in the other 8; QOL improved from 51.7±21.4 to 64.0±17.7%, p<0.03. The Tei index significantly decreased from 0.87±0.17 to 0.53±0.29, p<0.03. Conversely both ejection fraction (EF) and transmitral Doppler flow analysis did not show significant improvements despite a trend towards amelioration (EF from 35.7±9.1, to 39.3±9.5%, p=ns; E/A from 0.74±0.33 to 0.96±0.50, p=ns; atrial contribution from 0.55±0.38 to 0.39±0.14, p=ns). There were no significant changes in basal heart rate (from 70.6±10.5 to 64.3±10.8, p=ns) and walking distance (from 544.8±191.5 to596.7±160.0 m, p=ns) while a significant reduction of RPP at peak exercise (from 11898±4227 to 10190±4081, p<0.01) was observed.
Conclusions: Combined systolic and diastolic function assessment by the Tei index could represent an earlier marker to evaluate left ventricular function in patients with heart failure and might be helpful to monitor the left ventricular function during drug interventions.

P2180 Impact of spirinolactone on regional myocardial function in left-ventricular dysfunction measured by Doppler myocardial imaging

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The aim of the study was to assess whether spirinolactone (SP), in addition to standard therapy, may affect regional myocardial function in patients (pts) with left ventricular (LV) dysfunction, using pulsed wave Doppler myocardial imaging (PW-DMI).
Method: We studied 42 pts (mean age 58.7 ± 9.1 years) with ejection fraction (EF) < 40%. Patients were randomized to treatment with SP, titrated up to 50 mg/die (SP group, n = 25) or control (C group, n = 17). In all pts echocardiography studies were performed at baseline and six months after randomization. Regional myocardial function, was obtained from apical approach, with PW-DMI sample volume within any LV segment at basal and medium level. In each adequately visualized segment we calculated myocardial velocities (m.v.) of systolic (S), early (E) and late (A) diastolic waves and their ratio E/A - index of regional diastolic function.
Results: After six months in the SP group regional myocardial function of basal and medium LV segments showed: increased ratio E/A by 15.2% (P<0.01) and 13.3% (P<0.02) and increased S m.v. by 12.5% (P<0.05) and 9.8% (NS) compared to baseline values. In the C group after six months regional myocardial function of basal and medium LV segments slightly changed: ratio E/A increased by 4.9% and 3.8% (NS both), and S m.v. increased by 3.2% and 3.3% (NS both) compared to baseline values.
Conclusion: In LV dysfunction low dose of SP in addition to standard therapy induced favorable modification of regional myocardial function, expressed through significant increased of basal S m.v. and ratio E/A of basal and medium LV segments.

P2181 Prognosis of patients having silent versus symptomatic myocardial ischaemia during dobutamine stress echocardiography

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Background: Myocardial ischemia during dobutamine stress echocardiography predicts future cardiac events. Currently it is not clear whether the prognosis of patients with ischemia is influenced by the presence of angina pectoris. The aim of this study was to compare the prognosis of patients having silent versus symptomatic ischemia.
Methods: A total of consecutive 615 patients (age 60±11 yrs, 446 men) with myocardial ischemia during dobutamine stress echocardiography were followed up for the occurrence of cardiac events. Myocardial ischemia was defined as the occurrence of new or worsening wall motion abnormalities. Follow-up was successful in 612 of 615 patients (99.5%). Forty patients underwent early revascularization (<60 days) and were excluded. Univariate and multivariate Cox regression models were used to identify independent predictors of cardiac events.
Results: Angina during the test occurred in 226 (40%) patients, silent myocardial ischemia was present in 346 (60%) patients. Clinical characteristics and echocardiographic data were similar in patients having silent versus symptomatic ischemia. The number of dysfunctional segments was comparable (8.5± 5.1 vs 8.6±4.8, respectively, p=0.8); also the number of ischemic segments was comparable (3.4±2.0 vs 3.5±2.5; p=0.7). During 3.2±2 yrs follow up, there were 124 (22%) deaths, of which 75 (60%) were attributed to cardiac causes. Nonfatal infarction occurred in 75 (13%), and late revascularization in 143 (25%) patients. There was no difference in cardiac mortality and cardiac events between patients with and without angina. Multivariate analysis showed that independent predictors of cardiac death were age (hazard ratio 1.05 CI 1.03-1.07) male gender (hazard ratio 2.0 CI 1.2-3.4), heart rate at rest (hazard ratio 1.27 CI 1.13-1.43), and number of dysfunctional segments (hazard ratio 1.7 CI 1.1-2.7).
Conclusion: The clinical outcome of patients with ischemia is not influenced by the presence of angina pectoris. Patients having silent versus symptomatic myocardial ischemia have a comparable prognosis.

P2182 Influence of dobutamine on mitral regurgitation due to dilated cardiomiopathy

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Introduction: The increase of left ventricular (LV) diameters in dilated miocardiopathy (DCM) frequently leads to mitral valve (MV)annulus (MVA) dilatation and mitral regurgitation (MR). We designed this study in order to assess if modifications in left ventricle or haemodinamics with infusion of dobutamine may influence MR.
Methods: We enrolled 30 patients (mean age 56.3±12.1 years, 66% male) with non-ischemic DCM and LV ejection fraction (EF) < 0.35. Echocardiography and haemodinamic measuraments, using a thermodilution catether were performed before (PRE) and after (POST) dobutamine infusion of 10ug/kg/min during 1 hour.
Results: We noted significant elevations of the heart rate (HR), systolic arterial pressure (SBP), cardiac output (CO) and EF. There was a significant decrease of the MV jet area assessed by color-doppler (MJAn), MV regurgitation fraction (FR), MV regurgitant orifice area (ROA), LV systolic (LVSD) and diastolic diameters (LVDD) - See table.

Echocardiographic and Haemodinamic data

	PRE	POST	p
HR (beats/min)	81.9±14.3	93.7±20.6	0.0001
SBP (mmHg)	120.7±18.4	133.9±19.6	0.0001
CO (l/min)	2.96±1.11	4.35±1.27	0.0001
EF (%)	26.4±8.2	31.8±10.1	0.0001
MJA (cm^2)	11.3±5.0	7.0±4.1	0.0001
MVAn (cm)	3.11±0.45	2.95±0.39	0.0001
RF (%)	37.9±19.6	25.5±20.9	0.0026
LVSD (mm)	6.3±0.8	5.9±0.9	0.0045
LVDD (mm)	7.4±0.8	7.2±0.8	<0.05
ROA (cm^2)	0.15±0.1	0.11±0.17	<0.05

HR - heart rate, SBP - systolic arterial pressure, CO - cardiac output. EF ejection fraction, MJA - mitral jet area, MVAn - Mitral valve annulus, RF - mitral valve regurgitation fraction, ROA - regurgitant mitral valve orifice area, LVSD - systolic and LVDD - diastolic diameter of the left ventricle. PRE - pre infusion of dobutamine, POST - post infusion of dobutamine

Conclusion: Dobutamine infusion leads to significant decrease of mitral regurgitation in DCM by changing on left ventricle diameters and reduction of MVA, and were associated with an improvement on LV performance.

P2183 Tissue Doppler imaging to assess improvement in contractile function and resynchronization after biventricular pacing in idiopathic cardiomyopathy patients

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Background: Biventricular (BV) pacing as a therapeutical option for drug-refractory heart failure patients results in improvement of systolic left ventricular (LV) function, functional status and well being of the patient. Myocardial Tissue Doppler imaging (TDI) is an echocardiographic technique that allows non-invasive, quantitative assessment of long-axis function with measurement of peak systolic velocity timing in relation to electrical activity (QRS on ECG). The aim of the present study was to evaluate whether TDI allows assesment of improved contractile function after biventricular pacing in idiopathic cardiomyopathy patients.
Methods: Twenty-two patients with dilated cardiomyopathy of idiopathic origin, LVEF <35%, NYHA class III or IV, QRS duration >120 ms and left bundle branch block underwent implantation of a BV pacemaker. Routine echo and TDI were performed before and after implantation of the BV device. The following parameters were derived: LVEF, peak systolic velocities in the septum and lateral wall, dyssynchrony between the septum and lateral wall (expressed as the delay in peak systolic velocity in the septum vs lateral wall).
Clinical parameters (NYHA class, quality of life score and 6-minute walking distance) were evaluated before and after 3 months of BV therapy.
Results: mean LVEF improved from 21±7% to 31±9% (P<0.05), the PSV increased significantly in the septum (from 2.1±1.3 cm/s to 3.9±1.8 cm/s, P<0.05) and lateral wall (from 2.4±1.7 cm/s to 4.5±1.5 cm/s, P<0.05). The reduction in the delay between peak systolic velocity of the septum vs lateral wall (from 97±35 ms at baseline to 28±21 ms after pacing, P<0.05) indicated that resynchronization was established. After 3 months of BV therapy, the NYHA class, quality of life score and 6-minute walking distance improved significantly.
Conclusion: The echocardiographic technique of TDI allows noninvasive assessment of improvement in contractile function and resynchronization after biventricular pacing.

P2184 Dose dependent effects of losartan versus high dose of captopril on post-infarction remodelling and heart failure

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As most trials were conducted with low losartan (L) doses and effects of high captopril (C) doses are already proven we compared effects of high and low L doses vs high C dose on LV remodeling (LVR), total ischemic burden (TIB) and heart rate variability (HRV) in postinfarction heart failure (HF).
Methods: 198 pts (13% female) with postinfarctionI LVR and HF (NYHA III/IV), aged 53±4 yrs were randomized to 3 groups (G): GL1 on L 50 mg/day (n=64); GL2 on L 100mg/day (n=66), GC on C 150 mg/day (n=68). LVR was revealed by EchoCG as anterior and posterior segments lengths indexes (ASL,PSL) in parasternal short axis view on papillary muscle level in random by two investigators unaware of the study aims.TIB as total time of ST depressions >1mm and >1min duration and HRV as SDNN were measured by 24-hour ECG monitoring. Measurements were done in 1, 30, 90, 180 days follow up.
Results: In 1d parameters were similar in Gs.In 30d ASL and PSL were greater in GL1 than in GL2 and G3 with no differences between two last Gs (ASL: GL1 6.5 ± 0.6* cm vs GL2 6.2 ± 0.7 cm vs GC 6.0 ± 0.6 cm, p<0.01; PSL: GL1 3.8 ± 0.2* cm vs GL2 3.3 ± 0.14 cm vs GC 3.4 ± 0.15 p<0.05) and stay greater vs GL2 and GC up to 180d. In 90d ASL and PSL were greater in GC vs GL2 (AS L: GL2 6.3 ± 0.5* cm vs GC 6.5 ± 0.6 cm, p<0.01; PS L: GL2 3.4 ± 0.15* cm vs GC 3.7 ± 0.16, p<0.01). TIB and SDNN were similar in Gs. However in 180d TIB and SDNN were better in GL2 vs GL1 and GC and similar in GL1 and GC. (TIB: GL2 27±12 min* vs GC 34±13 min, p< 0.001; SDNN: GL2 124.05±16* ms vs GC 110.03±12 ms, p< 0.01). ASL, PSL differences became more prominent: (ASL: GL2 6.4 ± 0.5* cm vs GC 6.9 ± 0.6 cm, p<0.001; PSL: GL2 3.5 ± 0.15* cm vs GC 4.2± 0.16, p<0.0001), Side effects were observed in GL2 10.3% vs GC 16.2%, p<0.01.
Thus high dose of L more effectively alter LVR and improve TIB and HRV than low dose L and high dose C and is better tolerated than high C dose.

P2185 Echocardiographic determinants of brain natriuretic peptide levels in patients suspected of heart failure

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Aim: High levels of B-natriuretic peptide (BNP) were related to systolic and diastolic dysfunctions or elevated systolic pulmonary artery pressure (PAP). We attempt to assess the complex relationships between BNP and combination of systolic, diastolic parameters and PAP in patients suspected of heart failure.
Methods: We studied 41 patients who underwent echocardiography to evaluate ventricular systolic function (ejection fraction (EF), PAP)), diastolic function (velocities of E and A mitral waves for E/A ratio, E wave deceleration time (DT), E wave color M-mode Doppler flow propagation velocity (Vp), peak E wave of the lateral annulus velocity by Doppler tissue recordings (Ea)) and BNP blood test 48 hours within echography. Simple linear regression analysis was used to evaluate the correlations between BNP and these parameters. Stepwise regression model was used to determine the best combined model.
Results: EF (46%±17; r=0.60/p<0.001), E/Vp (2.1±0.8; r=0.56/p<0.001), PAP (39mmHg±14; r=0.54/p<0.001), DT (189ms±79; r=0.40/p<0.005), E/Ea (10.9±4.8; r=0.38/p<0.02) and E/A (1.4±0.9; r=0.32/p=0.04) significantly correlated with BNP (522pg/ml±422) levels. Stepwise regression model demonstrated that the combined " systolo-diastolic models " (EF-PAP with 1 to 4 diastolic parameters) determined BNP levels with correlation coefficients above 0.8 (see table). The best model was the combined "EF - PAP - E/Ea" model with a correlation coefficient of 0.82.

Correlations: Stepwise regression model

Model size (parameters)	r	p (E/A)	p(DT)	p(E/Vp)	p(E/Ea)	p(EF)	p(PAP)
2 (EF, PAP)	0.757	-	-	-	-	<0.0001	<0.001
3 (E/Ea, EF, PAP)	0.819	-	-	-	<0.01	<0.0001	<0.0001
3 (E/vp, EF, PAP)	0.800	-	-	0.02	-	<0.001	<0.001
4 (E/Vp, E/Ea, EF, PAP)	0.824	-	-	0.12	0.047	<0.001	<0.0001
5 (DT, E/Vp, E/Ea, EF, PAP)	0.827	-	0.50	0.10	0.041	<0.001	<0.0001
6 (E/A, DT, E/Vp, E/Ea, EF, PAP)	0.830	0.43	0.33	0.10	0.06	<0.001	<0.0001

p(X)= p value for parameter "X" when including in the considered model.r = square root of R^2

Conclusion: In patients with heart failure, BNP levels are mainly determined by systolic dysfunction and PAP but are also significantly modulated by associated diastolic dysfunction.

STABLE ANGINA PECTORIS: MISCELLANEOUS

P2186 Carotid intima-media thickness and coronary atherosclerosis: differences between stable and unstable coronary disease

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Carotid intima-media thickness (IMT) has been shown to be significantly correlated to the risk of cardiovascular events and the presence of coronary atherosclerosis. To investigate the usefulness of carotid IMT to predict severity and extension of coronary atherosclerosis in patients (pts) scheduled for coronary angiography, 143 consecutive pts referred to the Cath Lab of our Institution (96 male, 43 with recent myocardial infarction, 24 with unstable angina, 76 with stable angina or stable silent ischaemia, 62.4 $\pm$ 10.4 years) were enrolled for this study. Each patient underwent high resolution (12-5MHz linear array probe) ultrasound evaluation of carotid IMT at 1cm from the carotid bulb (C-IMT) and at the point of maximum thickness of the bulb itself (B-IMT). The presence of atherosclerosis and critical (>70%) stenosis of the main coronary artery segments was assessed by computer-assisted quantitative coronary angiography (Advantix, GE). Of 1152 coronary segments evaluated, 416 (36,1%) appeared affected by angiographically evident atherosclerosis and 191 (16,6%) appeared to harbor at least 1 critical stenosis. In 98 pts was observed at least 1 coronary segment with 1 critical stenosis, while in 66 pts 2 or more critically stenosed coronary segments were observed. In a multiple regression analysis model (r=0.46, F<0.001) considering age, fasting blood glucose, total cholesterol, the number of cigarettes smoked daily, body mass index, mean arterial pressure, C-IME and B-IMT, B-IMT was the only parameter which was independently correlated to the number of atherosclerotic coronary segments (p<0.0001). The receiver operating curve (ROC) analysis demonstrated an high predictive value for the presence of plurisegmental critical coronary stenosis for both C-IMT and B-IMT only when the 76 pts with a "stable" coronary artery disease (CAD) were considered (SMIC: cutoff 0.9 mm, sensitivity 63.0%, specificity 80.0%, area under curve [AUC] 0.75 with 95%CI 0.63-0.87; SMIB: cutoff 1.6 mm, sensitivity 67,4%, specificity 90.0%, AUC 0.82 with 95%CI 0.72-0.93), while predictive value of theese parameters in the other 67 pts with "unstable" CAD appeared poor. In conclusion, in the population evaluated in this study, carotid IMT was correlated to the extent of coronary atherosclerosis, even if an high predictive value for plurisegmental critical coronary stenosis was observed only in pts with "stable" CAD. Higher incidence of thrombotic lesions and vasospasm in "unstable" pts and differences in the demographical features of the 2 groups of pts could account for this phenomenon.

P2187 C-reactive protein but not activated clotting factor VII plasma levels predict clinical outcome in patients undergoing elective coronary intervention

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Background: Both vascular inflammation as determined by C-reactive protein (CRP) and exstrinsic coagulation as measured by factor VII-activity (F VII) may predict clinical restenosis rate in patients with stable angina pectoris undergoing elective percutanous coronary intervention (PCI).
Methods and Results: Diagnostic angiography led to a significant increase in CRP levels after 16-20 hours in patients with discrete CAD (n=22) but not in patients without any signs of coronary atherosclerosis (n=27). During a six month follow-up after PCI, 17 out of 81 (21%) patients developed a major adverse coronary event (MACE). There was a significant increase in pre-procedural CRP levels of PCI patients suffering from a MACE as compared to patients without CAD (p=0.017). Tertiles of CRP levels independently predicted clinical restenosis, as it developed in 33.3% of patients with the highest CRP levels (0.7 – 4.8 mg/dl), in 16.6% of patients with second tertile CRP levels (0.23 – 0.7 mg/dl) and in 7.4% of patients with lowest tertile CRP levels (0.0 – 0.23 mg/dl). There was a significant difference in the restenosis rate between patients from the first and the third tertiles (p=0.018). Successful PCI was associated with a significant decrease of mean CRP levels after six months, whereas PCI in patients suffering from a MACE led to no change in CRP levels. There was no association between factor VII-activity and clinical outcome after PCI, and F VII-activity did not change over a 6 month period.
Conclusions: In patients with stable angina pectoris undergoing elective PCI, increased preprocedural and 6-month follow-up CRP plasma levels are associated with clinical restenosis. Factor VII plasma activity lacks such correlations.

P2188 IgA anticardiolipin antibodies are markers of the extent of daily life ischaemia in patients with stable angina

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Anticardiolipin antibodies (ACA) present procoagulant activity and cause significant endothelial cell dysfunction when binding on the cell surface. We investigated whether ACA plasma levels are related to platelet activation, thrombin generation and daily life ischaemia in patients with stable angina (SA). **Methods:** We measured (mean$\pm$SE) IgG, IgM, IgA ACA plasma levels (Units), prothrombin fragments (PF1+2, nmole/l), 24h urine excretion of 11-dehydrothromboxane B2 (DHTXB2, ng/ml, creatinine) in 60 patients with SA and in 20 controls matched for age and atherosclerotic risk factor. Patients had angiographically documented disease and underwent a 48h Holter monitoring for assessment of the number and duration of ischaemic episodes. **Results:** Patients had higher IgA-ACA plasma levels than controls (4.3$\pm$0.45 vs 2.2$\pm$0.17, p<0.01). Increased IgA-ACA were related to increased number and duration of ischaemic episodes (r=0.41 and r=0.48, respectively, p<0.01). Patients with >10 ischaemic episodes (n=14) or duration of ischaemia >30min (n=18) had higher IgA-ACA than those with <10 episodes or <30 min duration of ischaemia (6.4$\pm$0.9 vs 3.4$\pm$0.4, p=0.007 and 5.6$\pm$0.7 vs 3.2$\pm$0.5, p=0.018). ROC curve analysis showed that IgA-ACA levels > 3.5 units predicted a number of ischaemic episodes >10 or duration of ischaemia >30min with 75% and 78% sensitivity and 80% and 65% specificity respectively(area: 0.80, CI: 0.63-0.96, p=0.006 and 0.78, CI: 0.58-0.94, p=0.01 respectively). High IgA-ACA levels were related to reduced platelet count and 11DHXTB2 concentrations (r=-0.39 and r=-0.33, p<0.01). There was no relation of ACA to prothrombin fragments. **Conclusion:** Increased IgA-ACA levels are associated with low platelet activity and increased ischaemic burden in patients with stable angina. IgA-ACA are related with the extent of daily life ischaemia likely, because they cause endothelial dysfunction after binding on the cell surface and thus,lead to reduced nitric oxide levels and transient reduction of coronary blood flow.

P2189 Thermal heterogeneity in stable human coronary atherosclerotic plaques is underestimated in vivo: the "cooling effect of blood flow

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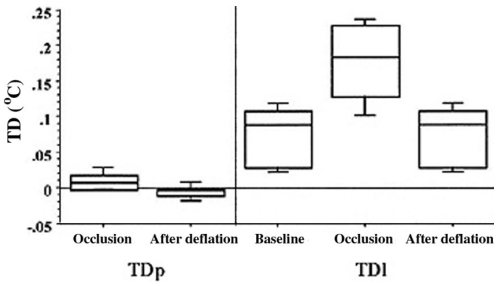
Despite the marked thermal heterogeneity that was shown in previous ex vivo studies in atheromatic plaques, in stable lesions trivial in vivo temperature (T) variations were recorded, perhaps due to the 'cooling effect' of blood flow. The impact of coronary blood flow on T measurements in the coronary vessels was investigated in this study.
Methods: We enrolled 18 patients (pts) with effort angina (EA). The coronary flow velocity was continuously recorded by a flow-wire, over which a balloon catheter was advanced proximally to the lesion. By inflating the balloon complete interruption of flow was achieved. T measurements were performed by a thermography catheter (Medispes Co., Switzerland) at the proximal vessel wall and at the lesion before, during and after complete interruption of blood flow. TDp:difference between the proximal vessel wall and the maximal T during and after balloon inflation. TDI:difference between the atherosclerotic plaque and the proximal vessel wall T at baseline, during and after flow obstruction.
Results: The procedure was uncomplicated and reproducible. TDp during and after the complete flow interruption was 0.012$\pm$0.01°C and -0.006$\pm$-0.01°C (p<0.001) respectively. TDI was 0.08$\pm$0.04°C at baseline, 0.18$\pm$0.05°C (60.5$\pm$14.1% increase) during and 0.08$\pm$0.04°C after flow interruption (p<0.001). TDI was greater than TDp during and after flow impairment (p<0.001). There was a correlation between the baseline average peak velocity and TDI during flow interruption (R=0.57, p=0.01). In 7 pts without thermal heterogeneity (TDI<0.05°C) at baseline, TDI was increased by 76.0$\pm$8.4% during balloon inflation.
Conclusions: In pts with EA, thermal heterogeneity of atherosclerotic plaques is underestimated, possibly due to the 'cooling effect' of coronary blood flow.



P2190 Prognostic value of QT dispersion changes during exercise in patients with stable angina

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QT dispersion reflects the local difference in the ventricular repolarization time. It has been reported that extending of rate-corrected QT dispersion (QTcD) at peak of exercise associated with myocardial ischaemia.
Aim: To assess the prognostic value of QTcD changes during exercise in patients (pts) with stable angina.
Methods: 68 consecutive pts with stable angina, age 54.3±8.2, 61men, 7 women underwent coronary angiography and exercise bicycle testing. All pts had coronary artery (CA) stenoses over 50% of luminal diameter. Main left CA stenosis over 50%, high or long proximal stenosis (or subocclusion) of one or more CA, multivessel CA disease were considered as predictors of unfavourable prognosis. ST segment slope and QTcD were determined from a 12-lead ECG obtained at baseline and peak of exercise. ST depression (STD) 0.2mV or more was considered as prognostically unfavourable. During 36±12 months follow-up three variants of clinical course were determined: group 1 (G1) - unfavourable course (cardiac events: sudden death, fatal and nonfatal myocardial infarction, urgent revascularization) - 20 pts, group 2 (G2) - stable course - 30 pts, group 3 (G3) - improvement or clinical remission - 18 pts.
Results: At baseline of the stress mean values (M±SD) of QTcD were statistically comparable between all groups. At peak of exercise the same values increased from 55.7±31.6 to 93.2±41.8 msec in G1 ($p<0.05$), from 53.0±25.2 to 69.0±32.2 msec in G2 ($p<0.05$), from 42.8±19.8 to 44.3±16.4 msec in G3 ($p>0.05$). Significant differences in mean values of QTcD extending (EQTcD) were observed between all groups: 37.5±39.3 msec in G1 vs 16.0±23.7 msec in G2 vs 1.5±15.6 msec in G3; $p<0.05$. Mean values of QTcD at peak of exercise were statistically different between all groups too. EQTcD 20 msec or more was assessed as a sign of unfavourable course: it was observed in 75% of pts in G1 vs 33.3 and 11.1% of pts in G2 and G3, respectively; $p<0.05$.
The sensitivity and specifity of EQTcD prognostically unfavourable values compared to STD and angiographic predictors of unfavourable course were 55.6% vs 53.3% and 63.2%, respectively and 66.7% vs 85.4% and 85.4%, respectively. The combination of EQTcD and STD signs of worse prognosis increased they sensitivity and specifity: 66.7% and 93.8%, respectively.
Conclusion: QT dispersion may be used as a simple, accurate and inexpensive complementary tool for evaluation of prognosis in pts with stable angina. Significantly extended rate-corrected QT dispersion during exercise may predict unfavourable course of disease.

P2191 Coronary revascularization in octogenarians, percutaneous coronary intervention or coronary artery bypass grafting

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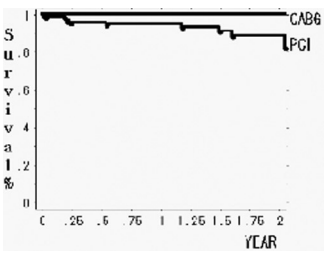
Background: Increasingly more elderly patients are receiving percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). High age is usually thought of the great risk of CABG, so elderly patients are performed more PCI than CABG. But which strategies are more beneficial for elderly patients is still uncertain.
Objectives: This study sought to determine the short- and long-term outcome of PCI and CABG for ischemic heart disease in elderly patients (>80 years).
Methods: We studied 191 elderly patients treated with PCI between 2000 and 2002, compared with 43 elderly patients treated with CABG. Clinical outcome was measured by taking the end points of procedure success, death, myocardial infarction in hospital, and major adverse cardiac events (MACEs) including death, myocardial infarction and CABG in 2-year follow up.



Results: CABG group were more likely to have multivessel disease (95.3% vs 57.6%, $P<0.0001$) and left main disease (41.9% vs 9.4%, $P<0.0001$). Hospital stay was significantly longer in CABG group (23.9±10.3 vs 8.4±11.3, $P<0.0001$). Procedure success was significantly higher in CABG group than PCI group (100% vs 91.6%, $P<0.05$). MACEs occurred in hospital was similar in both groups (CABG group: 0% vs PCI group: 4.7%, P=NS). 2-year survival and survival free from MACEs rate were significantly higher in CABG group (2-year survival: PCI 88.5% vs CABG 100%, free from MACE: PCI 78.4% vs CABG 100%, $P<0.01$).
Conclusion: Paradoxically elderly patients have greater risk reductions from CABG than PCI in short- and long-term outcomes in this study. There is a possibility that CABG is also beneficial in elderly patients.

P2192 Treatment of patients with stable angina and first angiographic diagnosis of coronary artery disease in Germany: results of the STAR Registry

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Background: Coronary artery disease (CAD) contributes considerably to the overall morbidity and mortality of cardiovascular disease in Germany. Little information exist on the extent of CAD in patients (pts) with stable angina pectoris (AP) as well as their invasive and medical treatment in clinical practice.
Methods: Since September 2001 consecutive pts with stable AP, in whom CAD was documented angiographically for the first time, have been enrolled into the STAR-Registry (STable Angina Registry, 53 hospitals).
Results: Out of 1551 consecutive pts (70.5% male, mean age 67 years) 18.5% were classified CCS I, 46.6% CCS II and 36.9% CCS III. Cardiovascular risk factors were as follows: 39.0% smoking, 66.7% hyperlipidemia, 26.4% diabetes mellitus, 26.1% family history of CAD. Prior myocardial infarction was present in 8.4% of the patients. The mean cholesterol was 217±50 mg/dl, LDL-cholesterol was 140±43 mg/dl. Peri-interventional complications (angiography and PTCA) were as follows: death 0.2% (3 pts), acute myocardial infarction 0.2% (3 pts) and emergent CABG in 1 pt.

Treatment of CAD with stable angina

1-vessel-CAD	45.9%
2-vessel-CAD	30.0%
3-vessel-CAD	24.1%
LV-EF	65±13%
PTCA	45.6%
Stent (relative to PTCA)	70.1%
IIb/IIIa-antagonists (relative to PTCA)	19.4%
CABG	2.0%
ASA	89.9%
Betablockers	75.6%
ACE-inhibitors	58.3%
Statins	70.9%

Conclusion: Almost half of the pts with angiographically documented CAD and stable AP were treated by PTCA, two thirds of those received stents, half of the pts received IIb/IIIa antagonists. Peri-interventional complications (death, MI, CABG) occurred in 0,4%. The use of ASA, betablockers, ACE-inhibitors and statins was high, 34.4% of the pts received all 4 medications as chronic therapy of CAD.

P2193 Clinical and angiographic predictors of invasive versus conservative treatment in stable coronary artery disease in Europe: the Euro Heart Survey on coronary revascularization (EHS-CR)

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Background: It is unclear which patient characteristics determine invasive versus conservative treatment, and coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI), in patients with stable coronary artery disease in clinical practice.
Aim: To assess the relation between patient characteristics and the choice of therapy in patients with stable coronary artery disease.
Methods/Results: Between September 2001 and March 2002, 5,767 consecutive patients with angiographically proven coronary artery disease were enrolled in 130 centers throughout 31 countries in the EHS-CR. Totally, 2,971 patients (52%) presented with stable coronary artery disease with a mean age of 63,2 years. Among them, the intended treatment was conservative in 619 patients (21%), and invasive in 2,352 patients (79%), either with CABG, 841 patients (36%), or with PCI, 1,511 patients (64%). Among a broad range of clinical and angiographic characteristics, multivariate logistic regression analyses revealed that the extent of coronary artery disease and the lesion morphology were the most significant determinants of the therapeutic decision. Table shows the 8 most significant characteristics from the 25 considered. In patients with multivessel disease the therapeutic choice was twice more likely to be invasive treatment, and if chosen invasive treatment it was ten times more likely to be CABG, as compared with single vessel disease.

Table: Determinants of treatment

	Invasive vs conservative	CABG vs PCI
Multivessel disease	2.13 (1.73-2.62)	10.2 (7.75-13.4)
Type C lesion	0.90 (0.85-0.97)	1.24 (1.15-1.34)
Previous CABG	0.26 (0.20-0.34)	0.13 (0.08-0.19)
Hypercholesterolemia	1.18 (0.97-1.44) *	0.61 (0.49-0.75)
Chronic renal failure	0.79 (0.49-1.27) *	0.45 (0.25-0.78)
Valvular heart disease	0.89 (0.62-1.27) *	5.17 (3.44-7.77)
Prior myocardial infarction	0.76 (0.63-0.91)	0.86 (0.70-1.05) *
Hypertension	0.80 (0.66-0.98)	0.92 (0.75-1.13) *

Presented as odds ratio with 95% confidence interval; * not significant

Conclusion: Throughout Europe, coronary revascularization was the preferred choice of therapy in the vast majority of patients with stable coronary artery disease. Therapeutic decisions were predominantly determined by angiographic characteristics.

P2194 Effects of mental stress on platelet reactivity in patients with coronary artery disease or cardiac syndrome X

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Background: Previous studies have shown that physical exercise increases platelet reactivity in patients with significant coronary artery disease (CAD). In contrast, we recently found that platelet reactivity is decreased by exercise in patients with cardiac syndrome X. In this study we investigated whether the response to mental stress of platelet reactivity also differs in patients with significant CAD or cardiac syndrome X.
Methods: We studied 16 patients (56±6 years, 4 women) with stable angina pectoris and angiographically documented CAD, and 23 patients (46±6 years, 17 women) with syndrome X. All patients underwent arithmetic mental stress test, consisting of sequential substractions for a period of 5 minutes. Blood samples were drawn from an antecubital vein at baseline and after the mental stress test. Platelet reactivity was measured on flowing blood as time to occlude a ring coated with collagen-adenosin diphosphate (ADP), using the platelet function analyzer (PFA-100) system. By this method, the time to occlusion (closure time) is taken as a measure of platelet adhesion/aggregability, with shorter times indicating greater platelet reactivity.
Results: At baseline, closure time was 99.6±25 and 97.8±16 sec in CAD patients and syndrome X patients, respectively (p=NS). The response to mental stress in the 2 groups differed significantly, as closure time decreased in CAD patients (to 91.7±20 sec.), whereas increased in syndrome X patients (102±20 sec, p for trend=0.036).
Conclusions: Thus, our data show that platelet reactivity to collagen/ADP is increased by mental stress in patients with significant CAD, whereas, in contrast, it is decreased in syndrome X patients. This different trend is similar to that recently observed with physical exercise and may have implications for the different incidence of stress-related acute cardiac clinical events in these two groups of patients.

PLAQUE COMPOSITION, INFLAMMATION AND VULNERABILITY I

P2195 Evidence for carotid plaque stabilisation by statin therapy

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Purpose: It is increasingly evident that statin therapy reduces the risk of cardiovascular events independent of lipid-lowering properties, possibly by anti-proteolytic and anti-inflammatory mechanisms. The aim of this study was to investigate the effect of statin therapy on the levels of proteolytic enzymes and pro-inflammatory cytokines within carotid plaques.
Methods: Atherosclerotic plaques were collected from 137 patients undergoing carotid endarterectomy. A detailed history of statin therapy was taken pre-operatively. Plaques were homogenised prior to MMP and cytokine quantification using the ELISA technique. Non-parametric statistics were employed and p-values were calculated using the Mann-Whitney U-test.
Results: Significantly lower plaque concentrations of MMP-1, MMP-9 and IL-6 were observed in those patients taking statins compared to those not on statin therapy (see table). No differences were seen in the levels of MMP-8, MMP-13, IL-1b and TNF-a between the two groups.

	Statin use (n=49)	No statin use (n=88)	p-value
MMP-1	21 (7-51)	42 (19-104)	0.004*
MMP-9	112 (64-325)	309 (122-722)	<0.001*
IL-6	1329 (727-3000)	2732 (1475-5146)	<0.001*

Median values (and inter-quartile ranges) expressed in ng/g wet weight of plaque are shown.

Conclusions: MMP-1 and MMP-9 combined can degrade all of the components of the atherosclerotic plaque, and IL-6 has been suggested as a marker of acute plaque disruption. These data suggest that statins stabilise plaques by decreasing the levels of MMP-1, MMP-9 and IL-6, providing further evidence that all patients with atherosclerotic disease should be on statin therapy.

P2196 Antiapoptotic and apoptotic proteins expression in specimens from stable and unstable coronary lesions

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Background: The regulation of apoptosis in atherosclerosis is not completely defined and is thought to play a prominent role in destabilization of advanced atherosclerotic plaque. The aim of this study was to determine the expression of Bcl-2, Bcl-x, Bax, Bak, Bcl-xL, Fas and Caspase 3 in relation to apoptosis in unstable angina versus stable angina advanced atherosclerotic lesions.
Materials and Methods: We examined 100 coronary atherosclerotic plaques derived from postmortem examinations, 40 atherectomized specimens obtained via Directional Coronary Atherectomies (DCA) from coronary arteries from patients clinically diagnosed with either stable (n=62, 44,3%) or unstable angina (n=78, 55,7%) and 10 specimens (controls) derived from internal thoracic arteries without any signs of atherosclerosis All specimens were analysed for the presence of apoptosis was using TdT dUTP nick end labelling (TUNEL) and nuclear morphology (karyorrhexis/pyknosis) and expression of apoptosis regulators by immunohistochemistry Bcl-2, Bcl-xL Bcl-x, Bax, Bak, Fas and Caspase 3. Morphometrical analysis of each atherosclerotic plaque was performed using the digital image analysis software Lucia. Special attention was payed at shoulder region and fibrous cap expression of apoptosis.
Results: Unstable angina expressed higher apoptotic index (39% vs 9%) stable compared with controls (<2%). The predominant cell type undergoing apoptosis were smooth muscle cells. In all of TUNEL-positive apoptotic cells, Bax, Bak, Bcl-x were present, while Bcl-xL and Bcl-2 was absent. In 79% of TUNEL positive cells Fas and Caspace 3 were also expressed. In 70 unstable angina specimens the tunnel positive cells strongly expressed all 5 proteins Bcl-x, Bax, Bak, Fas, Caspase 3 with almost absent Bcl-2, Bcl-xL expression in the non apoptotic cells. While, 57 of the stable angina specimens the tunnel positive cells strongly expressed Bcl-x, Bax, Bak, almost absent Fas and Caspace 3 and the rest non apoptotic cells very strongly expressed Bcl-2 and Bcl-xL.
Conclusions: In our study the increased expression of Bax, Bak, Bcl-x, Fas and Caspace 3 coupled with lack/paucity of Bcl-2 and Bcl-xL are associated with SMC apoptosis in unstable coronary lesions, which could be important factors contributing to the progression of atherosclerotic plaques. Both Bcl-2 and Bcl-xL expressed in non-apoptotic cells appear to contribute to prolonged cell survival and therefore more stable plaques.

P2197 Worldwide experience on safety and feasibility of a novel intracoronary thermography system in patients with stable and unstable angina

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A thermography system has been developed to identify intracoronary absolute and relative vessel wall temperatures in coronary arteries (2.5 - 4.0 mm). 73 patients (at 6 sites) underwent this novel diagnostic procedure. This abstract summarizes and concludes the current initial experience on safety and feasibility as well as correlations of temperatures with angiographic and intravascular ultrasound (IVUS) information.
The Thermography System (Volcano Therapeutics, USA) consists of a catheter and a computer console, to display the analysis of temperature in real time. The 3.3F catheter provides 6 thermocouples mounted on a 5-armed basket at the distal end of the catheter including one central thermocouple to measure the blood temperature. The catheter is applied through a 6F guiding catheter (min) and over a regular 0.014" guide wire. The procedure is integrated in the interventional procedure and can be correlated with IVUS.
Demographics: (n = 73), 63 = male, 10 = female; 59.7 $\pm$ 9.9 years of age; 37% stable AP (27/73), 40% unstable AP (29/73), 4% MI (3/73); Procedure: (n=73), RVD 3.2 $\pm$ 0.5 mm; Stenosis 81.0 $\pm$ 15.9%; lesion length: 45.4 $\pm$ 33.1 mm; Vessel distribution: LAD= 39, RCA= 21, LCX= 13, Other=3; 30 = elective, 7 = urgent, 5 = emergency, 5 = PTCA, 65 = stent.
The catheter was able to successfully cross the culprit lesion in 88% of the procedures. Upon crossing the lesion, temperature measurements could be successfully completed in 86% of the procedures.
No MACE occurred during or after successful Thermography. 64/64 (100%) patients have been event free at FU (1 week). In 17/73 the Thermography has been correlated with IVUS.
This first experience can be considered as positive. Further catheter developments may facilitate positioning in angulated anatomy or tight stenosis.
The system can be suggested as safe and feasible. Additional studies are required to understand the relation between temperature distribution and histological aspects in order to position the temperature measurement as an additional diagnostic and to improve the risk profile differentiation of patients with acute and/or sub-acute coronary syndromes.

P2198 The prostaglandin E receptor subtype EP4 mediates PGE2-dependent plaque instability in humans

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Background: Recently, we have demonstrated enhanced expression of inducible cyclooxygenase and PGE synthase-1 (COX-2/mPGES-1) in human symptomatic plaques, and provided evidence that it is associated with metalloproteinase (MMP)-induced plaque rupture. However, the specific transmembrane cellular receptor(s) by which PGE2 may influence MMP generation in plaque macrophages is still unknown.
The aim of this study was to characterize the expression of the four different PGE2 receptors (EP1-4) in human carotid plaques and to correlate it with the extent of inflammatory infiltration, COX-2/mPGES-1 and MMP expression and with clinical features of patients' presentation.
Methods and Results: Plaques were obtained from 60 patients undergoing carotid endarterectomy and divided into 2 groups (Symptomatic and Asymptomatic) according to clinical evidence of recent TIA or stroke. Plaques were analyzed for COX-2, mPGES-1, EP1-4, MMP-2 and MMP-9 by immunocytochemistry, RT-PCR and western blot, whereas zymography was used to detect MMP activity. Immunocytochemistry was used to identify CD68+ macrophages, CD3+ T lymphocytes and HLA-DR+ cells.
We observed strong EP4 immunoreactivity, but only very weak staining for EP2 and no expression of EP1 and EP3 in atherosclerotic plaques. EP4 was more abundant in COX-2/mPGES-1-rich, MMP-rich symptomatic lesions. In contrast, we did not observe any difference regarding EP2 expression. Finally, EP4 was especially noted in plaque shoulder, co-localizing with HLA-DR+ macrophages.
Conclusions: In conclusion, this study demonstrates that EP4 overexpression is associated with enhanced inflammatory reaction in atherosclerotic plaques, and this effect in turn may contribute to plaque destabilization by inducing culprit metalloproteinase expression.

P2199 Elevated C reactive protein levels predict inadequate improvement of relative coronary flow velocity reserve after uncomplicated stent implantation because of periprocedural microembolisation

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Purpose: C reactive protein (CRP) is a marker of inflammation and is increased in patients (pts) with acute coronary syndromes. Its predictive role for normalization of coronary blood flow parameters after stent implantation with or without release of ischemia markers is unknown. Aim of this study was to use preinterventional CRP levels to predict normalisation of absolute (CVR) and relative coronary flow velocity reserve (CVRrel) after uncomplicated stent implantation.
Methods: In 200 patients (pts) with single vessel disease and uncomplicated coronary stent implantation CVR and CVRrel were measured at the end of the procedure by a Doppler flow wire. CRP, CPK, CPK-MB and Troponin I were monitored before intervention and for the next 24 hours. Receiver Operator Characteristics analysis was performed to define predictive cut-off values for CRP. Positive (PPV) and negative predictive values (NPV) are reported.
Results: Predefined normalisation of CVR ($>$2.86) and of CVRrel ($>$0.88) after uncomplicated stent implantation were achieved in 120 and 162 pts, respectively. No correlation was found between CRP and CVR (r=0.049), while an inverse correlation was found between CRP and CVRrel (CVRrel=-0.0515.CRP+0.942; r=0.44; $p<0.001$). CRP cut-off value was 0.66 mg/dl (sensitivity 90%, specificity: 51%, PPV: 86%, NPV:60%) to predict CVRrel normalisation. An abnormal CVRrel (0.71$\pm$0.16) after stenting was associated with a significantly higher preinterventional CRP level (1.31$\pm$0.32 IU/L versus 0.33$\pm$0.12 IU/L; $p<0.001$) and postinterventional release of ischemia markers (CPK: 212$\pm$75 IU/L versus 89$\pm$33 IU/L; $p<0.001$; CPK-MB: 35$\pm$11 IU/L versus 14$\pm$5 IU/L; $p<0.001$; Troponin I: 1.9$\pm$0.6 ng/ml versus 0,3$\pm$0.2 ng/ml; $p<0.001$).
Conclusion: A preinterventional CRP $>$ 0.66 mg/dl predicts inadequate improvement of CVRrel after stent implantation with subsequent release of ischemia markers probably due to periinterventional microembolisation from more unstable plaques.

P2200 The expression of pro-oxidant enzyme myeloperoxidase is associated with plaque destabilization in human coronary atherosclerotic lesions

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Background: Previous studies have shown that inflammation and oxidative stress in coronary atherosclerotic lesions relate to rapidly progressive plaque destabilization. We have recently demonstrated that neutrophils play an important role in mediating destabilization of human coronary atherosclerotic plaques(Naruko T et al, Circulation, 2002). Recent studies have demonstrated the presence of active pro-oxidant enzyme myeloperoxidase (MPO) and products of MPO-mediated reaction in human atherosclerosis. We have studied the expression of MPO in coronary atherectomy specimens obtained from patients with stable angina (SAP) and unstable angina pectoris (UAP) by using immunohistochemical methods, in order to elucidate the role of MPO in plaque destabilization in human coronary atherosclerotic lesions.
Methods: All patients underwent atherectomy at primary atherosclerotic lesions responsible for SAP (n=37) and UAP (n=31). Frozen samples were studied with antibodies against smooth muscle cells, macrophages, MPO and neutrophils (CD66b, CD11b, and elastase). The presence of MPO, macrophage, and neutrophil immunoreactivity was quantified, respectively, using computer-aided planimetry. For the identification of cell types which stain positive for MPO, immunodouble staining was also performed.
Results: Quantitative analysis demonstrated that neutrophil, macrophages, or MPO positive area in patients with UAP was significantly ($P<0.001$) higher than in patients with SAP. Immunodouble staining for MPO and neutrophils revealed that the majority of MPO-positive cells were neutrophils. Immunodouble staining for MPO and macrophages, moreover, showed that occasional macrophages were also positive for MPO.
Conclusions: These findings strongly suggest that strong expression of MPO plays an important role in the pathogenesis of plaque destabilization in human coronary arteries.

P2201 Cycloxygenase-2 levels are not increased in unstable carotid plaques

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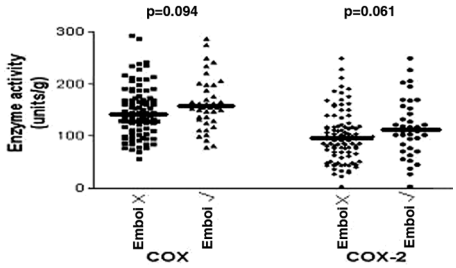
Purpose It has been suggested that the cyclooxygenase (COX) enzyme, in particular COX-2, may play an important causative role in atherosclerotic plaque rupture, the preceding event in most strokes and myocardial infarctions. The aim of this study was to measure the activity of these enzymes in carotid plaques, in relation to features of plaque instability.
Methods Plaques were collected from 138 consecutive patients undergoing carotid endarterectomy. Patients were divided into 4 groups depending on symptomatology (1: asymptomatic; 2: >6 months pre-op; 3: 1-6 months pre-op; 4: <1 month pre-op). Levels of both total COX and COX-2 activity, in carotid plaque homogenates, were measured using a colorimetric assay kit. Pre-operative embolisation was recorded by transcranial Doppler.
Results There was no significant difference in the levels of either COX or COX-2 activity across the symptom groups, or between the plaques that were embolising and those that were not (see table and figure).

Symptom group vs COX and COX-2 activity

	1	2	3	4	p-value
COX	139.8	132.2	144.9	158.9	0.325
COX-2	104.2	95.3	94.1	103.0	0.531

Median values in activity units/g wet weight of plaque, are shown.



Conclusions Previous reports have suggested a role for COX-2 in atherosclerotic plaque instability, and the potential for plaque stabilisation with COX-2 inhibitors. However, we have found no evidence of an association between COX-2 activity and symptomatology or spontaneous particulate embolisation.

P2202 Systemic infection leads to infiltration of macrophages in adventitia of human atherosclerotic coronary arteries: clue to triggering effect of acute infections on acute coronary syndromes

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Infections affect initiation and progression of atherosclerosis and trigger destabilization of vulnerable plaques. One third of acute myocardial infarctions follow an upper respiratory infection. In atherosclerotic animal models, diffuse arterial inflammation has been observed after several infections. Effect of systemic infections on human coronary artery atherosclerosis is largely unknown. We studied extent and pattern of macrophage infiltration in the coronary arteries of atherosclerotic patients dying with systemic infection.
Methods: We studied pathology files of St. Luke's Episcopal Hospital between 1991 and 2002. After exclusion of patient with HIV infection, cancer, and those taking immunosuppressive or corticosteroid drugs, 14 patients (11M, 3F, mean age: 67 yrs) with atherosclerosis and an acute systemic infection prior to their death (average 2 weeks) were selected. 13 pts (9M, 4F, mean age: 65 yrs) with atherosclerosis and without infection were selected as controls. Slides were stained with H&E, and CD68 marker for macrophages (MQ). Computerized morphometric analysis was used for counting cells, and measuring areas. Plaque area was defined as the area inside the internal elastic lamina (IEL). Periadventitial fat was defined as up to 250 μm beyond the adventitia. MQ density was the number of MQ per square mm. Mann-Whitney U and Wilcoxon Signed Ranks tests were used for non-linear data.
Results: There wasn't a significant difference between percent stenosis in cases and controls (67±14 vs. 55± 25, P=0.23). MQ density showed a non-significant trend toward higher levels in pts with systemic infection (582±774 vs. 281±321, P=0.41). However, there was a significantly higher number of MQ in adventitia of coronaries in pts with infection compared to controls (1,577±1,872 vs. 265±185, P=0.047). MQ density in periadventitial fat showed a non-significant trend toward higher levels in pts with systemic infection (776±821 vs. 212±219, P=0.085). Of interest, while macrophage density in controls was not different between plaque and adventitia areas (281±321 vs. 265±185, P=0.85), MQ density in patients with systemic infection was significantly higher in adventitia than in plaque area (582±774 vs. 1,577±1,872, P=0.028).
Conclusion: This report shows for the first time that systemic infections are associated with a significant increase in macrophage density in adventitia of human atherosclerotic coronary arteries. This suggests a mechanism for the triggering of AMI observed following acute infections and offers a new therapeutic target for preventing heart attacks.

P2203 Reproducibility of three-dimensional palpography

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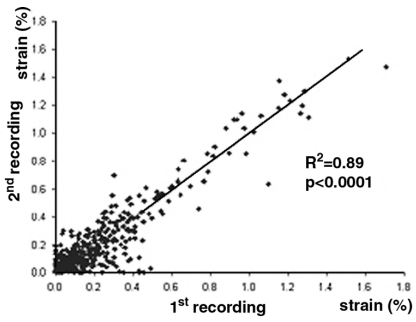
Background: Palpography has proven to detect vulnerable plaques features in vitro with a high sensitivity and specificity by giving mechanical information of the vessel wall. Furthermore it is feasible to assess palpograms in patients. We tested in this study the reproducibility of 3D palpography in humans.
Method: In 12 patients a total of 14 pullbacks with intravascular ultrasound (IVUS) were performed two times at the same location using standard 20 MHz ultrasound catheters (Avanar®, JOMED Inc). The pullback-speed in all recordings was 1.0 mm/s. 3D IVUS-echograms were used for alignment of corresponding acquisitions. Landmarks like side branches, stents or calcified spots guided the matching. Data at the beginning and the end of an acquisition, which did not match with the corresponding recording, e.g. due to a different location of the pullback start, were rejected. After aligning, 3D palpograms were created from rf-data giving strain measurements over a pullback length of about 1.8 cm. Palpograms were displayed as map representing the continuous strain distribution of the vessel wall. One map consists of about 18 lines in the longitudinal and 512 angles in the circumferential direction. The maps were subdivided in regions representing 3 lines by 32 angels covering 3mm by 22.5 degrees. The median strain of the corresponding regions of first and the second recording were compared.
Results: 512 regions were compared using orthogonal regression (figure 1). The R^2 of the model is 0.89 with a $p < 0.0001$.



Reproducibility of 3D palpography.

Conclusion: Three-dimensional palpography is highly reproducible in humans. This data add evidence that palpography is a robust technique to detect vulnerable plaque features.

PLAQUE COMPOSITION, INFLAMMATION AND VULNERABILITY II

P2204 Predicting factors of inflammatory response following non-drug eluting stent implantation

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Background and Objectives: The systemic inflammation triggered by percutaneous coronary intervention (PCI) is a powerful predictor of both early and late outcomes in patients undergoing PCI. This study aimed to assess the inflammatory reaction (IR) induced by PCI and to determine the clinical, biological and procedural predictors of such a response.
Methods: A total of 81 consecutive patients referred for PCI were prospectively included for PCI with stent implantation. Inflammation was assessed by erythrocyte sedimentation rate, C reactive-protein (CRP) and fibrinogen measurement. Samples were performed in fasting patients before and 24 hours after PCI. IR was defined by the combination of a post-PCI CRP concentration higher than 5 mg/l and a raise from pre-PCI CRP higher than 0.6 mg/l, which corresponds to 2 fold value of the analytical error. We registered clinical and biological data, procedural variables and registered the revascularization strategies as complementary stenting (CS) and direct stenting (DS).
Results: In the whole population, CRP concentration (14.6 $\pm$ 2.4 to 19.6 $\pm$ 2.8 mg/l), fibrinogen (4.3 $\pm$ 0.1 to 4.7 $\pm$ 0.1 g/l) and erythrocyte sedimentation rate (16.8 $\pm$ 1.7 to 21.3 $\pm$ 2.3 mm) increased significantly ($p< 0.0001$) without any myocardial damage documented. IR was detected in 41 patients (50.6%). The clinical, angiographic and biological parameters predicting an individual IR were respectively a non ST elevation acute coronary syndrome (ACS) in comparison with stable angina (SA) or recent myocardial infarction (RMI), the diameter of the treated vessel and the triglycerides concentration (table).

	IR (n=41)	Non IR (n=40)	p
SA vs ACS	7 (32%) vs 15 (68%)	15 (72%) vs 6 (28%)	0.009
Coronary diameter (mm)	3.00 $\pm$ 0.06	2.82 $\pm$ 0.05	0.03
Triglycerides	1.87 $\pm$ 0.19	1.45 $\pm$ 0.10	0.05
Stent implantation	66.49 $\pm$ 7.53	50.58 $\pm$ 3.74	0.06
Number of treated lesions	1.49 $\pm$ 0.11	1.23 $\pm$ 0.08	0.06
CS vs DS	26 (50.9%) vs 15 (50%)	25 (49.1%) vs 15 (50%)	ns

Values expressed as mean $\pm$ SEM

Conclusions: Non drug eluting stent implantation induced a systemic IR, suggesting the role of a stranger body reaction. Non ST elevation ACS seems to be the most powerful individual pre-PCI predictive factors.

P2205 Determination of plaque composition in human coronary arteries using intravascular ultrasound virtual histology

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Introduction: Traditional methods for studying human coronary artery disease have significant limitations. Angiography allows evaluation only of the geometry of the unobstructed part of the lumen; it cannot provide information on the structure of the arterial wall. Intravascular ultrasound (IVUS), however, holds the potential to quantify the structure and geometry of normal and atherosclerotic coronary arteries. Previous studies by our group have shown that analysis of the IVUS RF or backscattered data can lead to an accurate determination of plaque composition ex vivo. The goal of this study is to evaluate the efficacy of the methodology in patients undergoing diagnostic catheterization.
Methods: Gated IVUS RF data were collected from coronary arteries of eight patients using a continuous automated pullback rate of 0.5 mm/s. The lumen and medial-adventitial borders were detected using automated software and the vessel and plaque dimensions calculated. The plaque composition was determined using spectral analysis and Virtual Histology™ images produced. Plaque components were classified as fibrous, fibro-lipidic, lipidic/necrotic, or calcified (figure 1).
Results: A total of 874 IVUS images were reconstructed from RF data. The average lumen, plaque, and vessel volume for the eight vessels were 372, 388, and 760 mm^3, respectively. Mean lumen, plaque, and vessel areas were 7.1, 7.2, and 14.3 mm^2, respectively. Mean areas of fibrous, fibro-lipidic, lipidic/necrotic, or calcified regions were 2.3, 1.3, 1.3, and 0.4 mm^2, respectively. The average medial area was 1.9 mm^2. Calculation of the Virtual Histology images on a Pentium PC took 29 seconds per slice.
Conclusions: Spectral analysis of backscattered RF data can estimate plaque composition in vivo. No changes in clinical practice were required and the Virtual Histology images can be reconstructed in a clinically viable time frame. In these moderately diseased vessels the major plaque component was dense fibrous tissue whilst the lipid components had similar relative abundances. Calcium, as expected, was the least abundant material.

P2206 Apoptosis in plaque destabilization: involvement of endothelial specific transcription factors in the progression towards programmed cells death

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Purpose: Coronary atherosclerosis is the main cause of ischemic heart disease. Plaque composition and particularly its fibrous cap are crucial factors in determining rupture and thrombosis. Apoptosis (programmed cells death) is thought to be one of the mechanisms leading to the superficial erosion of atherosclerotic plaques through a magnification of local inflammatory process.
Methods and Results: In order to establish the existence of different gene expression in the apoptotic pathway, we made use of a collection of 48 TaqMan assays (PCRs) in coronary plaques collected by means of therapeutic directional coronary atherectomy from 13 patients with stable angina (SA) and 19 with acute coronary syndromes without ST elevation (ACS). Total RNA was extracted from the 32 plaques and the cDNA was amplified using a specific set of primers and TaqManO. Analysis of the results confirmed that the expression of apoptotic genes (i.e. BCL2, CPP32, FAS, FAS ligand, c-FOS, GRP78, CASP1, c-JUN, NF-kB, p53, PCNA,) was significantly higher ($p<0.001$) in the plaques from the ACS patients. Furthermore, among the screened genes we found a positive correlation ($p<0.001$) with specific transcription factors for inflammatory genes.
Conclusions: The results of this Real Time PCR study confirm a strongly committed apoptotic pathway in patients with ACS. Our data strengthened the hypothesis that the programmed endothelial cell death can stimulate in situ the expression of inflammatory mediators; those molecules can in turns recruiting locally cytolitic T-cells thus leading plaque fissuring and disruption.

P2207 High shear stress is predictive for markers of plaque inflammation

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Introduction: Acute coronary syndromes have been associated with plaques that are either ruptured or superficially eroded. Disrupted atherosclerotic plaques consist typically of a large lipid pool, covered with a thin fibrous cap and infiltrated macrophages (MF) in the shoulder of these caps. Recently, it was shown that rupture occurs predominantly upstream of the plaque implying a local mechanism underlying plaque rupture. In the present study we tested, whether local shear stress (SS) plays a role in localization of plaque rupture.
Methods: In 8 NZW rabbits plaque was generated by denudation the infrarenal aorta over a region of 5 cm. The rabbits received from that moment a high cholesterol diet for 2 months. Before denudation, and after 2 months FU a motorized IVUS pullback was performed with a 40 MHz IVUS(CIVUS, Boston Scientific) catheter. IVUS derived vessel wall-lumen and vessel-wall adventitial contours were determined with a well-validated computer program and the resulting contours were reconstructed in 3D with in Erasmus MC developed software. These reconstructions served as an input for a computational fluid dynamics program, from which the 3D SS field was calculated. Plaques were defined as an increase in the IVUS derived wall thickness and identified in the fixated vessel segment. The plaques were divided in 5 regions. These segments were sectioned with a microtome and stained for smooth muscle cells (SMC), MF and collagen.
Results: Histological ($3.4\pm1.5mm^2$) and IVUS derived plaque thickness ($4.2\pm0.6mm^2$) were highest in the central zone of the plaque ($p<0.05$), while MF, displayed the highest density upstream of the plaque ($4.8\pm$ 1.0%, $p<0.05$). In addition, the SMC exhibited a maximum downstream of the plaque. High SS was unrelated to plaque size (due to remodeling), but was directly related to MF distribution and inversely related to the SMC and collagen distribution.
Conclusion: An animal model was developed displaying upstream accumulation of macrophages. It was shown that low SS is related to plaque stability thereby confirming earlier (human) studies, while high shear stress relates to markers of plaque inflammation.

P2208 Plasma MMP-9 – a marker of cerebral damage

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Purpose: Plaque and plasma MMP-9 levels are elevated in patients undergoing spontaneous particulate embolisation and while MMP-9 almost certainly contributes to acute plaque disruption, the elevated plasma level may be a reflection of cerebral damage. The aim of this study was to determine whether the elevated plasma MMP-9 concentration arose from the atherosclerotic plaque or from a systemic source.
Methods: Blood samples were taken pre-operatively and on the second post-operative day from 72 consecutive patients undergoing carotid endarterectomy. Plasma MMP-9 concentrations were measured using the ELISA technique. Cerebral embolisation was detected during the dissection phase of the operation by transcranial Doppler, and on the basis of these results, patients were divided into emboli-positive and emboli-negative groups.
Results: The pre-operative samples showed no difference in MMP-9 concentration between the emboli-positive and emboli-negative groups. However, plasma levels of MMP-9 were significantly higher on the second post-operative day in those patients in whom cerebral embolisation was detected during the dissection phase of the operation (see table).

Emboli groups vs plasma [MMP-9]

	Emboli-positive	Emboli-negative	p-value
Pre-op sample	8.7 (3.4-16.2)	7.6 (4.1-14.3)	0.755
Post-op sample	13.9 (6.5-27.1)	7.7 (3.9-21.0)	0.049*

Plasma MMP-9 concentrations (median values and inter-quartile ranges) are shown.

Conclusions: These data suggest that the carotid plaque is not the source of elevated MMP-9 in the plasma of patients undergoing cerebral embolisation. Rather, the elevated plasma level appears to be a consequence of cerebral damage caused by particulate embolisation.

P2209 Impact of intimal pathogen burden in acute coronary syndrome lesions: correlation with C-reactive protein

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Background: Increasing evidence supports a link between serological evidence of prior exposure to infectious pathogens (pathogen burden) and the risk for future myocardial infarction and death in patients with coronary artery disease. Based on this concept, we evaluated the intimal presence of 4 pathogens in human coronary atheroma, clinically associated with acute coronary syndromes (ACS) and stable angina (SA), and the effect of pathogen burden on the expression of intimal C-reactive protein (CRP), that plays a major role in systemic and local inflammation.
Methods: Coronary atherectomy specimens retrieved from 35 primary target lesions of patients with ACS (n=15) or SA (n=20) were assessed immunohistochemically for the presence of Chlamydia pneumoniae (C. pn.), Helicobacter pylori (H. p.), Cytomegalovirus (CMV) and Epstein-Barr-Virus (EBV), and for the expression of CRP.
Results: Immunohistochemical analysis revealed 4 lesions without, 13 lesions with 1, 10 lesions with 2, 4 lesions with 3 and 4 lesions with 4 infectious agents. C. pn. was present in 67%, H. p. in 32%, CMV in 16% and EBV in 36%. Exclusively C. pn. revealed a prevalence in ACS (76%) vs. SA (39%; $p<0.05$). Mean value of all 4 infectious pathogens was 1.7 per lesion. As an important finding, the mean value in ACS-lesions was significantly increased compared to those in SA (2.0 vs. 1.3; $p<0.05$). ACS-subgroup analysis revealed a higher mean value in patients with pain at rest (Braunwald classes II/III; 2.2) compared to those without (class I; 1.0; $p<0.05$). In addition, expression of CRP was significantly higher in ACS (2.3%) compared to SA (1.1%; $p<0.05$). Most interestingly, the number of infectious pathogens correlated highly significant ($p<0.01$) with the expression of CRP ($r=0.61$).
Conclusion: Our data demonstrate the impact of pathogen burden in plaque instability thereby associated with clinical acuity, and suggest local proinflammatory effects via CRP upregulation as an important pathomechanism that may contribute to acute coronary syndromes.

P2210 Incidence of vulnerable plaques in humans: assessment with intravascular palpography

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Background: Intravascular palpography can detect vulnerable plaques in vitro with a high sensitivity and specificity by measuring the strain of the coronary vessel wall. Vulnerable plaques show typical high strain patterns in-vitro. Similarly, high strain patterns reflect vulnerable plaque features in animal studies. Based on these experimental data, we hypothesized that it is possible to detect vulnerable plaques in-vivo in human coronary arteries by scanning the coronary artery for typical high strain patterns.
Method: Intravascular palpography was performed in 49 patients scheduled for PCI by using standard 20 MHz intravascular ultrasound (IVUS) catheters (Avanar, JOMED Inc) with motorized pullback (1.0mm/s) Analysis included the complete length of the target vessel, starting distally and ending at the ostium. The recorded data were stored and processed in a dedicated workstation for palpography
The population was divided into 3 groups: Patients with [1] antecedent (<24h) myocardial infarction (post MI) [2] unstable angina (ST depression and/or Troponin positive)(unstable)[3] Stable angina (stable). Per patient one coronary artery was investigated. A typical strain pattern was defined as a high strain region (>1%)next to low strain regions (< 0.5%).
Results: Palpography was successful performed in all patients. The number of typical strain patterns reflecting the number of vulnerable plaques per coronary artery are given in the table. There was a significant difference between the stable vs. unstable group ($p<0.001$) and stable vs. post MI group ($p<0.0001$). No difference was seen between the unstable group and post MI group ($p<0.056$).

Incidence of high strain spots

	Stable	unstable	post MI
n (patients)	17	16	16
High strain spots	0.7 ± 0.6	1.6 ± 0.5	2.1 ± 0.8

Conclusion: Palpography can be used to assess vulnerable plaques in human. This pilot study revealed a clear association between clinical presentation and the amount of vulnerable plaques. However, additional validation has to be performed to assess the predictive value of the technique to identify vulnerable patients.

P2211 Treatment of thin cap fibroatheroma with drug eluting stents: importance of fibrous cap injury, neointimal formation and vascular healing after β-oestradiol and everolimus coated stents

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Purpose: Neointimal formation after stenting may increase fibrous cap thickness and therefore stabilize vulnerable plaques. However, human autopsy studies demonstrated an exaggerated response when the stent ruptures
the fibrous cap, increasing the risk of restenosis. Drug-eluting stents may modulate this response. This study was designed to investigate the incidence of fibrous cap rupture (FCR) after stenting and to quantify the healing response using bare, Everolimus (EV) and Beta Estradiol (BE) stenting in an experimental, chronic, hypercholesterolemic rabbit model of thin cap fibroatheroma (TCFA).
Methods: Sixteen New Zealand White rabbits on a 1% pulsed cholesterol diet were followed for 4 years (equivalent to 60 years in humans). Six rabbits were treated with bare (Penta), 5 with EV coated and 5 with BE coated stents (Guidant, Santa Clara, CA). Each animal received 4 stents sequentially in the abdominal aorta, deployed at 14 + 2 Atm with a 1:1 stent/vessel ratio. Neointimal area (NA) was measured by computerized planimetry. Inflammation, hemorrhage, fibrin deposition, and endothelialization around struts were evaluated using a severity score (1 to 4).
Results: Sixty-four stents and 1584 struts were evaluated for FCR in TCFA (lipid area > 30% and cap thickness < 65 microns). Two hundred and fourteen struts met these criteria, 79 (37%) with intact fibrous cap and 135 (63%) with RFC. Bare stents increased NA after FCR (66 ± 6 Vs. 85 ± 5 mm^2; P=0.03. However, NA was similar with or without FCR after BE (53 ± 11 Vs. 71 ± 8 mm^2; P=0.16), and after EV stenting (45 ± 6 Vs. 53 ± 5 mm^2; P=0.46). When compared to bare stents, NA after FCR was not reduced by BE (P=0.17) but significantly reduced by EV (P=0.001) stenting. Scores were low for all stents indicating adequate healing. Nevertheless, when compared to bare stents, inflammation, fibrin and hemorrhage scores were greater in EV stents (1.2 ± 0.2; 1.3 ± 0.2; and 0.4 ± 0.2) Vs. (0.9 ± 0.1; 0.6 ± 0.1; and 0.1 ± 0.0) (P lower than 0.05 for all comparison).
Conclusion: The incidence of FCR after stent deployment is high (63%), increasing NA formation. This response is not reduced by BE but significantly reduced by EV stents. Healing scores were low for all stents suggesting that DES is safe for TCFA treatment. However, individual scores for inflammation, fibrin deposition and hemorrhage were mildly but significantly increased by EV stenting. These results highlights strut-induced fibrous cap rupture and the importance of drug selection in stenting TCFA.

P2212 A comparative study of white blood cell count, neopterin and C-reactive protein for prediction of stenosis complexity in patients with non-ST-segment elevation acute coronary syndromes

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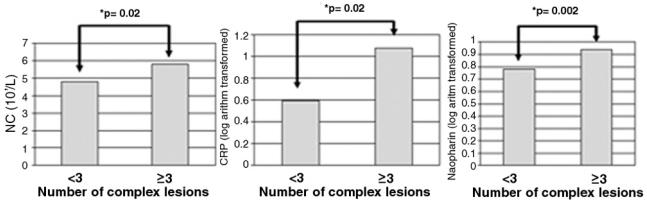
Purpose: Inflammation plays a role in the pathogenesis of acute coronary syndromes by promoting rupture and erosion of vulnerable coronary plaques. Angiographically complex stenoses are often the expression of plaque vulnerability or disruption in patients with unstable angina. We compared the ability of three inflammation markers i.e. neutrophil count (NC), C-reactive protein (CRP) and neopterin to predict angiographic plaque complexity in patients with non ST segment elevation acute coronary syndromes.
Methods: We studied 55 patients with non ST segment elevation acute coronary syndromes and angiographically documented coronary disease (>50% stenosis). Blood samples were obtained at study entry for the assessment of high sensitivity CRP, NC and neopterin. All coronary stenoses with ≥30% diameter reduction were assessed using quantitative computerised angiography and classified as complex (irregular borders, ulceration or filling defects) or smooth (absence of complex features). Extent of disease was also assessed using a validated angiographic score.
Results: NC (p=0.02), CRP (p=0.02) and neopterin levels (p=0.002) correlated with the number of complex lesions. Patients with multiple (≥3) complex lesions had higher NC (p=0.02), CRP (p=0.02) and neopterin (p=0.002) levels (figure). Multiple regression analysis showed that neopterin levels (p=0.002) and extent of disease (p=0.04) were independently associated with the number of complex lesions in patients with acute coronary syndromes.



Conclusions: Inflammation markers such as NC, CRP and neopterin correlate with angiographic plaque complexity. Neopterin was the most powerful of the three markers for prediction of angiographically complex coronary artery stenoses.

IN-STENT RESTENOSIS: EVALUATION, PREVENTION, TREATMENT

P2213 Clinical presentations of in-stent restenosis from a French registry of 1570 consecutive patients with coronary stenting

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Purpose: In-stent restenosis is the major limitation of percutaneous coronary intervention, though clinical presentations of this process remain poorly characterized.
Methods: We analyzed 1570 consecutive patients, from January 2000 to December 2002, who had undergone percutaneous coronary angioplasty with stenting for de novo lesions. Clinical follow-up was performed for a mean duration of 1 year with exercise tolerance testing in asymptomatic patients. If ischemia was documented a second coronary angiogram was performed.
Results: 1570 patients were treated with 1994 stents (1.27 stent/patient). 263 in-stent restenoses were documented and dilated (target lesions revascularisation 13.19%). 19 in-stent restenoses occurring in asymptomatic heart transplant patients were excluded from the analysis. The clinical presentations of the 244 in-stent restenoses in non transplanted hearts were as follows: 58 with ischemia positive tests without symptoms (23.8%), 91 with stable angina (37.3%), 9 with symptoms of left heart failure (3.7%), 71 with non-ST elevation acute coronary syndromes (29.1%) and 15 with acute coronary syndromes with ST elevation (6.1%). Of the ST elevation cases 5 were due to acute thrombosis within one month of the procedure (2.0%), 2 were late thrombosis after one month related to interruption of treatment (0.8%), and 8 were acute myocardial infarctions (AMI) (3.3%) without treatment interruption observed at a mean of five months (2-8 months). No specific cause for AMI was evident in these 8 patients.
Conclusions: Non-ST elevation acute coronary syndromes are common presentations of in-stent restenosis whereas acute coronary syndromes with ST elevation remain rare and with no evident cause in most cases. Asymptomatic patients need to be evaluated, as well as patients with stable angina who represent the most frequent clinical presentation of in-stent restenosis leading to coronary angioplasty.

P2214 Predictive factors of complex ISR with repeated recurrence: "impact of the metallic allergy

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Background: Previous studies have been reported the several factors which can predict restenosis after coronary stenting. However, restenosis is not eliminated.
Especially, therapeutic approach for complex In-stent restenosis (ISR) with repeatedly recurrence have shown disappointing results. Therefore, the other potential factors of Complex ISR should be defined to make a decision of optimal strategy. We hypnotized that allergic and inflammatory reactions to the metals were related to the development of Complex ISR.
Methods: We prospectively analyzed a total of 154 consecutive stented patients (pts) who underwent follow-up angiography. According to the results of follow-up angiography, we identified three groups; No restenosis group (89 pts; < 50% diameter stenosis); First ISR (42 pts; PCI were underwent only once for ISR); and Complex ISR (23 pts; PCI need for ISR with more than two times). These pts received a patch test applied substances included nickel, dichromate, manganese, titanium, molybdenum. Patch tests were assessed after 48 hours.
Results: Clinical features among the 3 groups are shown in table. Univariate analysis showed 4 factors were related to the Complex ISR. There were positive patch test(p=0.001), CRP value(p=0.06), lesion length(p=0.03), number of stent(p=0.04). By multivariate logistic regression analysis, positive patch test were independently associated with the Complex ISR (odds ratio 6.4, 95% CI 1.5 to 28.2; p=0.01).

clinical features among the 3 groups

	No restenosis	First ISR	Complex ISR	P value
Diabetes, %	37	33	48	0.51
Stent length, mm	21±9	32±20	27±12	<0.0001
CRP value, mg/dl	0.47±0.60	0.55±0.72	1.05±1.65	0.07
Patch test positive, %	9	14	39	0.001

Conclusions: Metallic allergy does not have any correlation with the First ISR. However, positive metal allergy was frequently observed in patients with Complex ISR.
This study also revealed that metallic allergy is a strong predictor of Complex ISR. Metallic allergy may contribute to the mechanisms in repeat recurrence of ISR.

P2215 Trapidil eluting coronary stent: protection from restenosis without cellular toxicity?

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Rapamycin or paclitaxel coated stents are eligible to avoid the instent restenosis after coronary stent impantation (RAVEL/SIRIUS; TAXUS III/ELUTES). The protection from instent restenosis has proven only for cytotoxical substances associated with high costs. The aim of this study was to investigate the influence of locally released trapidil as a platelet derived growth factor inhibitor avoiding the instent restenosis.
Patients/Methods: This prospective study includes 62 pts. (mean age 62 ± 11) with coronary artery disease. In 37 patients (pts.) coronary arterial stenosis was treated by implantation of a 3.0/15mm BiodivYsio DD/Matrix LO® stent loaded by trapidil. Stenting using a 3.0/15mm BiodivYsio OC Stent® without trapidil was performed in 25 pts. as a control group. There was no difference in risk profile, age and sex between trapidil and control group. The dimension of stenosis was measured by quantitative coronary analysis. In 75% of the pts. treated with trapidil-stents the left artery decending was the target lesion, right coronary artery in 14%, left circumflex in 7% and a venous bypass graft in 4%, comparable with the control group. The post interventional antiplatelet regime was identical (ASA, Clopidogrel for 4 weeks).
Results: Primary stenting was successful in 80% of all treated pts., predilatation was necessary in 20%, post-dilatation was performed in 20%. All stents were implanted within 21-240 seconds (s). Mean angioplasty balloon pressure was 11 ± 5 bar, mean balloon inflating time was 37 ± 7 s. Up to now 80% of all pts. were followed up by angiogram after 6 months. There was a significant reduction of instent restenosis rate in the trapidil group compared to the control group (14% vs. 33%) requiring redilatation.
Conclusion: BiodivYsio OC® stent without delivering substance shows the common rate of instent restenosis. The loading by trapidil of the BiodivYsio Matrix LO® stent reduce the incidence of the instent restenosis. Decreasing the incidence of instent restenosis is caused by the local effect of trapidil. Compared by conventional stent implantation no different antiplatelet regime is required. The costs are considerable less than in comercial coated stents.

P2216 Estradiol coated stents for the prevention of restenosis in native coronary arteries: results

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Introduction: in vitro and animal models indicate that 17 beta-estradiol inhibits intimal smooth muscle cell proliferation and migration and accelerates re-endothelization after balloon angioplasty and stenting. This study prospectively and randomly compare stents loaded with 17 beta-estradiol(BiodivYsio DD Matrix, Biocompatibles, Ireland) to bare metal stents in reducing restenosis rate.
Methods: we report the immediate and one-month follow-up results of the 2 different stents in de novo lesions on native coronary arteries. In the study 104 patients with 124 lesions (49% in the estrogen arm and (51% in the control arm) have been enroled. Lesions were located on LAD in 41%), on LCX or OM branches in 28%, on RCA in 31% and on the left main in 1% of the cases. Complex lesions (B2, C type ACC/AHA) were 42% and 44% in the estrogen and in the control arm respectively (p=n.s.). Baseline and post stenting angiographic measurements are reported in table. No statistically significant differences were noted between the 2 groups. After discharge, all patients have been treated with double antiplatelet therapy for three months.
Results: angiographic success was obtained in all cases. During the hospital stay there were no death or repeat revascularizations. Non Q-wave myocardial infarction (MI) occurred in 2 (2%) cases in the control arm (p=n.s.). After one months, no deaths occurred. One patients in the estrogen arm had a non-Q wave MI three days after the procedure and target lesion revascularization with re-PTCA was repeated. All the patients have been scheduled for a 6-month angiographic follow-up that will be available at the time of presentation.

QCA measurements

Stent type	Basal ref. (mm)	Basal MLD (mm)	Lesion length (mm)	Final MLD (mm)
Estrogen loaded	2.89±0.60	0.97±0.61	11.7±8.5	2.57±0.88
Bare metal	2.95±0.57	1.02±0.58	13.9±9.6	2.67±0.80

Conclusions: Stenting with the estrogen coated stents is safe and is associated with high procedural success rate. In hospital course and 1-month follow-up indicate that estrogen coating do not increase the risk of acute or sub-acute stent thrombosis compared to bare metal stent. The efficacy of this therapy in reducing the incidence of restenosis will be assessed after the 6-months angiographic follow-up results will be available.

P2217 Serial intravascular ultrasound analysis in TAXUS II: beneficial distal edge effect with paclitaxel-eluting stents

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Background: So-called 'edge stenosis' is a critical problem with radioactive stents or following brachytherapy. It has been of concern that a similar effect might occur after implantation of drug eluting stents. Using the TAXUS II database with serial ultrasound analysis post-procedure and at 6 months, the present study evaluates the vessel response to polymer-controlled local paclitaxel eluting in the proximal and distal edges adjacent to the stent.
Methods: TAXUS II is a randomized, double-blind trial with two consecutive cohorts comparing slow- (SR) and moderate-release (MR) polymer formulations of a paclitaxel-eluting stents with control bare stents. As per protocol, all patients were followed with intravascular ultrasound (IVUS) post-procedure and 6-month follow-up. The quantitative IVUS edge analysis was performed by an independent blinded core laboratory. The proximal and distal 5mm edge segments were subdivided into five 1mm long sub-segments.
Results: For this analysis serial IVUS was available in 100 SR, 98 MR and 201 control patients. Negative vessel remodeling (significant reduction in edge vessel area) occurred only in the proximal edges of the control group (proximal -0.48 $\pm$ 2.16mm^2, $p<0.005$) and was absent in distal edges of the control as well as in both edges of SR and MR. Proximal edge lumen area at 6-months was comparable for SR (-0.54 $\pm$ 2.10mm^2), MR (-0.89 $\pm$ 1.87mm^2), and control(-1.02 $\pm$ 1.91mm^2). The change in distal edge lumen area was significantly improved in SR (+0.08 $\pm$ 2.01mm^2, $p<0.0001$)and MR (-0.19$\pm$ 1.68mm^2, $p<0.005$)when compared to control (-0.87 $\pm$ 1.99mm^2).
Conclusion: Decreased in-stent restenosis with TAXUS-SR or -MR stents is not associated with increased edge stenosis at 6-month follow-up IVUS when compared to bare metal control stents. Instead a beneficial increase at the distal edges was observed for the TAXUS stents.

P2218 Brachytherapy of coronary in-stent restenosis: randomized prospective study of cutting-balloon versus standard-balloon angioplasty

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To evaluate cutting-balloon angioplasty (CBA) as an adjunct to brachytherapy of coronary in-stent restenoses, we prospectively studied 100 patients (73 men, 64 $\pm$ 9 years) in whom predilation of the target lesion was randomly assigned to either CBA (n = 50) or standard-balloon angioplasty (SBA, n = 50). After predilation, all lesions were irradiated using the Novoste Beta-Cath system (BETACUT study). Primary end point was angiographic restenosis at 8 months. Enrollment of patients began in January 2001; the final patient was enrolled in July 2002. Risk factors present in our patients were diabetes mellitus (28%), arterial hypertension (64%), hyperlipidemia (80%), and smoking (46%); there were no statistically significant differences with respect to the prevalence of these risk factors in the CBA and SBA subgroups. A total of 103 lesions (CBA, n = 52; SBA, n = 51) were treated in the 100 patients, located in the main stem in 1 case and in the left anterior descending, the right, and the left circumflex coronary artery in 43, 37, and 22 cases, respectively. Mean reference vessel diameter was 2.62 mm, mean minimal lumen diameter (MLD) was 0.68 mm, and mean lesion length was 17 mm, with no statistically significant difference between CBA and SBA patients for either variable. A total of 98 lesions (95.1%) were irradiated, using a 40-mm source in 63 cases and a 60-mm source in 35 (CBA: n = 50 [total]/32 [40-mm]/18 [60-mm]). After angioplasty, MLD was significantly increased in the CBA subgroup (2.08 mm vs SBA 1.82 mm, p = 0.02). Quantitative angiographic 8-month analysis will be performed in March 2003.
Summary: BETACUT is a randomized prospective study to evaluate cutting balloon angioplasty in brachytherapy of coronary in-stent restenoses. Randomized patients in the 2 subgroups are well-matched with respect to clinical and angiographic variables. After the intervention, a significantly wider lumen was achieved by CBA. The primary end point of angiographic restenosis at 8 months will be presented at the meeting.

P2219 Coronary spasm after intracoronary β-radiation is a risk factor for target vessel restenosis

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Background: Intracoronary radiation is currently the only proven treatment for the prevention of in-stent restenosis. However, in-vitro, animal and human studies have shown that irradiation induces endothelial dysfunction and vascular spasm. The aim of this study was to determine the incidence of coronary spasm after β-radiation therapy and to evaluate its impact on long-term angiographic results.
Methods and Results: We analyzed 126 vessels of 122 consecutive patients undergoing β-radiation (18 Gray at 1mm depth into vessel wall) after percutaneous coronary intervention (PCI) for in-stent restenosis. Postradiation coronary spasm in the target vessel was documented by quantitative coronary angiography immediately after PCI, after removal of the radiation catheter and at the end of the procedure. Long-term angiographic results of those patients showing coronary spasm were compared with those patients not showing spasm. There was a 25.4% (32 vessels) overall incidence of coronary spasm after β-radiation during the baseline procedure. In 22% spasm was severe (>90% diameter stenosis [%DS]), in 47% moderate (50 to 89%DS) and in 31% mild (15 to 50%DS). In 13% spasm occurred proximal to the stent, in 59% distal and in 28% proximal and distal. At angiographic follow-up, which was performed in all patients (6.7±2.3 months), binary target vessel restenosis rate was significantly higher in those vessels displaying coronary spasm compared with those vessels not showing spasm after radiation therapy (53.1% versus 24.5%; $P<0.003$). The majority (65%) of these target vessel restenoses occurred at the site of the periprocedural spasm.
Conclusions: Coronary spasm after β-radiation therapy is a risk factor for target vessel restenosis.

P2220 Quantification of dose perturbation due to atherosclerotic plaque in vascular brachytherapy

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Background: Dose prescription and reporting in vascular brachytherapy is based on the assumption that the vessel wall is water equivalent, which does not consider a possible dose perturbation by atherosclerotic plaque. The aim of the present study was to quantify dose attenuation for beta- and gamma-radiation.
Methods: 90Sr/Y and 192Ir sources in respective delivery catheters were attached to a polystyrene phantom embedded in water-equivalent gel. The delivered doses with and without human peripheral arteries surrounding the delivery catheter were determined from radiochromic films. The distance between the source and the film was constant for all measurements. Plaque and vessel wall thickness were measured using light microscopy. We assessed 38 sections irradiated with 90Sr/Y and 7 sections irradiated with 192Ir. From the ratio attenuated dose/unattenuated dose (dose perturbation factor, DPF) we determined averaged attenuation coefficients for atherosclerotic plaque (μP) and the remaining part of the vessel wall (μW) by regression analysis based on the exponential function DPF = exp(-μP$*$plaque thickness -μW$*$remaining wall thickness).
Results: The attenuation of 192Ir was smaller than the measurement uncertainties. For beta-radiation there was a moderate correlation between measured and fitted dose perturbation without discrimination for vessel wall morphology (r=0.648). Assuming the entire vessel wall to be non-diseased tissue in mildly atherosclerotic sections, the regression coefficient improved to r=0.845 at μP=0.5356 mm-1 and μW=0.0663 mm^{-1}.
Conclusions: Plaque thickness should be considered for dose prescription and dose calculation in vascular brachytherapy with beta-radiation in order to correct the irradiation time according to plaque thickness. For retrospective analysis, the DPF gives the ratio between the actually applied and the initially prescribed dose.

P2221 Short and long-term results of intracoronary brachytherapy for in-stent restenosis in 200 consecutive patients

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Background: The major concern from randomized intracoronary brachytherapy (ICBT) trials was edge restenosis due to use of short source. Target lesion revascularization (TLR) with use of longer ICBT sources appears to be favorable.
Methods: We analyzed 200 consecutive patients with in-stent restenosis (225 vessels and 242 lesions) who had cutting balloon (CB PTCA) and/or rotational atherectomy followed by beta radiation using the Novoste system (30 mm source in 114 and 40 mm source in 86 patients) and followed for mean 5$\pm$3 months.
Results: Mean age was 66$\pm$11 years, male sex 67%, CCS class III-IV 26%, $>$1 prior restenosis 50%, restenosis interval 182$\pm$52 days. Periprocedural CK-MB elevation occurred in 16% patients, average in-hospital stay was 2.0$\pm$1.8 days, GP IIb/IIIa use 65%. Plavix was recommended for 6 months. At follow-up: TVR 9% (18 pts, 14 TLR, and 4 non-TLR), delayed acute closure/subacute thrombosis 0%, death 2% (1 in-hospital, 3 at follow-up).

Procedural Characteristics & QCA

Lesion length (mm)	17.5$\pm$8.9	Ref. vessel size (mm)	2.91$\pm$0.04
LAD/LCX/RCA (%)	44/28/21	MLD-Pre (mm)	0.72$\pm$0.31
Total occlusion	10%	MLD-Post (mm)	2.21$\pm$0.42
CB PTCA$\pm$Rotablator	65%	MLD-Post ICBT (mm)	2.12$\pm$0.32
Rotablator	30%	Re-dilatation post ICBT	6%
Re-stent	5%	Vessel spasm	5%

Conclusion: Debulking followed by ICBT provides sustained long-term, acceptable restenosis in single digits. In comparison with randomized trials, these favorable results in the real world are perhaps due to better understanding of the restenotic process after ICBT and represent the benefit of full lesion coverage by long source, leaving moderate residual stenosis and very low need for restenting.

P2222 Efficacy of vascular brachytherapy with beta-radiation in longer lesions and smaller reference diameter vessels

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Aims: The aim of present study was to assess the medium-term out-come in patients undergoing vascular brachytherapy (VBT) in various risk group patients, such as smaller vessels, longer lesions, diabetics, hypertension and sub-optimal angiographic result.
Methods & Results: The RENO (European Surveillance Registry with the Novoste Beta-Cath) registry has prospectively collected procedural and clinical outcome data on 1092 patients treated with beta-radiation. In its prospective database review, patients were retrospectively divided in to the following three groups determined by estimated residual stenosis (RS) prior to delivery of radiation: Group-I; RS $<$10% (n=637), Group-II; RS 10-30% (n=410) and Group-III; RS 30-50% (n=45).
There were more hypertensive patients in Group-I (64.1%) compared to Group-II (61.2%) & Group-III (55.6%); p$<$0.001. Diabetic patients were common in Group-I (23.6%) and Group -II (24.6%) compared to Group-III 15.6%); p=NS. Lesion characteristics revealed smaller reference diameter in Group-II (3.14$\pm$0.47mm; p=0.031) & Group-III (3.05$\pm$0.45mm; p=0.032) compared to Group-I (3.2$\pm$0.53 mm). Lesion lengths were longer in Group-II (20.17 $\pm$ 13.07 mm; p=0.028) & Group-III (21.22 $\pm$ 11.22 mm; p=0.002) compared to Group-I (18.03$\pm$10.8 mm). There were more graft lesions in Group II (7.5%; p=0.03) & Group-III (15.7%; p=0.002) compared to Group-I (4.3%).
Effectiveness of VBT was determined by major adverse cardiac events {MACE: death, non-fatal MI, target vessel revascularisation (TVR)} and improvement in angina at six months. There was similar improvement in angina in all groups (Group-I 82.7%, Group-II 88.3% & Group-III 90.7%; p=NS). The incidence of TVR was low in all groups (Group-I 16.5%, Group-II 16.4%, Group-III 15.6%). Incidence of MACE at six months was also similar in all groups (Group-I 18.7%, Group-II 18%, Group-III 17.8%; p=NS). Despite of the fact that Group-II & Group III patients had longer lesions, smaller reference diameter, included more graft lesions and also had sub-optimal angiographic results compared to Group I, the outcomes as measured by TVR, MACE and improvement in angina were similar. Similarly higher prevalence of hypertension and diabetes in Group-I and Group-II did not affect final outcomes.
Conclusion VBT appears to be a potent treatment for in-stent restenosis regardless of the vessel size, lesion length, sub-optimal angiographic result and other underlying risk factors such as hypertension and diabetes mellitus.

P2223 Long-term outcome after intracoronary beta radiation therapy

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Background: intracoronary beta radiation therapy (IRT) has shown promising results in the prevention of instent restenosis, albeit in the short term. However, the long term results are not yet established. We present the clinical outcomes of a large cohort of patients treated at our center.
Methods: we retrospectively reviewed all patients (n=302) who received IRT during coronary angioplasty (PCI) at our institution. Mean follow-up period was 38.7 months. Patients were assessed for major adverse cardiac events (MACE) comprising death, acute myocardial infarction (AMI) or repeat revascularisation (TLR, TVR, or non-TLR/TVR).
Results: baseline characteristics: male sex 217 (72%), hypertension 98 (33%), hypercholesterolaemia 172 (57%), current smoking 59 (20%), diabetes 45 (15%). Previous history: AMI 105 (36%), PCI 164 (55%). Clinical presentation at reintervention: 64% stable angina, 30% non-ST elevation acute coronary syndrome, 6% AMI. Mean time between IRT and first TLR procedure was 10.7months (range 0.3-48.5months). Incidence of death was 3% (n=10). Reintervention of the total population is presented in the table in a hierarchical ranking scale. 17 (6%) patients were referred for CABG. At least one revascularisation procedure was undergone by 41%; overall MACE-free survival was 40%.

Table of reinterventions

	$<$6 months	$<$12 months	$<$24 months	$\geq$ 24 months
TLR (%)	29 (9.6%)	65 (21.5%)	78 (25.8%)	93 (30.8%)
TVR (%)	4 (1.3%)	15 (5.0%)	17 (5.6%)	15 (5.0%)
non-TLR/TVR (%)	6 (2.0%)	12 (4.0%)	13 (4.3%)	15 (5.0%)
Overall (%)	39 (12.9%)	92 (30.5%)	108 (35.8%)	123 (40.7%)

Reinterventions of the total population in a hierarchical ranking scale.

Conclusions: in the long-term follow-up of patients following intracoronary beta radiation therapy there is an incremental adverse cardiac event rate beyond the first 6 months. This is predominantly due to reintervention which is mainly TLR. All patients treated with IRT require longer follow-up evaluation than those treated with standard techniques.

FRACTIONAL FLOW RESERVE: CLINICAL APPLICATIONS

P2224 Validation of fractional and relative coronary flow reserve measurements in patients with prior myocardial infarction

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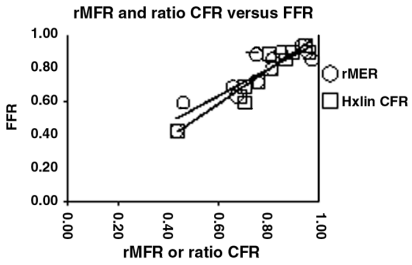
Background: The accuracy of the fractional flow reserve (FFR) and coronary flow reserve (CFR) to identify significant coronary stenoses is well established in normal myocardial regions. The validity of FFR has been demonstrated with PET in non-infarcted areas. In partially infarcted regions, the mass of viable myocardium depending on the infarct related artery (IRA) is smaller and resistive vessels may be dysfunctional. The purpose of the present study was to assess wether FFR measurements are also valid in IRAs.
Methods: Patients with prior infarction and 1 or 2 vessel disease were studied. Relative myocardial flow reserve(rMFR), defined as the ratio of maximum perfusion in the infarcted area to the maximum perfusion in the contralateral normally perfused area during hyperemia (IV adenosine), was assessed by 15O-labeled water and PET. The ratio of CFR (ratio of maximum to baseline flow) in the infarted area to CFR of the reference region was also compared with FFR. On the same day, during catheterization FFR (ratio of mean aortic to distal conary pressure at maximum hyperemia) was measured with a pressure wire in the IRA.
Results: Measurements were performed in 12 patients. Percent diameter stenosis in the IRA ranged from 27% to 83% (mean 47 $\pm$ 20%), FFR from 0.42 to 0.94 (mean, 0.77 $\pm$ 0.16), rMFR from 0.43 to 0.97 (mean, 0.76 $\pm$ 0.18) and the ratio of CFR from 0.44 to 0.97 (mean 0.78 $\pm$ 0.14). A close correlation was found between rMFR and FFR (R2 = 0.83) and between the ratio of CFR and FFR (R2 = 0.84).



rMFR and ratio CFR versus FFR.

Conclusion: FFR correlates well with rMFR and the ratio of CFR derived from PET measurements in patients with a prior myocardial infarction. This validates the use of the pressure and Doppler flow wires in the assessment of coronary stenoses in IRAs.

P2225 Real world validation of coronary thermodilution: the week 25

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Background: Thermodilution-derived coronary flow reserve (CFR)thermo), the ratio between resting and hyperemic transit time (Tmn), has been recently validated in humans. However, in vivo, quite some scatter persists in the relationship between CFRthermo and Doppler-derived coronary flow reserve (CFRDoppler). Among the factors that may account for these differences are: 1) the injection of the bolus of saline in the coronary circulation; 2) the algorithm used to calculate the Tmn; 3) high baseline flow status might affect more the CFRthermo than CFRDoppler.
Aim: 1) To compare CFRDoppler to CFRthermo, with a simplified injection technique and an improved algorithm in the setting of a multicentric study; 2) To assess the feasibility and timing for CFRthermo as compared to CFRDoppler.
Methods: Patients were recruited from the 8 participating centers during a five day period. Patients had at least one vessel stenosis to be functionally evaluated or treated percutaneously. Ostial lesions, tortuous vessels and poor Doppler tracings quality were exclusion criteria. Vessels under study were instrumented with a Doppler wire (Jomed) and a Pressure Wire 4 (Radi Medical System). Three measurements of Tmn and of the average peak velocity (APV) were obtained at baseline and after hyperemia, as induced by IV adenosine. The ratio between the 3 baseline and 3 hyperemic Tmn values represented CFRthermo. The ratio between the 3 hyperemic and 3 baseline APV values represented CFRDoppler.
Results: Among the patients recruited, 31% were excluded upfront because of poor Doppler tracings, 3% were excluded because of unreliable CFRthermo. The time needed to measure CFRDoppler was 6$\pm$2 min, while the time needed to measure CFRthermo was 5$\pm$1 min. A good linear correlation (r=0.79, $p<0.01$) was observed between CFRDoppler and CFRthermo.
Conclusion: In a multicentric setting, closer to everyday clinical practice, a good correlation was found between CFRDoppler and CFRthermo. The higher feasibility makes CFR measured by thermodilution technique a valid alternative to CFR measured by Doppler.

P2226 Index of myocardial resistance: a simple way to quantify microvascular disease invasively

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Purpose: Using a pressure-temperature sensor-tipped guidewire, distal coronary pressure (Pd) and temperature can be measured simultaneously during coronary catheterization. Using thermodilution principles after injection of 3 cc of saline into the coronary artery, mean transit time (Tmn) can be obtained and its inverse is a correlate to absolute blood flow. Therefore, an index of coronary microvascular resistance (IMR) can be defined by the product of Tmn and Pd at hyperemia.
In this in-vitro study, we compared the IMR with true myocardial resistance (Rmyo) at different degrees of myocardial resistance and in the presence of different degrees of stenosis.
Methods: The in-vitro model consists of a pump providing pulsatile flow and a systemic and a coronary circulation. In this model, also arterioles and the microvasculature are mimicked realistically and true myocardial resistance is calculated using electromagnetic flow measurements and can be varied over the complete physiological range. Six different levels of myocardial resistance were applied. At every level of microvascular resistance, 4 different degrees of epicardial stenosis were induced, using an external occluder. For each combination of myocardial resistance and epicardial stenosis, IMR was determined and compared to Rmyo. Simultaneously, distal coronary pressure, aortic pressure and fractional flow reserve (FFR) were measured throughout the experiment.
Results: A total of 24 measurements were performed. Blood flow varied from 42 -203 ml/min and Rmyo varied from 0.39 to 1.63 dynes.s.cm-5. An excellent correlation between IMR and Rmyo was found (R^2=0.94, $p< 0.0001$). Importantly, IMR was not dependent on the severity of any stenosis in the epicardial vessel, and thus specific for true myocardial resistance.
Conclusion: In this in-vitro set up, IMR correlates well with true myocardial resistance and is not dependent on the severity of the epicardial stenosis. Therefore, using one single guide wire, both FFR and microvascular resistance can be measured in an easy and simple way as indexes of epicardial and microvascular disease, respectively.

P2227 Randomized comparison of balloon angioplasty and stent implantation guided by flow velocity measurement: in-hospital results and long-term outcome

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Background: Several guide-wire methods have been proposed to assess the functional coronary lesion severity in the catheterization laboratory. Coronary flow velocity reserve (CFVR) is an accepted functional measure of stenosis severity. We assessed anatomic and coronary flow velocity changes in patients (pts) who underwent percutaneous coronary intervention (PCI) and their impact on clinical outcome.
Methods: Among 379 pts who underwent Doppler flow-guided PCI, as part of the Doppler Endpoints Balloon Angioplasty Trial Europe (DEBATE) II study, 187 were randomized to stent implantation (group ST) and 192 to balloon angioplasty (group BA). Demographics (DE), risk factors profile (RF), clinical presentation (CL), medications used (MED) and angiographic data (ANG) were not different between 2 pts group. QCA measurements (diameter stenosis, DS) and CFVR pre and post successful PCI procedure were evaluated. All pts had 12 months (MO) clinical follow-up. Major adverse cardiac events (MACE) were considered as death, non-fatal myocardial infarction, and percutaneous or surgical target lesion revascularization.
Results: No difference in DS and CFVR pre-PCI was observed between BA and ST group of pts. Following successful PCI, CFVR was 2.78±0.84 and 2.60±0.74 (p=0.03) and %DS 7.8±7.9 and 23.0±9.0 (p=0.0001) in the ST and BA group respectively. DE, RF, CL, MED, ANG, % DS, CFVR and DS/CFVR pre-and post-PCI were compared in pts with and without MACE at 12 MO in each group. In the ST group CFVR post-PCI was lower in pts with MACE (2.45±1.23 vs 2.81±0.78, p=0.01), but in the BA group no difference was observed. In a multivariate model a CFVR>=2.5 post-PCI (OR, 0.225; p=0.01) and the ratio of the differences DS/CFR pre- and post- PCI (OR, 0.995; p=0.01) were independent predictors of MACE at 12 MO only in the ST group of pts. Pts with MACE in the ST group had %DS and DS/CFVR post-PCI lower compared to pts in the BA group (p=0.0001).
Conclusion: In selected pts with single lesion PCI, ST implantation is associated with higher CFVR compared to BA. A CFVR post-ST PCI>=2.5 and a low ratio of DS/CFVR differences (pre-and post-PCI) are independent predictors of MACE at 12 mo.

P2228 Clinical decision-making in patients with angiographically suspect left main stenosis by intracoronary pressure measurements

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Background: The evaluation of suspect left main stem lesions in patients with atypical angina and/or non-conclusive stress test results represents a difficult clinical situation with important consequences for the patient.
Patients and Method: Sixteen patients with atypical angina and/or non-conclusive stress test results with regard to the dependent myocardium were investigated by intracoronary pressure measurements. All cases presented with intermediate lesions of the left main (angiographically 50-80% diameter stenosis). Following the induction of maximal hyperemia with adenosine 140μg/kg/min for > 90 sec the fractional myocardial flow reserve (FFRmyo) was determined. A pullback curve was performed if indicated in order to identify the exact location of the hemodynamically significant stenosis.
Results: Additional intracoronary pressure measurements were considered necessary because of an unclear clinical and angiographical situation that could not be resolved with certainty otherwise. Functionally significant left main stem lesions were identified in 10 of 16 patients. The FFRmyo ranged from 0.61 to 0.78 in this group. Consequently, bypass surgery was recommended as further therapy in all of these patients. In the remaining group of 6 patients FFRmyo was non-significant ranging from 0.83 to 1.0. Following conservative treatment in these patients neither typical angina nor major adverse cardiac events occurred over a mean follow-up period of 22 months. An additional IVUS investigation performed in 4 of 16 patients reliably helped in the decision-making process in only 1 case in which a significant left main stenosis could be excluded in accordance with the FFRmyo measurement.
Conclusions: The hemodynamic significance of angiographically dubious left main stem lesions in patients with atypical symptoms and/or non-conclusive stress test results has clinical but also prognostic relevance. Intracoronary pressure measurement can be the decisive factor for an online clinical and apparently safe decision-making in these patients. The method might be superior to additional IVUS investigations.

P2229 Effects of microvascular resistance index on the evaluation of fractional flow reserve and epicardial stenosis resistance index

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Objectives: Fractional flow reserve(FFR) had been applied to evaluate the hemodynamic severity of epicardial coronary stenosis. However, FFR may be affected by microvascular resistance of lesion distal segment and influence of hyperemic microvascular resistance to FFR and epicardial stenosis resistance is not clearly defined.
Methods: Twenty-eight lesion of 27 patients(13 AMI related arteries, 15 non-AMI related arteries) were studied. IVUS % area stenosis(IVUS-%AS), FFR, coronary flow reserve(CFR) and hyperemic epicardial stenosis resistance index(h-ESRI) were measured before and after PCI and hyperemic microvascular resistance index(h-MVRI) of lesion distal segment was measured after PCI. Fifty-one studied lesion site were divided into two groups according to post-stent h-MVRI(Group 1, h-MVRI<2.2, n=29; Group 2, h-MVRI[>=]2.2, n=22; 2.2 is best cut off value for CFR 2.5).
Results: There was no significant difference in IVUS-%AS between two groups(47±37% vs. 45±36%, p=0.817). FFR was lower and h-ESRI was higher in Group 1 than Group 2(0.78±0.19 vs. 0.88±0.10, p=0.018; 0.80±0.98 vs. 0.37±0.31, p=0.031, respectively). There were significant correlation between FFR, h-ESRI and IVUS-%AS(r=0.86, p<0.001; r=0.76, p<0.001, respectively). The best cut off values of FFR and h-ESRI for 75% of IVUS-%AS in Group 1 were 0.75 and 0.69(sensitivity 89%, specificity 85%, AUC 0.892; sensitivity 89%, specificity 85% AUC 0.897 respectively). However, best cut off values of FFR and h-ESRI for 75% of IVUS-%AS in Group 2 were 0.87 and 0.41(sensitivity 85%, specificity 93%, AUC 0.948; sensitivity 85%, specificity 93% AUC 0.943 respectively).
Conclusion: FFR and h-ESRI were affected by hyperemic resistance index of lesion distal segment. FFR and h-ESRI may underestimate the severity of anatomical stenosis in cases of increased hyperemic resistance index of lesion distal segment.

P2230 Comparison of coronary flow reserve derived by intracoronary pressure measurement and frame count method

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Background: The pressure-derived myocardial fractional flow reserve (FFR) is regarded as lesion specific parameter of the severity of the epicardial coronary stenosis. The flow-based coronary flow reserve (CFR) also characterises the epicardial stenosis, but it is influenced by the microvascular function.
Aim: To compare the pressured-based CFR (CFRp) and the CFR calculated by the frame count (CFRfc) in relation to the FFR.
Method: The CFRp is defined as the ratio of the flow calculated from the pressure gradient during vasodilatation to the calculated flow at the basal condition. The CFRfc is estimated from the flow velocity of intracoronary contrast material. In 12 patients 15 coronary arteries were measured by pressure wire in resting condition and during maximal ic. or iv. adenosine induced vasodialatation, and the flow velocity was assessed by frame count during injection of the contrast material. We used the calculations below where Pdv is the ic. distal pressure during vasodilatation, Pav is the aortic pressure during vasodialatation, Pa is the aortic pressure, Pd is the ic. distal pressure in the basal condition, C is the frame count in resting state, Cv is the frame count during vasodilatation.

$$CFRp = \sqrt{\frac{Pav - Pdv}{Pa - Pd}} \quad FFR = Pdv/Pav,\ CFR_{fc} = C/Cv$$

Results: Correlation was found between the CFRp and CFRfc (r= 0.74, p= 0.05). Comparing the FFR with the CFR there was a closer correlation between FFR and CFRp than FFR and CFRfc (r=0.68 and r= 0.48, respectively).
Conclusion: In our opinion, the CFRp and CFRfc are both useful and easily generable parameter to estimate the CFR during intracoronary pressure measurement with vasodilatation. This flow assessment has additional value for indicating intervention in cases where the FFR is borderline.Calculations

P2231 Correlation between hypertensive left-ventricular hypertrophy and coronary flow velocity reserve in patients with negative coronary angiograms

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Background: Hypertension and left ventricular hypertrophy (LVH) associated with increased myocardial wall stress and decreased perfusion of the subendocardial region. The aim of the present study was to investigate the relationship between hypertensive LVH, antihypertensive treatment and coronary flow velocity reserve (CFR).
Patients and methods: 53 patients with a normal coronary angiogram (23 men, 30 women, age: 54±10 years) were examined by dipyridamole transoesophageal echocardiography. The CFR was calculated by the ratio of average peak diastolic flow velocity (APV) during hyperaemia to the resting APV. Patients with myocardial infarction, dilated cardiomyopathy, haemodynamically significant valvular heart disease, uncontrolled diabetes mellitus or hypercholesterolaemia were excluded. The patients were devided into subgroups depending on the lack or presence of hypertension, and in the hypertensive patients on the degree of LVH. The CFR of the hypertensive patients was compared via the effectivity of antihypertensive therapy.
Results: The CFR was significantly lower among patients with serious LVH as compared with normotensive (1.79±0.39 vs 2.64±0.70; p=0.009), hypertensive patients with no LVH (vs. 2.63±0.69; p=0.003), and patients with mild LVH (vs. 3.01±0.67; p=0.002). Among the hypertensive patients, a correlation was observed between CFR and the degree of LVH (R=0.425, p=0.008), and between the CFR and the left ventricular mass (R=0.48, p=0.001). The CFR was significantly higher in patients who had received effective antihypertensive therapy as compared with ineffective medication (3.24±0.90 vs. 2.11±0.56; p=0.001).
Conclusions: 1. Among the patients with normal coronary angiograms the CFR was significantly influenced by LVH. 2. The CFR was significantly higher among patients who had participated in effective antihypertensive therapy.

P2232 Outcomes of multivessel patients with one vessel deferred on the basis of fractional flow reserve measurements

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Background: Fractional-flow reserve (FFR) is an established tool to assess coronary stenosis severity. It has been shown that it is safe to defer an intervention in single vessel diseased patient (pt) when FFR > 0,75. Little is known about the accuracy of such approach in pts with multivessel disease.
Methods: 91 pts (66 ± 11 years, 29% female) with multivessel coronary artery disease, in whom at least one vessel was treated by PCI and at least one other vessel was deferred based on FFR, were followed up for at least one year. The primary combined end-point was all cause mortality, myocardial infarction or ischaemia requiring revascularisation at 30 days, 6 months and longest follow-up.
Results: The average clinical follow-up was 28 ± 14 months. FFR on the deferred vessel was 0,86 ± 0,06 with a mean percentage of stenosis of 47 ± 13%. No end-point was observed at 30-days. Neither death nor myocardial infarction (due to the deferred vessel) were recorded during the follow-up period. One (1%) pt required intervention on the deferred vessel because of recurrent ischaemia at 6-months and 4(4%) additional pts at late follow-up. Two (2%) pts were hospitalised for recurrent angina.
Conclusions: In pts with multivessel disease at angiography, FFR allows discrimination between functionally significant and non significant stenoses. PCI of the latter can be safely deferred, even though initially planned on the basis of the angiogram.

P2233 Myocardial viability detection in post-myocardial infarction patients by pressure wire techniques

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Purpose: The aim of the study was to validate in a clinical setting a new index predicting myocardial viability after myocardial infarction (MI). This new index is based on pressure wire techniques.
Methods: The myocardial blood flow of an infarcted territory equals to (Pd-Pv)/R or [(Pa-Pd)/Rs]+[(Pa-Pd)/Rc] (1), where Pd, Pv and Pa are the mean intracoronary pressure distal to the stenosis, the central venous and mean arterial pressure, respectively, while Rs, Rc and R are the resistance caused by the coronary artery stenosis, the collateral circulation and the resistance myocardial vessels, respectively. Pv is usually close to zero and (1) can be transformed to: [(Pa/Pd)-1]=(RcRs)/[R(Rc+Rs)]= k (2). In infarcted territories with considerable amount of viable tissue, induced hyperaemia reduces R, while in cases with mainly scarred tissue, R remains unchanged or decreases marginally. In both cases Rc is minimal and Rs is unchanged. Based on (2) we developed a new index of viability (V), related to the changes of k pre (k) and post vasodilation (k', after 40mcg intracoronary bolus of adenosine): V=k'- k or V =(Pa'/Pd')-(Pa/Pd). We assume that index V has higher values when the infarcted territory is viable. Index V can be measured easily using the pressure wire.
Results: 45 patients with recent (7-15 days) ST-elevation MI and infarct-related artery with a diameter stenosis 70-95% were treated with percutaneous coronary intervention (PCI). Prior to PCI index V was calculated using the pressure wire (Endosonics). All patients underwent 2D-echocardiography 1-2 days prior to PCI and at 6 months and repeat angiography at 6 months. 4 patients had significant restenosis at follow-up and were excluded from the analysis. 25 patients (61%) were proven to have substantial amount of viable myocardial tissue at 6 months (improved contractility at follow up echocardiography in at least 2 segments or at least 1 segment when only 2 segments were abnormal at baseline). The estimated cut off point of index V for myocardial viability using ROC analysis, was 0.28. The specificity and sensitivity of index V in discriminating these patients were 93.6% (15/16) and 76.0% (19/25), respectively. 83% of the patients (34/41) were correctly classified. There was a significant correlation between the wall motion recovery index and the number of recovered segments per patient with index V (r=0.480, p<0.01 and r=0.469, p<0.01 respectively).
Conclusion: The present study demonstrates that the new pressure-derived index V may be of value in detecting the presence of viable myocardium in post-MI patients.

P2234 Application of pressure-derived myocardial fractional flow reserve in assessing the functional severity of coronary-artery stenosis in patients with diabetes mellitus

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Although the development of coronary pressurewire facilitates the measurement of fractional flow reserve (FFR) to assess the functional severity of coronary-artery stenoses, theoretical limitations include DM due to impaired microvascular function. Accordingly, 209 patients with 251 vessels and their coronary territories were evaluated with a coronary pressurewire and thallium scintigraphy. The cut-off point in FFR for detecting myocardial ischemia was evaluated using receiver operating characteristic curve (ROC) analysis. The best cut-off point in FFR to detect myocardial ischemia as demonstrated by thallium scintigraphy was 0.755 in patients with DM and 0.745 in those without DM. In addition, the areas under these 2 curves were similar (0.833 vs 0.835). Sensitivity of 83% and specificity of 74% in patients with DM were also similar to those without DM (sensitivity 83% and specificity 81%). However, DM patients with HbA1c ≥7.0 showed lower specificity in comparison to DM patients with HbA1c <7.0 (55 vs 95%; p=0.008). Moreover, DM patients complicated with both nephropathy and retinopathy also had lower specificity compared with DM patients without either of these complications (29 vs 81%; p=0.02). In contrast, sensitivities were similar regardless of serum HbA1c level (83 vs 84%; p=NS), and the presence or absence of diabetic complications (90 vs 79%; p=NS). These results indicate that the same cut-off point of 0.75 in FFR can also be applied to detect myocardial ischemia even in patients with DM. However, caution is necessary when applying FFR measurements to DM patients with inadequate blood glucose control or to those with multiple diabetic complications.

PREVENTION OF IN-STENT RESTENOSIS: EXPERIMENTAL STUDIES

P2235 Statins are promising compounds for drug coated stents to prevent restenosis following percutaneous coronary intervention

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Local stent-based vascular drug therapy utilizing cell cycle inhibiting compounds such as sirolimus or paclitaxel, has been proven to be effective in reducing the risk of restenosis following vascular interventions. Therapeutic targets include inhibition of smooth muscle cell proliferation and migration, however, these particular targets should not be altered in endothelial cells, thus not interfering with reendothelialization of the injured vascular segment which may result in late thrombotic events. Cycling dependent kinase inhibitors of the cip/kip family such as p21 and p27 play a prominent role in the pathophysiology of neointima formation. The goal of this study was to examine the impact of statins on mitogen induced proliferation and migration both in human coronary artery smooth muscle (CASMC) and endothelial cells (CAEC) and the effect of local administration via a drug coating stent animal model on vascular restenosis. There was a 50% reduction of CASMC proliferation at 5nM cerivastatin, whereas the same effect on CAEC proliferation was not achieved until 5-10 fold higher concentrations. Cell cycle analysis showed time dependent decrease of cyclin A and ongoing expression of cyclin E. There was a prominent induction of p21 and later p27 following statin therapy, mitogen-mediated dephosphorylation of Rb was abrogated. In addition, cerivastatin inhibited fibronectin mediated CASMC migration but not adhesion. There was no evidence of accelerated cell death (LDH ELISA) or apoptosis in both cell types at the respectively applied doses. In a pilot study, local cerivastatin elution by a drug coated stent device reduced neointima formation in the experimental rat model of carotid injury followed by stent placement by 51% (n=6 animals, $p<0.05$) compared to non coated stents. Stent thrombosis rate was not increased in cerivastatin coated stents. Analysis of release kinetics showed cerivastatin release by more than 90% within 24h. Conclusion: Cerivastatin induces pleiotropic anti-growth and anti-migratory effects in coronary artery smooth muscle cells. Analogous effects in CAEC were only induced at significantly higher cerivastatin dosage suggesting a protective effect regarding reendothelialization. Stent based local administration of cerivastatin may effectively reduce neointimal hyperplasia.

P2236 Effects of tacrolimus and paclitaxel stent coating on neointimal proliferation in the porcine coronary model

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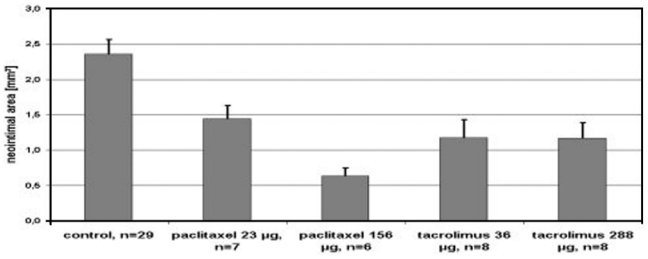
Background: The ideal agent for local coronary drug delivery should exert antiproliferative action on vascular smooth muscle cells while sparing endothelial cells. Tacrolimus (FK506) is a potent antiproliferative and immunosuppressive agent. Cell culture experiments indicate that tacrolimus could allow improved endothelial regeneration compared to other agents. Therefore, tacrolimus is a promising new candidate for stent coating. The aim of our studies was to compare different stent coating technologies using tacrolimus or paclitaxel as antiproliferative agents. **Methods and Results:** Stents were implanted in LAD and CX coronary arteries of domestic pigs. Quantitative coronary angiography and histomorphometry of the stented arteries asserted statistic equality of the baseline parameters between the control and treatment groups. After 28 days, tacrolimus stent coating based on a polymer basis led to a significant reduction of neointimal formation. In contrast, high dose paclitaxel stent coating was complicated by unexpected deaths of two pigs and thrombotic stent occlusion at control angiography in two cases. In another porcine study, tacrolimus stent coating showed a similar efficacy with different coating technologies such as ceramic and microporous surfaces loaded with tacrolimus, or direct tacrolimus coating of bare stents. **Conclusion:** The present study demonstrates efficacy and safety of tacrolimus stent coating in restenosis prevention. It seems to be superior to paclitaxel due to the broader therapeutic window.



P2237 A novel biodegradable coronary polymer stent with drug-delivery capacities: paclitaxel-loading inhibits neointimal hyperplasia in a porcine model of coronary restenosis

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Background: Due to high rates of in-stent restenosis and permanent nature of metal stent implants, synthetic polymers have been proposed as surrogate materials for stents and local delivery systems for drugs, such as paclitaxel. For this substance effective inhibition of vascular smooth muscle cell proliferation and migration was shown.
Methods and Results: A novel biodegradable double-helical stent was manufactured using controlled expansion of saturated polymers (CESP) for the molding of a bioresorbable poly(D,L)-lactid acid (PDLLA). Extensive machanicl studies proved sufficient mechanical stability. The Chandler loop model revealed good in vivo hemocompatibility. A modified balloon catheter for stent deployment was developed according to the mechanical stent properties. Six paclitaxel-loaded polymer stents (170 µg), 6 unloaded polymer stents, and 6 316L bare metal stents were deployed in porcine right coronary arteries. Drug release of loaded paclitaxel for at least one month and therapeutic tissue concentrations could be demonstrated by in vivo pharmacokinetics with a slow release profile. Fibrin deposition, cell proliferation, and inflammatory response was analysed by immunohistochemistry. Fibrin deposition was equal in all groups, while cell proliferation and inflammation was significantly reduced in drug-loaded stents compared to unloaded control. Histomorphometric evaluation demonstrated that mean coronary stenosis of paclitaxel-loaded PDLLA stents (30±5%) was significantly inhibited by 53% compared to unloaded PDLLA stents (65±10%, $p<0.01$) and by 44% compared to metal stents (53±6%, $p<0.05$) after 3 weeks.
Conclusions: These results indicate that high-molecular polylactids constitute attractive materials for polymer stents in combination with new manufacturing techniques. This novel polymer stent showed sufficient mechanic stability, and by incorporation of paclitaxel, a significant potential to reduce restenosis development after vascular intervention.

P2238 Cytochalasin D polymer-coated stents reduce neointima formation in a porcine coronary model

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Background: In-stent neointima formation remains a major limitation of coronary stenting. Cytochalasin D (CD) is an inhibitor of the actin-filament formation, thereby inhibiting cell migration and proliferation. This study evaluates the efficacy of stent-based delivery of CD on in-stent neointima formation in a porcine coronary model. **Methods and Results:** Stents were coated with a slow-release, nonerodable polybutyl methacrylate (PBMA)/polyvinyl acetate (PVAC) polymer containing 20 µg CD. In-vitro release measurements in NaCl at 37°C showed that 13% of the initial dose was relased after the first 24 hours, which was gradually sustained towards a 78% release after 3 weeks (n=2). After 7 days implantation in rabbit iliac arteries, significant local arterial CD tissue levels (0.21 and 0.24 µg/artery, n=2) were found, without exerting systemic toxic effects. Thirty stents (bare, n=10; polymer-only, n=10; polymer + CD, n=10) were then randomly deployed in the right or left coronary artery of 15 pigs. Six weeks later, angiography showed higher late lumen loss in polymer-only stents as compared to bare stents (0.55±0.03 vs 0.34±0.09 mm, $p>0.05$), significantly reduced, however, by CD-coated stents (0.19±0.05 mm, $P<0.01$). These angiographic data were confirmed by morphometry, showing for similar injury-scores in all groups, higher neointimal area in polymer-only stents as compared to bare stents (2.46±0.22 vs 1.42±0.12 mm^2, $P<0.05$), significantly reduced by CD-coated stents (1.57±0.20 mm^2, $P<0.05$). Immunostaining of the proliferation marker Ki-67 and macrophage marker mac-387 around stent struts showed a respective 60% (5.2±1.2 vs 12.8±3.3 cells/mm^2, $p>0.05$) and 78% (19.8±5.1 vs 88.2±29.3 cells/mm^2, $p>0.05$) reduction in CD-coated stents as compared to polymer-only stents. Lectin staining showed almost complete staining of the endothelium in all 3 groups. However, higher focal fibrin deposition and intra-intimal haemorrhages around stent struts were seen in the polymer-only group as compared to the other two groups ($p>0.05$), indicating delayed healing induced by the polymer itself. Finally, focal medial necrosis or (sub)acute thrombus formation were not observed in any group.
Conclusion: Stent-based delivery of 20 µg CD via a non-biocompatible PBMA/PVAC polymer matrix is feasible and results in significant local arterial concentrations. These 20 µg CD-coated stents effectively reduce in-stent neointima formation in a porcine coronary artery model, due to a reduction in the proliferative and inflammatory response and without inducing local arterial toxic effects.

P2239 Local stent mediated methotrexate delivery reduces neointimal hyperplasia in a porcine coronary model

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Background: Smooth muscle cell migration and proliferation contribute to neointimal formation after coronary stenting. Methotrexate is a potent anti-proliferative and anti-inflammatory agent. Stent-based methotrexate delivery has failed to reduce neointimal hyperplasia in a porcine coronary artery model, most probably due to the lack of biocompatibility of the polymer coating used. In the current study we used a biocompatible biologic polymer coating to load methotrexate on stents and determined the efficacy of stent-based methotrexate delivery to inhibit neointimal hyperplasia in a porcine coronary model.
Methods: Thirty coated stents and bare stents were randomly deployed in the right and left coronary arteries of 15 crossbred pigs at a balloon/artery ratio of 1.1:1. The pigs were sacrified after 5 days (10 stents) and 4 weeks (20 stents) respectively. In a second study stainless steel coronary stents were dipcoated in a 10mg/ml methotrexate/biologic polymer solution, resulting in a total load of 150μg methotrexate. Seventeen coated stents and 20 methotrexate loaded stents were implanted in porcine coronary arteries with a balloon/artery ratio of 1.2:1.
Results: The coated and the bare stents elicited a similar tissue response at 5 days follow-up. Inflammatory response and thrombus formation were not significanly different in both groups. At 4 weeks, the neointimal hyperplasia induced by the coated stents was even less pronounced compared to the bare stents (1.32$\pm$0.66 vs 1.73$\pm$0.93 mm^2, $p>0.05$) although the oversizing and the vessel injury were similar. In vitro drug release studies showed that 50% of the loaded methotrexate was released in 24h, 87% was released after the first week and all drug was released after 4 weeks. At 4 weeks the neointimal hyperplasia (1.22$\pm$0.34 vs 2.25$\pm$1.28 mm^2, $p<0.01$) and area stenosis (21$\pm$8 vs 36$\pm$21, $p<0.01$) of the methotrexate loaded stents were significantly lower than the polymer coated stents.
Conclusions: Stent-based delivery of methotrexate using a biocompatible biological coating reduces neointimal hyperplasia in a porcine coronary stent model.

P2240 Tissue inhibitor of matrix metalloproteinase 3 over-expression via stent-based adenoviral delivery effectively reduces restenosis in porcine coronary arteries

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Background: Intracoronary stent deployment triggers a vascular injury response, which in up-to 50% of patients results in in-stent restenosis. We aimed to assess the effect of locally infecting coronary arteries with an adenovirus (AdV) overexpressing Tissue Inhibitor of Metalloproteinase 3 (TIMP3). TIMP3 plays a crucial role in the regulation of metalloproteinase activity & uniquely promotes apoptosis of smooth muscle cells, thus inhibiting neointimal proliferation.
Method: We used a Matrix HI phosphorylocholine-coated stent platform (Abbott, USA), modified to elicit increased positive cationic charge, thereby enhancing the binding of negatively charged AdV. Preliminary in-vitro & short-term in-vivo studies were performed to confirm enhanced AdV transduction & transcription with the novel coating. Subsequently, we deployed stents $\pm$ TIMP3 AdV, in porcine coronaries for 28 days (n=5 per group). Following sacrifice stented arteries were fixed & resin embedded to allow histological processing. Planimetric measurements & Injury Scores were recorded in 4 sections per stent.
Results: Preliminary work with beta-Galactosidase AdV confirmed effective transduction in-vitro. TIMP3 AdV transduction & transcription was demonstrated at 7 days in-vivo, with PCR & Immunohistochemical methods. Comparison with control stents, at 28 days, revealed that TIMP3 stents significantly reduced neointimal area (μm^2) 127.1$\pm$84.6 vs 212.1$\pm$87.5, $p<0.005$, without any difference in medial area (μm^2) 103.7$\pm$21.0 vs 112.6$\pm$17.2, p=0.15, or injury score (2.0$\pm$0.6 vs 1.8$\pm$0.3, p=0.36).
Conclusion: Our novel stent coating effectively promotes TIMP3 AdV transduction & transcription, in-vitro & in-vivo. TIMP3 can successfully reduce neointimal proliferation by up-to 40%, thus confirming its role in the prevention of in-stent restenosis. The combination of a therapeutic AdV & a biosynthetic stent coating may represent an alternative to drug-eluting coatings in preventing restenosis.

P2241 Dendritic cells in neointima post-angioplasty: presence of anti-apoptotic mediators as determinants of their survival

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Purpose: We recently identified large numbers of dendritic cells (DCs) in early neointimal lesions after balloon angioplasty in rat carotid arteries and suggested their circulatory origin. The aim of the present study was to assess the presence of anti-apoptotic determinants in neointimal DCs. Specifically, we sought to analyze the expression of the Bcl-2 protooncogene that is known to inhibit apoptosis in DCs and other cells. In addition, we determined the presence of Receptor Activator of NF-kB (RANK) whose activation by TNF-related ligands like RANK-L mediates anti-apoptotic effects in DCs.
Methods: Bcl-2, RANK, and RANK-L were detected by immunohistochemistry in rat carotid arteries at 7, 14 and 28 days post balloon angioplasty (n=6 per time). OX-62 and S100 antibodies were used to identify DCs, and double-immunolabeling was performed to determine their co-localization with anti-apoptotic mediators. In addition, neointimal cell types and apoptosis were characterized by transmission electron microscopy (TEM).
Results: At day 7, neointimal OX-62+S100+ DCs were co-localized with strong signals of both RANK and RANK-L. In addition, double immunostaining revealed anti-apoptotic Bcl-2 signals in early neointimal DCs. TEM demonstrated cells with typical ultrastructural features of DCs, whereas apoptosis was observed in $<$5% of all neointimal cells. With increasing neointimal area at days 14 and 28, signaling for RANK and RANK-L was preserved along the luminal surface, coincident with OX-62 and S100 expression. Accordingly, TEM analysis revealed DCs exclusively in the apical neointima, while basal areas contained smooth muscle-like cells. Bcl-2 expression was most prominent in apical, DC-rich regions, but sporadic signaling was also located in deep neointima. Neointimal apoptosis was $<$1% at this time. While media and adventitia consistently revealed no immunolabeling for DCs, RANK and RANK-L, Bcl-2 signals were consistently found in both compartments, most in adventitial layers.
Conclusions: The present data identify the anti-apoptotic determinants Bcl-2, RANK and RANK-L in viable neointimal DCs. While expression of RANK, co-localized with its ligand RANK-L, was restricted to DCs, Bcl-2 signals were also present in other vascular cells post angioplasty. Therefore, modulation of RANK/RANK-L interactions may selectively modulate DC survival at the angioplasty site.

P2242 Augmentation of wall shear stress inhibits neo intimal hyperplasia and inflammation after stent implantation

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Background: Low wall shear stress (WSS) increases neointimal hyperplasia (NH) in vein grafts and stents. We studied the causal relationship between WSS and NH formation in stents by locally increasing WSS with a flow divider (ARED® EndoartSA, Lausanne, Switzerland) placed in the center of the stent.
Methods and Results: In 9 rabbits fed a high cholesterol diet for 2 months to induce endothelial dysfunction, 18 stents were implanted in the right and left external iliac arteries (1 stent per vessel). Lumen diameters were measured by quantitative angiography (QCA) at pre- and post-implantation and at 4-week follow-up, at which time, macrophage accumulation and interruption of the internal elastic lamina (IEL) was determined. Cross-sections of stents segments within the ARED® (STENT+ARED), outside the ARED® (STENT-ARED) and in corresponding segments of the contralateral control stent (SCTRL) were analyzed. Changes in WSS, induced by the ARED® placement, were derived by computational fluid dynamics (CFD).
CFD analysis demonstrated that WSS increased from 0.38 N/m^2 to 0.82 N/m^2 in the STENT+ARED immediately after ARED placement. This augmentation of shear stress was accompanied by i) lower mean late luminal loss by QCA (-0.23$\pm$0.22 mm vs. –0.58$\pm$0.30 mm p=0.02), ii) reduction in NH (1.48$\pm$0.58, 2.46$\pm$1.25 and 2.36$\pm$1.13 mm^2, $P<0.01$, respectively for STENT+ARED, STENT-ARED, SCTRL) and iii) a reduced inflammation score and a reduced injury score. Increments in shear stress did not change the relationship between injury score and NH and inflammation score and NH.
Conclusion: The newly developed ARED® flow divider significantly increases WSS and this local increment in WSS is accompanied by a local reduction in NH, and a local reduction in inflammation and injury. The present study is therefore the first to provide direct evidence for an important modulating role of shear stress related inflammation on in-stent neointimal hyperplasia.

P2243 Presence of endothelial precursor and dendritic cells in intimal hyperplasia at the time of clinical in-stent restenosis

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Background: Development of in-stent restenosis (ISR) has been traditionally attributed to smooth muscle cell (SMC) migration, proliferation and mitigated apoptosis. However, the pathobiological events are still poorly understood, and only a few reports described histological changes after stenting in human coronary arteries. Recently, several lines of evidence revealed the existence of bone marrow derived cells for participating in wound healing. Therefore, the study aim was to assess cellularity, markers of proliferation (Ki67), SMC (alpha-actin) and of bone-marrow derived cells (CD34, AC133), dendritic cells (S100) and other neural crest derived cells (GFAP, NSE, NGFR).
Methods: Atherectomy specimens from 10 patients with coronary ISR (time post stent implantation 6±2 months), 7 patients with peripheral ISR (7±3) and 10 with de novo lesions were examined immnunohistochemically for the presence of these determinants and analyzed by computer-aided morphometry.
Results: Samples from ISR consistently demonstrated a homogenous, extensive hypercellularity (993±345 cells/mm^2) compared to de novo lesions (431±148 cells/mm^2) and revealed Ki67 only in 3 of 17 ISR (18%). SMCs occupied 65±14% of total plaque area in ISR. As a key finding, expression of precursor cells (CD34: 7.1±2.5% vs. 0.6±0.7%, $P<0.05$; AC133: 7.0±3.4% vs. 1.0±0.7%, $P<0.05$), dendritic cells (S100: 9.8±5.6% vs. 1.4±1.1%, $P<0.05$) and other neural crest derived cells (GFAP: 7.9±2.4% vs. 3.1±1.0%; NSE: 4.4±2.6% vs. 1.3±1.6%; NGFR: 4.2±2.5% vs: 1.1±0.7%; each $P<0.05$) was significantly increased in ISR compared to de novo lesions.
Conclusions: ISR at the time of its clinical presentation is of pronounced hypercellularity without evidence of significant proliferation and is composed predominantly of alpha-actin positive SMCs. The significant presence of bone marrow derived and dendritic cells suggests the additional recruitment of primarily non-vascular cells with neointima formation.

P2244 Superior biocompatibility of titanium stents in hypercholesterolemic rabbits

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Background: Biocompatibility of stent material is crucial for its performance in vessels effecting immediate and long-term results after stenting. Titanium (Ti) is highly corrosion resistant non-noble metal with known good tolerance in tissue and anti-inflammatory properties demonstrated in experimental works. Pure titanium has not been used as a material for intravascular stents although Ti–coated stents have been tested and yielded promising results.
Objective: The purpose of this study was to test a biocompatibility of pure titanium as a material for intravascular stents in comparison with stainless steel stents (STS).
Materials and methods: The self-made, balloon expandable pure titanium (Ti=99,6+%) coil stents (TTS) were compared with STS of the same design, in a rabbit model. New Zealand hypercholesterolemic rabbits were used in the experiment. Each animal received oversized TTS and STS stent to both iliac arteries. After 4-5 week follow-up control angiography was obtained and morphometric analysis was performed to asses: lumen area (LA) internal elastic membrane area (IEMA) area stenosis (AS), minimal luminal diameter (MLD), late luminal loss (LLL) and diameter stenosis (DS).
Results: A total of 10 rabbits received 10 TTS and 10 STS stents. A degree of arterial injury was similar in both groups. Mild inflammatory reaction was observed exclusively near struts of the STS stents. Quantitative angiography and morphometric results are shown in the table (mean±SD).

	STS	TTS	P-value
Lumen area (mm^2)	2,05 ± 1,12	3,04 ± 0,88	0,05
Internal elastic membrane area (mm^2)	4,08 ± 0,53	3,95 ± 0,76	0,721
Area stenosis (%)	49 ± 29	23 ± 19	0,05
Minimal luminal diameter (mm)	1,52 ± 0,66	2,08 ± 0,22	0,036
Late luminal loss (mm)	1,25 ± 0,65	0,63 ± 0,23	0,007
Diameter stenosis (%)	34 ± 30	11 ± 8	0,047

Conclusions: Titanium coil stents yield better angiographic results and in comparison with stainless steel stents histopathological response is negligible. Titanium proves to be a suitable material for highly biocompatible endovascular stents.

P2245 Detection of DNA Chlamydia pneumoniae in coronary atherectomy tissues is predicted by its presence in circulating leukocytes, but not by serologic markers

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Background and Purpose: There is growing clinical and experimental evidence that infections with Chlamydia pneumoniae might contribute to the development and progression of atherosclerosis. C. pneumoniae may circulate via monocytes and migrate into plaques by leukocyte infiltration. Recent studies show that C. pneumoniae DNA in circulating leukocytes is correlated with C. pneumoniae DNA in atherosclerosic plaque material from carotid arteries and abdominal aortic aneurysm. However, there is no data on relation between C. pneumoniae DNA detected in coronary plaques and in circulating leukocytes. Thus we analyzed atherosclerotic plaques obtained by directional coronary atherectomy (DCA) and circulating leukocytes from the same patients for the presence of C. pneumoniae.
Methods: Circulating leukocytes and coronary tissue specimens obtained from 23 consecutive patients undergoing directional coronary atherectomy were analyzed by nested polymerase chain reaction (nPCR) for C. pneumoniae- specific DNA. Blood for leukocytes was drawn within 6 h prior to DCA procedure. We also determined IgA and IgG titers specific for the pathogen and plasma levels of IL-1B, fibrynogen and C-reactive protein in these patients.
Results: In nine patients (39,1%) C. pneumoniae- specific DNA were found - in 8 (34,8%) in circulating leukocytes and in 6 (26,9%) in atherosclerotic plaques. Among them in 5 pts (21.7%) C. pneumoniae DNA was detected in both leukocytes and coronary plaque, in 3 (13%) in leukocytes only, and in 1 (4,3%) in the coronary artery specimen only. The presence of C. pneumoniae- specific DNA in leukocytes significantly coincided with the presence of the respective DNA in coronary arteries plaques (P=0.002). No association between the presence of C. pneumoniae and specific IgA or IgG levels was seen. IL-1B levels were significantly higher in pts with C.pneumonia positive leukocytes than in pts with negative leukocytes (P=0.001). There were no significant diference in CRP and fibrynogen levels between C.pneumonia positive and negative groups.
Conclusions: C. pneumoniae DNA is quite frequent in atherosclerotic plaques and in circulating leukocytes. We show that C. pneumoniae DNA in circulating leukocytes, but not serologic test, correlate with presence of C. pneumoniae in coronary atherosclerotic tissue. Our results suggest that this non-invasive method may be of value in further research on infected coronary plaques.

DRUG-ELUTING STENTS: THE REAL WORLD

P2246 Drug-eluting stents in a large patient population with coronary lesions prone to restenosis

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Rapamycin-eluted stents (RES) have proven to inhibit exaggerated, post-implant neo-intimal proliferation in Benestent-type coronary lesions. However there is still little information on the clinical, angiographic and ultrasonic effects of RES in coronary lesions at higher risk for restenosis.
Methods: Since May/02 we have treated 286 lesions in 265 patients (pts) with documented myocardial ischemia secondary to coronary lesions prone to restenosis. The high risk of restenosis was based on the following reasons: 1) in-stent restenosis (n=101), 2) chronic total occlusion (n=60), 3) bifurcated lesions (n=104), 4) long-diffuse coronary stenoses (n=156), 4) small coronary arteries in diabetic pts (n=47); 176 pts had more than 1 risk condition for restenosis. The mean age at treatment was 63±10 years. The underlying clinical condition was stable angina in 43 pts (15%), unstable in 186 (65%) and post-myocardial infarction in 57 (20%). We implanted 389 RES (1.5 per patient) and 136 bare stents (0.5 per patient) in other associated coronary lesions at lower risk for restenosis. Angiographic evaluation and intracoronary ultrasound examination of the treated segment were planned at 6-month follow-up or sooner if patient became symptomatic.
Results: Primary success was obtained in 252 pts (95%). We failed in 8 pts because of inability to pass through chronic total occlusions (13%); non-Q wave myocardial infarction occurred in 4 other (1%). The only case with cardiac tamponade (0.4%) was resolved by puncture drainage. One patient died due to mesenteric ischemia. No other major complications occurred during the hospital phase. All patients became symptom free. One-month major adverse cardiac events (MACE) included 2 additional deaths secondary to subacute stent thrombosis (0.8%). After a mean follow-up time of 4±2 months, 240 pts (96%) remain symptom free. Six-months MACE were as follows: acute myocardial infarction in 3 (1%), target lesion revascularization in 3 (1%) and repeat revascularization at other non-related sites in 3 (1%). From 76 eligible pts with 6-month follow-up we performed angiographic re-evaluation in 49 pts (64%). Angiographic focal restenosis (>50%) was observed in 3 (6%); none of them at the edges. The mean neo-intimal area at the site of minimal lumen diameter was 0.9±0.8 mm^2. Maximal focal thickening in pts without restenosis (0.2±0.1 mm) was never related to the site of minimal lumen diameter.
Conclusion: RES provides excellent initial and mid-term results in pts with coronary lesions at high risk for restenosis.

P2247 The use of the sirolimus drug-eluting stent for "real life coronary lesions: the Milan experience

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Background: Encouraging results from the use of the sirolimus drug-eluting stent (CYPHERTM, Cordis) in the first clinical trial have been recently published. We report our experience with the use of Cypher stent in everyday clinical practice.
Methods: We included all lesions treated with Cypher stent in Centro Cuore Columbus hospital between 15 of April 2002 and 28 January 2003. Patients were treated with dual antiplatelet therapy for at least 3 months post-procedure. Angiographic follow-up is planned for all patients at 9 months. Major adverse cardiac events (MACE) were defined as death, myocardial infarction or target vessel revascularization (TVR).
Results: The Cypher stent was implanted in 322 patients to treat 733 lesions. Sixty patients (18.6%) were diabetics and 250 (77.6%) had multi-vessel coronary artery disease. Five hundred ninety-seven (81.4%) lesions were complex (ACC/AHA classification B2 or higher); 111 (15.1%) were in-stent restenosis and 73 (10.0%) chronic total occlusions. Intravascular ultrasound guidance was used in 103 (14.1%) lesions. The reference vessel size was 2.68±0.55mm, the minimal lumen diameter (MLD) 0.86±0.51mm and the lesion length 17.45±11.83mm.
The stent length per lesion was 27.7±14.2; IIb/IIIa inhibitors were used in 144 patients (44.7%). The maximum inflation pressure was 16.2±2.2 atm and the balloon to artery ratio 1.13±0.19. The post-procedure MLD was 2.69±0.57mm, resulting in acute gain of 1.74±0.65mm.
There were 4 cases of stent thrombosis during the procedure (1.2%). One of these patients required urgent coronary artery bypass surgery and died the next day. There were 2 Q-wave (0.6%) and 9 non-Q wave (2.8%) myocardial infarctions (AMI) during hospital stay.
Clinical follow-up has been completed in 264 patients (91%) at 3.1±2.2 months. Two patients died from non-cardiac cause and one from AMI after discontinuation of antiplatelet therapy 2 months post-procedure. There was also one case of Q-wave AMI after discontinuation of antiplatelet therapy 3 months post-procedure. Angiographic follow-up has been performed in 58 lesions, mostly in symptomatic patients and the first planned cases. Angiographic in-stent restenosis occurred in 14 lesions. Mid-term clinical and angiographic follow-up will be available at the time of presentation.
Conclusions: The implantation of Cypher stents in "real life" lesions is feasible and safe. The clinical and angiographic follow-up already attained suggests that events' rates may be higher compared to clinical trials.

P2248 Initial results of the German drug-eluting stent registry

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Drug-eluting stents reduce in-stent restenosis rates below 10% and, therefore, represent a major achievement in interventional cardiology. This has been documented in several well designed randomized trials. However, there is some concern whether these favorable results can be repeated in clinical routine. Currently, the use of these stents is limited mainly to patients who are considered by the operator as being at high risk for restenosis.
Due to this lack of information, a registry was initiated in Germany to assess indications, acute and long-term results in patients receiving drug-eluting stents. Currently, 1348 patients with 1630 stents from 86 centers have entered the database, and 282 patients have completed 6-months' follow-up. Stents were placed in RCX (44%), LAD (28%), RCA (26%), and main stem lesions (2%). In 58% of patients, an acute coronary syndrome was present, 26% received GPIIb/IIIa antagonists. The stent was used in 34% for lesions with known risk for restenosis (proximal LAD, bifurcation, ostial) and in 32% for small vessels (<2.5 mm) or long lesions (>30 mm). In 21% type C lesions were stented. In 24%, in-stent restenosis was restented, and 3% of patients had previous brachytherapy. Risk factors were typically distributed (27% diabetics). Acute mortality (0.1%), peri-interventional myocardial infarction (1.2%), and emergency CABG (0.1%) rates were low. In the current 6-months' follow-up, only 8% re-PTCA and 0.4% CABG were necessary. Further information is expected from the ongoing analysis of the data.

P2249 Drug-eluting stents for the treatment of bifurcated coronary lesions. A randomized comparison of simple- versus complex-strategy approach

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Recent studies on conventional bare stent treatment for bifurcational lesions have not reported any advantages of side branch stenting over simple balloon dilatation. Rapamycin-eluting stents (RES) have proven to eliminate restenosis almost entirely in many types of lesions. However, to date, the full reconstruction with RES of the entire bifurcation has not been proven to improve the results of a simple strategy.
Methods: To compare both stategies we carried out a randomized study in 68 patients with true coronary bifurcation lesions. All patients first received a RES at the main vessel, covering the side branch ostium. Patients from group A (n=35) were assigned to balloon dilatation of the involved side branch (simple strategy); 33 patients (group B) were randomized to receive a second stent at the side branch origin (complex strategy). There were no differences between groups regarding baseline clinical and angiographic data (age, sex, diabetes, unstable angina, lesion location, vessel size, lesion length, and ejection fraction). One patient from group A crossed-over to complex strategy due to poor immediate result after balloon dilatation of the side branch, whereas it was impossible to implant a stent at the ostium of the side branch in 4 patients from group B, so the intervention was limited to only balloon dilatation.
Results: The table summarizes the 1-month and follow-up results on an intention to treat basis. Six-month angiographic re-evaluation was obtained in 11 patients (92% of the 12 eligible patients). Restenosis of the parent vessel was observed only in one patient from group B, while restenosis of the side branch appeared in one patient in group A and in 2 from group B. At the time of the meeting, complete clinical and angiographic data will be available.

	Non-Q AMI	Death	TLR	Total MACE (4 ± 2 months)
Group A (n=35)	2 (6%)	0	0	2 (6%)
Group B (n=33)	0	1 (3%)	1 (3%)	2 (6%)

AMI.- Acute myocardial infarction; TLR.- Target lesion revascularization; MACE.- Major adverse cardiac event.

Conclusion: At this stage of the study we preliminarily conclude that both strategies are effective, without any differences in terms of clinical outcome.

P2250 Low incidence of subacute stent thrombosis after sirolimus-eluting stent implantation in daily practice – results from the rapamycin eluting stent evaluated at Rotterdam hospital (RESEARCH) registry

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Background: The incidence of subacute stent thrombosis (SAT) after sirolimus-eluting stent (SES) implantation for complex lesions is currently not known. We analyzed the occurrence of SAT in a large series of consecutive patients treated with this new technique.
Methods: Since 16th April 2002, SES implantation has been adopted as the default strategy for all patients treated with percutaneous intervention at our institution, as part of the RESEARCH registry. Patients were included irrespective of clinical presentation and lesion morphology. SAT was defined as any thrombotic in-stent occlusion occurring after the index procedure.
Results: By 8th September 2002, a total of 479 consecutive procedures were performed utilizing at least one SES. Mean age was 61±11 years, 71% were men. Overall, 229 (48%) patients presented with an acute coronary syndrome and 92 (19%) were diabetic. Platelet glycoprotein inhibitors were used in 119 (25%) procedures. From a total of 1004 SES utilized, 708 (71%) were implanted in type B2/C lesions and 100 (10%) had small nominal diameter (2.25 mm). Reference diameter was 2.69 ± 0.57 mm. Post-procedure MLD and diameter stenosis were 2.28±0.54 mm and 14.7±13.2%, respectively. To date (mean follow-up period 63±38 days; median 60 days), SAT occurred in 2 patients (0.4%), one re-admitted with acute myocardial infarction (within 6 hours after the initial procedure) and one with rest pain unstable angina (after 11 days). Both were successfully treated with percutaneous re-intervention.
Conclusions: Utilization of sirolimus-eluting stent implantation as the strategy of choice in the "real world' of interventional cardiology is associated with a very low incidence of subacute stent thrombosis.

P2251 Sirolimus-eluting stent implantation and occurrence of thrombosis: value of glycoprotein 2b/3a inhibitors

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The problem of intra-procedural stent thrombosis have been rare throughout development of coronary stenting. The aim of our study was to determine the frequency of intra-procedural stent (IPS) thrombosis and to study the association between usage of sirolimus-eluting stent (SES) and glycoprotein 2b/3a inhibitors (2b3a) in the occurrence of this event.
Methods: IPS thrombosis was defined as angiographically confirmed intraluminal filling defect within the stent resulting in TIMI grade 0 or 1 anterograde flow occurring during procedure.
This study included all patients undergoing elective coronary stenting between April 2002 and December 2002 at Emo-Centro Cuore Columbus and San Raffaele Hospital. Patients were excluded if they had myocardial infarction and if treated with brachytherapy. Patients were divided in 4 groups according to the usage of SES and 2b3a: group 1 (SES+2b3a); group 2 (SES+ no2b3a); group 3 (no SES+ 2b3a); group 4 (no SES+ no 2b3a). Exact permutation resampling implemented in Proc Multtest (SAS) was performed to test the interaction between SES and 2b3a (both unadjusted and adjusted for confounding factors such as stent lenght, minimal lumen diameter-MLD and diabetes mellitus).
Results: 1036 percutaneous coronary interventions requiring stent implantation were performed. IPS thrombosis occurred in 4 patients. Usage of SES was associated with higher incidence of IPS thrombosis compared to bare metal stents (respectively 1.08% vs.0%; p=0.016). The interaction between SES and 2b3a was statistical significant (p=0.022) demonstrating that the usage of 2b3a prevented the occurrence of IPS thrombosis in patients treated with SES (Table). When the analysis was stratified for stent lenght, MLD and diabetes mellitus the interaction between usage of SES and 2b3a was still significant (respectively p=0.039=; p=0.022 and p=0.024).

	SES+2b3a (n=134)	SES+no 2b3a (n=235)	no SES+ 2b3a (n=165)	no SES+no 2b3a (n=502)	p value for interaction
Intra-procedural stent thrombosis n%	0 (0%)	4 (1.7%)	0 (0%)	0(0%)	0.022

Conclusions: The usage of SES is associated with higher occurrence of IPS thrombosis. The usage of 2b3a reduces significantly the incidence of IPT in pt treated with SES.

P2252 Rapamycine eluting stents for the treatment of in-stent restenosis: results from a single centre experience

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Rapamycine eluting stents already proved to be efficient in prevention of restenosis in de novo lesions and have been already proposed as a potential treatment of ISR.
We report our experience in a series of ISR lesions treated with rapamycine eluting stent (RES) implantation. The study involves 75 lesions located in native coronary arteries from 52 patients treated from April 2002 to February 2003. Patients with previous brachytherapy were excluded from the analysis. The mean lesion length was 18.7±12.9mm, mean reference diameter was 2.80±0.46 mm, minimal lumen diameter (MLD) was 0.83±0.40 mm, mean stenosis was 71±12%. After RES implantation MLD increased up to 2.84±0.53 mm (acute gain 2.02±0.50 mm). Mean number of stents per lesion was 1.17±0.45, the average stent length was 30.5±13.8 mm. In all patients the procedure was successfully accomplished. In no cases in-hospital major adverse cardiac events (MACE) were observed. All patients were discharged with double antiplatelet therapy (aspirin 100 mg and ticlopidine 250 mg twice per day or clopidogrel 75 mg daily) for at least 6 months. After 30-days clinical follow-up no adjunctive MACE were recorded. All patients have been scheduled for an angiographic follow-up at 6-months. Complete data will be available for the date of presentation.
Our experience with unselected in-stent restenotic lesions showed good immediate angiographic and clinical results without evidence of acute or sub-acute thrombosis. The effectiveness of this mode of treatment in reducing repeat restenosis needs to be confirmed by the angiographic mid-term follow-up.

P2253 Immediate and late results of drug-eluting stents for the treatment of in-stent restenosis

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In-stent restenosis still remains the main limitation of percutaneous coronary revascularization. The use of drug-eluting stents to control exaggerated neointimal proliferation could substantially modify these results. Recent initial experience shows promising findings, however many questions still arise. The purpose of this study was to prospectively analyse the clinical, angiographic and late ultrasonic findings obtained from a series of 101 consecutive patients (pts) with in-stent restenosis who were treated with rapamycin-eluting stents (RES). The mean age at treatment was 66±10 years. In 80 pts (79%) the restenosis process was the first; in 16 (16%) second restenosis and in 5 (5%) third. Clinical presentation was stable in 19 pts and unstable in 73; 9 had markers of non-Q wave myocardial infarction; 48 pts were diabetic. At cardiac catheterization, the restenotic lesion was focal in 39 (39%), diffuse in 39 (39%) and proliferative 23 (22%). In 6 pts the restenosis had led to total occlusion. The mean lesion length was 22±12 mm. The restenotic lesion was located at the left anterior descending artery in 44 pts, the right coronary artery in 35, the circumflex in 10, the left main in 4 and a saphenous vein graft in 8. Once the lesion was crossed, the RES was directly implanted covering the whole restenotic lesion. The mean stented length was 29±14 mm and the final stent diameter was 2.6±0.4 mm; 3 pts received conventional stents to treat associated lesions at lower risk for restenosis involving other arteries. Primary success was obtained in 99 pts (98%). Two pts (2%) had a non-Q wave myocardial infarction. At 1-month evaluation 2 pts had died, one due to subacute stent thrombosis and another from acute mesenteric ischemia. After a mean follow-up of 4.5±2 months, most patients remain symptom free. However, the following late major adverse cardiac events were recorded: one patient had an acute myocardial infarction 5 months after treatment that was treated with thrombolysis; however, at late cardiac catheterization the treated artery was patent with no restenosis or residual intraluminal defects. Angiographic re-evaluation at 6-month was obtained in 20 out of 46 eligible pts (43%). Two pts had focal restenosis (>50%). Target vessel revascularization was needed in 2 pts (2%). The mean neo-intimal area, as derived by IVUS, in non re-restenosed lesions was 1.4±1.2 mm^2.
Conclusion: RES for the treatment of in-stent restenosis seem to substantially decrease target vessel revascularization. However, subacute or late stent thrombosis may appear in a small proportion of cases.

P2254 Patients with in-stent restenosis treated with sirolimus coated drug eluting stents

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Introduction: I-SR keeps to be a major challenge in interventional cardiology. The Sirolimus Coated Drug Eluting Stent has been succesfully implanted in patients with de-novo stenosis in the RAVEL and SIRIUS Trial so that it might also be effective in Patients with I-SR.
Patients and methods: The German CYPHER- Registry collected Data from 1187 consecutive patients with de- novo stenosis (825) and 302 (25,5%) with I-SR. Location was:104 RCA(32%)118 LCX (36,3%) and 103 LAD (31,7%). 26 Patients (8%) had pretreatment with brachytherapie. 24% had diabetes (50%IDDM) and 65% were smokers. Vein grafts were treated in 12% and bifurkation lesions in11,4% of the I-SR Patients. Preimplantation stenosis was 90% (visual assessment). 73% of ISR patients had a predilatation and 27% had direct stent placement. Implantation pressure ranged between 13 and 16 bar. Patients with I-SR more seldom had unstable angina or myocardial infarction than patients with de-novo stenosis. Angiographical follow up is scheduled 6 month after implantation
Results: Procedural success was achieved in 99% of the cases. Hospital mortalitiy was 0%. Myocardial infarction occurred in 1,1%, Postprocedural Troponin levels (I or T) were elevated in 19,6% of the patients. Re-PTCA was necessary in 4 patients. Up to now incomplete data (50 patients)are existing for angiographical follow up. They will be completed for all patients by the date of the presentation.

P2255 Sirolimus-eluting stents in unprotected left main

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The safety and efficacy of percutaneous coronary intervention in unprotected left main coronary arteries confronts with the problems associated with restenosis.
Methods From April 2002 14 consecutive patients with unprotected left main (LM) stenosis were electively treated in our instution with the implantation of Cypher Sirolimus-eluting stent (Cordis, Miami, FL).
Results 12 patients(85.6%) were male, with a mean age of 59.3±15.1 years. The site of the lesion in LM was ostial in 2 patients (14%), mid-portion of the artery in 2 patients (14%) and distal bifurcation in the remaining ten (72%). Angiographic as well as procedural success was achieved in all patients. In 12 patients stents were deployed after balloon angioplasty; only 2 patients had direct stenting. Elective intra-aortic balloon pump was used in 4 patients (28.6%) and GP IIb/IIIa antagonists were used in 8 (57.4%) of the patients. Largest balloon size was 3.4± 0.23 mm; balloon maximal lenght 13.37± 7.37 mm, and maximal pressure was 16,2± 2.08 atm. Stent lenght was 23.2± 8.36 mm. Minimal lumen diameter (MLD) increased from 1.23± 0.46 mm at baseline to 3.7±0.41 mm after the procedure, whereas mean diameter stenosis decreased from 61.8± 10.4% to 10.23±8.4%. Acute gain was 2.1± 0.7mm. During hospitalization, no patient died, or had myocardial infarction (MI) or repeated revascularization (CABG or re-PTCA). At 30 days clinical follow-up no patient suffered from death, MI, repeated revascularization or thrombotic event. All elegible patients will perform 6 month angiographic follow-up.
Conclusions In our preliminary data, the implantation of Cypher Sirolimus-eluting stent was safe and feasible and was not associated with any cardiac event either in hospital or at 1- month follow-up. Six month clinical and angiographic follow/up will be available for the presentation.

OUTCOME MARKERS IN CORONARY ARTERY DISEASE

P2256 Assessment of two different procedures of left atrial appendage exclusion during cardiac surgery

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Background: Previous studies have clearly demonstrated that thrombi, responsible for strokes in patients (pts) with permanent or paroxysmal atrial fibrillation (AF), are located in more than 90% of the cases in the left atrial appendage (LAA). It has been advised to exclude systematically this "anatomical nidus for thrombi" in patients at risk.
Objectives: The aims of the present study were 1) to report the potential deleterious effects of exclusion of the LAA by endocardial suture 2) to assess a safer solution.
Methods and Results: The study was divided in two periods including three groups of pts. In the first period, we performed a case-control study of 60 pts (2 groups of 30 pts) who underwent valvular surgery: 30 pts with LAA exclusion using endocardial suture and 30 patients without. We decided to interrupt this study when 3 pts in the LAA exclusion group had had strokes (10%), and none in the control group (NS). Trans-oesophageal echocardiography (TEE) performed in 2 pts showed mobile thrombi in a partially excluded appendage. After failure of the first strategy, a group of 30 pts (exclusively mitral valve surgery) with preoperative history of AF underwent a different procedure of LAA exclusion using an external ligature. No strokes were observed and TEE systematically performed after the 10th postoperative day visualized, in all the cases, a complete exclusion of LAA.
Conclusion: Exclusion of the LAA using endocardial suture may be a prothrombotic operation and should be avoided. Exclusion of LAA by external ligature seems to be the valid option.

P2257 Does gastroesophageal reflux provoke the myocardial ischaemia in patients with angiographically proven coronary artery disease?

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Background: Gastroesophageal reflux disease (GERD) may cause angina-like chest pain and therefore requires differentiation with coronary artery disease (CAD). Aim: To determine correlation between episodes of ST depression and pathological gastro-esophageal reflux during a simultaneous 24 hour monitoring of ECG and esophageal pH in patients with angiographically proven CAD. Influence of short-term "anti-reflux" therapy on the parameters of a 24 hour simultaneous esophageal pH and ECG monitoring in patients with GERD and CAD.
Methods: 50 patients with angiographically proven CAD, 42 men and 8 women, aged 37-74, mean age 55,9 were included into the study. All patients underwent simultaneous 24-hour continuous ECG and esophageal pH monitoring. We assessed the number of ST-segment depression episodes and duration of ischemic episodes during 24 hours of ECG monitoring (TIB - total ischemic burden). In esophageal pH-metry we assessed: time percentage of pH lower than 4 during 24 hours (FT-fractional time), total time of pH lower than 4 (TT - total time) and number of pathological refluxes (PR-pathological reflux). Patients fulfilling the GERD criteria (FT $>$ 5%)received a 7-day anti-acid therapy with proton pump inhibitor, omeprazol bid 20 mg. On the 7th day of therapy simultaneous Holter and esophageal pH monitoring was repeated.
Results: Total number of 224 episodes of pathologic gastro-esophagal reflux, which appeared in 42 patients (84%) was recorded during 24 hour esophageal pH-metry. GERD criteria were fulfilled in 23 patients (46%). Out of 218 episodes of ST depression, 45 (20,6%) were correlated with PR. GERD patients had statistically significant longer total ischemic burden and number of ST depression episodes compared to patients without reflux disease. In the result of 7 days anti-reflux therapy significant reduction of all analyzed parameters of esophageal pH monitoring was observed ($p<0,0022$) as well as significant reduction of number of ST depression episodes ($p<0,012$) and total ischaemic burden ($p<0,05$).
Conclusions: 1.Gastro-esophageal reflux disease is common in patients with angiographically proven coronary artery disease and may provoke myocardial ischemia in patients with significant coronary lessions (linked angina).
2. Short-term proton pump inhibitors therapy restores normal esophageal pH and significantly reduces myocardial ischemia. A possible mechanism of ischemia reduction in these patients is due to elimination of acid-derived esophago-cardiac reflex, diminishing the coronary perfusion.

P2258 Magnesium orotate lowers the severity of ventricular ectopic beats occuring after aorto- coronary by-pass surgery

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Ventricular ectopic beats (VEBs) are frequent early after cardio-surgery even in patients on beta-blockers or associated antiarrhythmic regimens and may be due to low magnesium tissue stores. In some cases these arrhythmias are life-threatening, difficult to manage and delay the start of rehabilitation programs. The study tested the efficiency of magnesium orotate for controlling these arrhythmias.

Material and Methods: The study was carried out on 60 selected patients (19F, 41M), mean age 56,85 ± 10,09, 7-10 days after aorto-coronary by-pass surgery, with an ejection fraction > 40%. Inclusion criteria were the presence of VEBs IIIA-IVB Lown on standard ECGs and 24 h Holter monitoring. Severity of VEBs was defined as highest detected according to Lown criteria. Cardioactive medication included metoprolol 25-50 mg bid in all cases. The patients were randomized to magnesium orotate 500 bid (gr.1, n=33) or placebo (gr.2, n=27). 24 h Holter monitoring was repeated after 14 days and the severity of VEBs was compared to entry in each case and between groups.

Results: VEBs were significantly less severe in 28 pts in gr.1 (84,8%) compared to 10 pts in gr.2 (37%) (p=0,0164), equally severe in 3 pts in gr.1 (9,1%) and 16 pts in gr.2 (59,3%) (p=NS) and more severe in 2 cases in gr.1 and 1 case in gr.2. Magnesium serum levels were 1,97±0,25 in gr.1 and 1,99±0,22 in gr.2 (p=NS), low (<1,8 mg/dl) in 5 cases in gr.1 and 7 cases in gr.2, within normal range in 26 cases in gr.1 and 18 cases in gr.2 and high (>2,4 mg/dl) in 2 cases in gr.1 and 2 cases in gr.2.

Conclusion: The efficiency of oral magnesium orotate in the control of VEBs in our study confirms the observation that normal or high serum levels of magnesium can still be associated with low tissue stores responsible for clinical effects. Besides being an efficient transsarcoplasmatic carrier for magnesium, orotic acid has been shown to have a direct protective effect on the myocardium. Magnesium orotate should be administered prior to surgery for prevention of VEBs and its cumulated effects need further study.

P2259 Preoperative use of sotalol versus atenolol for atrial fibrillation after cardiac surgery

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Purpose: Atrial Fibrillation is one of the most common complications of cardiac surgery. Beta blockers have been shown to decrease the incidence of post-operative atrial fibrillation. Preliminary investigations showing sotalol and atenolol to be effective in preventing post-operative atrial fibrillation are encouraging, but no studies have been conducted comparing both drugs.

Methods: A total of 253 consecutive eligible patients (66±8 years; m ± sd) scheduled to undergo cardiac surgery were enrolled in this study. Patients were randomized in a propective open manner 1.5:1 to Atenolol (50 mg/daily) group (153 patients) or Sotalol (80 mg twice daily) group (100 patients).

Results: Atrial fibrillation occurred in 44/253 patients (17,45%). A significant difference was found in the occurrence of atrial fibrillation in the atenolol group (34 patients, 22%) compared to those receiving Sotalol (10 patients 10%) (p=0.013).

Therapeutic efficiency and efficacy was 12% and 54% respectively.

Stepwise logistic regression analysis showed that age > 68 years (odds ratio, 2.72, 95% CI, 1.37 to 5.41; p=0.004), the use of beta-adrenergic agents (odds ratio, 2.74, 95% CI, 1.5 to 5; p=0.001), and sotalol (odds ratio, 0.46, 95% CI, 0.23 to 0.95; p=0.035) were independently associated with development of AF.

Conclusions: Oral low-dose sotalol provides a considerable reduction in the occurrence of atrial fibrillation. A selective approach based on clinical risk prediction should decrease the occurrence of atrial fibrillation after cardiac surgery.

P2260 Matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-9 (TIMP-1) are elevated in patients with acute coronary syndromes

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Introduction: Increased levels of metalloproteinases (MMPs), tissue inhibitor of metalloproteinase-1, C-Reactive Protein (CRP) and Interleukin-6 (IL-6) have been documented in patients (pts) with acute coronary syndromes (ACS). Their inter-correlations and the prognostic value of MMP-9 have not been examined.

Methods: We compared peripheral blood levels of CRP, IL-6, MMP-9 and TIMP-1 in 105 pts: Group 1 of 36 pts with stable CAD (29 males, age 61±8y), Group 2 of 48 pts with non ST elevation ACS (40 males, age 62±8.5y) and Group 3 of 21 pts with ST elevation ACS (19 males, age 57±14.5y). In groups 2 and 3 the blood levels were obtained within 48 hours from the last episode of resting ischemia and the admission with ST elevation respectively. The baseline demographic and coronary arteriographic data were similar in the three groups

Results: In group 2 and 3 combined, a significant correlation was seen between levels of CRP and IL-6 (r=0.66, p<0.001) and CRP and TIMP-1 (r=0.37, p=0.003).

	CRP(mg/lt)	IL-6(pgr/ml)	MMP-9(ng/ml)	TIMP-1(ng/ml)
Group1,N=36	2.08 ±1.7	4.4± 9.5	367 ±184	185± 44
Group2,N=48	8.3± 8.1*	5.6± 9.6	595 ±318*	253± 108*
Group3,N=21	14.4±10.6*	6.1± 3.9	766.1± 435.1**	357.8± 415.2

* P<0.001 vs respective Group1 ** P=0.005 vs respective Group1.

During 30 day follow up for death, acute myocardial infarction (AMI) and target vessel revascularization (TVR), the event (+) pts vs event (-) pts have higher concentration of MMP-9 (p=0.055) and IL-6 (p=0.032).Using ROC curves, pts with MMP-9 above 460.0ng/ml had an OR 2.73 and pts with IL-6 above 1.57pg/ml had an OR 3.85 for developing a 30 day event.

Conclusions: Pts with ACS have higher peripheral levels of MMP-9, TIMP-1 and CRP. TIMP-1 and CRP are correlated, suggesting a link between inflammation and a mechanism aiming at limiting the degradation of extracellular matrix in pts with ACS. MMP-9 and IL-6 appear to have prognostic value for short-term follow up.

P2261 No association of the −174G/C polymorphism of the interleukin-6 gene with coronary artery diaease

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Purpose: Interleukin-6 (IL-6) is an important stimulator of inflammatory reactions and is thought to be critically involved in initiation and progression of atherosclerosis. The -174G/C polymorphism of the IL-6 gene affects the plasma level of IL-6 and has been implicated as a risk factor for coronary artery disease (CAD). However, previous studies could not consistently demonstrate an association between the -174G/C polymorphism and CAD. We examined the possible association between the -174G/C polymorphism of the IL-6 gene and CAD in a large case-control study.

Methods: To establish the presence and severity of CAD, the study population of 2737 consecutive subjects was examined with coronary angiography. Genotype determination was achieved with allele-specific fluorogenic oligonucleotide probes added to the polymerase chain reaction (TaqMan method).

Results: Significant stenoses in 1 or more coronary arteries were observed in 2120 individuals (patients with CAD), while 617 individuals did not present with coronary stenoses (control group). The distribution of the genotypes, GG, GC, and CC, was not different among patients and control subjects (p=0.84). Adjustment for conventional risk factors of CAD, e.g. arterial hypertension, also did not reveal an association between the polymorphism and CAD (OR, 0.94; 95% CI, 0.76-1.15; p=0.53). In addition, genotype distribution (Table) and C allele frequency (p=0.71) did not change with the degree of the severity of CAD (stenoses in 1, 2, or 3 coronary arteries).

	-174GG	-174GC	-174CC
Control group (n=617), %	36.8	46.7	16.5
1-vessel disease (n=592), %	34.3	48.8	16.9
2-vessel disease (n=614), %	37.3	44.1	18.6
3-vessel disease (n=914), %	36.4	46.3	17.3

Lack of association between the -174G/C polymorphism of the IL-6 gene and the severity of CAD (p=0.79).

Conclusion: Our results suggest that the -174G/C polymorphism of the IL-6 gene is not correlated with CAD or the severity of CAD. These findings do not argue against the critical role of IL-6 in inflammatory reactions and atherogenesis. They rather indicate that, in the setting of this study, the -174G/C polymorphism is not a useful marker of CAD risk.

P2262 Paraoxonase 2 Ala148Gly mutation protects postmenopausal women from coronary artery disease

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Paraoxonase 2 (PON2) have been related with changes in metabolic quantitative phenotypes, such as plasma lipoproteins, plasma glucose, and coronary artery disease (CAD). Mutations at PON2 gene was associated with increased production and activity of the PON2 enzyme and though protection against CAD. But the association between PON2 Cys311Ser and Ala148Gly mutations and women with CAD is unknown.
Methods: We analyzed two common polymorphisms in PON2 at codon 311 (Cys311Ser) and 148 (Ala148Gly) in 130 women with angiographically defined CAD who were age-matched to control subjects. PCR with specific primers followed by DdeI and Fnu4HI restriction digestion was employed to identify Cys311Ser and Ala148Gly genotypes, respectively. One year of natural amenorrhea defined postmenopausal status and CAD greater than 50% narrowing in any subepicardial coronary artery.
Results: PON2 Ala148Gly mutation AA+AG vs GG genotype distribution in postmenopausal women were 41(31%) vs 25(18%) and 57(42%) vs 12(9%) (p=0,013) in controls and in women with CAD, respectively. Similar distribution was observed in control and in premenopausal women with CAD. GG genotype was associated with lower levels of LDL-cholesterol (p=0,02). Multivariate regression analysis showed GG genotype as an independent marker of protection against CAD in postmenopausal women (OR=0.58 (CI95%: 0.36-0.72); $p<0.0001$). PON2 Cys311Ser mutation did not show any association with lipid plasma levels and CAD.
Conclusion: PON2 Ala148Gly mutation protected postmenopausal women from CAD.

P2263 Alpha- and beta-oestrogen-receptor polymorphisms and coronary artery disease

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Estrogens have been shown protective against atherosclerosis through genomic and nongenomic effects. Great part of these actions are regulated by estrogen receptors (ER) alpha and beta. Despite the presence of both receptors in arterial wall, the distribution of them in arterial layers is unknown. Allelic variants of the gene encoding ER-alpha and ER-beta may alter its expression and function resulting in some genetic variability. Polymorphisms of ER-alpha have been associated with various diseases such as repeated spontaneous abortion, breast cancer, hypertension, altered concentrations of several proteins related to atherosclerosis, and coronary artery disease (CAD). Mutations in the ER-beta have been associated with changes in some phenotypic characteristics like altered serum concentrations of some hormones of the genital system such as estrogen and progesterone in anovulatory women. In the present case-control study, the prevalence of four mutations in estrogen receptors (two in ER-alpha identified by the restriction enzymes PvuII and XbaI and two in ER-beta identified by the enzymes RsaI and AlaI) was analyzed in 113 control individuals and in 154 patients with CAD. Mutation in the ER-alpha (PvuII) was more prevalent in control population (22% vs 11%; p=0.038) than in CAD patients and the mutation identified by the XbaI enzyme in the same receptor was found to be associated with reduced apolipoprotein B levels and low body mass index. Mutation of ER-beta (AlaI) was more prevalent in patients with CAD (20% vs 05%; p=0.005). The homozigozity for this mutation had an increased body mass index, elevated serum triglyceride and apolipoprotein B concentrations, and reduced HDL-cholesterol concentrations. Multivariate logistic regression analysis after adjustment for traditional risk factors showed dyslipidemia, low serum HDL levels and presence of ER-beta polymorphism (AluI) [OR=1.88 (IC 95%: 1.06 - 3.33); p=0.030] as independent risk factors for CAD. The present data suggest that mutation of ER-beta identified by the restriction enzyme (AluI) was an independent risk marker for CAD.

P2264 Interactive effect of the glutathione S-transferase genes and cigarette smoking on occurrence and severity of coronary artery risk

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Background: Glutathione S-transferase (GST) null M1 and T1 (GSTM1 and GSTT1) genotypes, which are involved in chemical detoxification, may modulate the risk for smoking-coronary artery disease (CAD).
Methods and Results: We performed PCR analysis to assess the distribution of the GST-genotypes in 430 patients angiographically-defined patients. We also examined the levels of DNA damage in CAD patients (n=66) by the micronucleus (MN) test, a sensitive assay for evaluating DNA damage.
The frequencies of GST null genotypes were not significantly different between patients with CAD (n=308) and without CAD (n=122). However, relative to never smokers with GST-present genotypes, in non-smokers carrying both null genotypes the odds ratios (OR) of CAD was 0.66 (CI 95%= 0.3-1.5, p=n.s). In smokers with both present genotypes, the OR was 1.5 (CI 95%= 0.7-3.3,p=n.s.) and was significantly increased in smokers with concurrent lack for GSTM1 and GSTT1 genes (OR= 4.0, 1.4-11.5 p=0.01). Smokers lacking GST genes had both higher number of stenosed vessels (chi-square=7.8, p=0.046) and elevated Duke score (49.0 ± 4.0 vs 38.0 ± 3.7 p=0.048, p=0.048) as compared to smokers expressing the genes. MN levels were higher in smokers with null genes as compared to smokers with present genes (18.0 ± 2.4 vs 7.5 ± 1.9, p=0.02; 22.5 ± 1.5 vs 6.0 ± 1.7, p=0.007; for GSTM1 null genotypes and both null genes, respectively).
Conclusion: The GST-null genotypes may strengthen the effect of smoking on CAD risk by modulating the detoxification of genotoxic atherogens.

P2265 Reliability of diagnosing myocardial injury by rapid bedside whole-blood quantitative cardiac troponin-T test in patients with coronary artery disease

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Background: The measurement of cardiac troponin T (cTnT) is a powerful tool for the diagnosis of myocardial injury. Recently, a rapid bedside whole-blood quantitative cTnT assay has been developed. We evaluated the reliability of this test for the diagnosis of myocardial injury in patients with coronary artery disease (CAD).
Methods: Whole-blood cTnT levels were measured in 96 patients with CAD using the rapid bedside Roche Cardiac Reader and were compared with serum cTnT levels of the same patients measured by the Roche Elecsys Immunoanalyzer. Forty patients (Group I) had clinical evidence of myocardial injury (13 with unstable angina and 27 with acute myocardial infarction) and 56 had no clinical evidence of myocardial injury (Group II). The cut-off value of cTnT used to assess for myocardial injury was 0.1 ng/ml.
Results: Rapid bedside whole-blood cTnT tests were positive in 36 patients in Group I and 3 patients in Group II with a sensitivity, specificity and positive and negative predictive values of 90%, 95%, 92% and 93%, respectively. From qualitative point of view (reporting negative or positive results), these values were identical to those obtained by the serum immunoanalyzer. From quantitative point of view (reporting the exact values), cTnT measurements by rapid bedside whole-blood tests correlated well with those of the serum immunoanalyzer for values between 0.1 and 2.0 ng/ml, but their mean value was significantly lower (mean $\pm$ SD, 1.20 ± 0.71 vs. 1.41 ± 1.03 ng/ml, p = 0.0007). Also, rapid bedside whole-blood tests could not give the exact measurements for values below 0.1 ng/ml (reported negative) or above 2.0 ng/ml (reported > 2.0).
Conclusion: The rapid bedside whole-blood cTnT tests are very sensitive and specific for the diagnosis of myocardial injury and correlate well with the immunoanalyzer measurements for values between 0.1 and 2.0 ng/ml. However, they tend to give significantly lower values and fail to give exact measurements for values above 2.0 ng/ml, which may affect their performance in monitoring patients and limit their use in predicting outcome.

P2266 Logistic EuroSCORE and preoperative prediction of costs and intensive care length of stay in cardiac surgery

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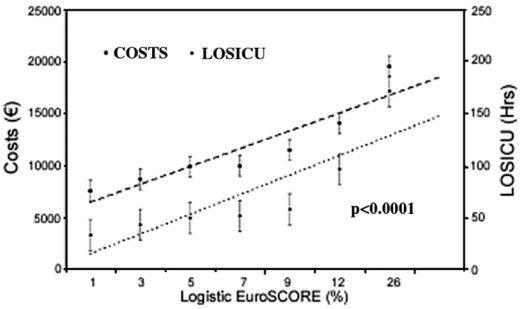
Purpose: The decrease of the hospital mortality in cardiac surgery together with the increase of non fatal complications suggest a higher survival rate, at the cost of a prolonged intensive care length of stay (IC-LOS) and a remarkable increase of direct variable costs. The aim of this study is to determine if the recently validated logistic EuroSCORE risk assessment system can predict both the IC-LOS and direct variable costs.
Methods: Of 488 consecutive patients operated on from March 2000 to March 2001 we calculated the logistic EuroSCORE according to the logistic regression equation presented in the official website; surgical and demographical variables were recorded for each patient using the Italian Society of Cardiac Surgery's Database. Direct variable costs were prospectively collected, surgical team costs excluded.
Results: The median logistic EuroSCORE of our population was 3.70%, (interquartile interval: 1.95 - 7.12%). (Median direct variable cost was 8020 Euro and median IC-LOS was 34 Hrs). Using linear regression analysis, we found that logistic EuroSCORE was directly correlated both with costs ($r = 0.43$, $p < 0.0001$), with a 2.6% cost increase for a unit rise of logistic EuroSCORE (95% CI 2.1%-3.1%), and with IC-LOS ($r = 0.31$, $p < 0.0001$), with 4.5 hours IC-LOS increase for a unit rise of logistic EuroSCORE (95% CI 3.2-5.7) (figure).



Logistic EuroSCORE/cost & ICU LOS.

Conclusions: Our preliminary study demonstrates that costs and IC-LOS are directly correlated with logistic EuroSCORE; therefore this model could be used to preoperatively predict both the costs and the IC-LOS in cardiac surgery.

RISK MARKERS IN CORONARY ARTERY DISEASE

P2267 Rapamycin-receptor FKBP12 in neointimal dendritic cells post-angioplasty

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Purpose: We recently reported the presence of bone marrow-derived dendritic cells (DCs) in post-angioplasty neointima. In view of remarkably low restenosis in rapamycin-eluting stents, we examined the temporospatial presence of FKBP12, the primary intracellular rapamycin receptor, during neointima formation. Herein, we specifically assessed whether neointimal DCs express FKBP12, since rapamycin may induce DC apoptosis.
Methods: The expression of FKBP12 was detected by immunohistochemistry in rat carotid arteries at 7, 14 and 28 days post balloon angioplasty (n=6 per time). OX-62 and S100 immunostaining, supplemented by complementary transmission electron microscopy (TEM), was used to identify DCs.
Results: At day 7, extensive immunoreactivity for FKBP12 was frequently found with neointimal cells. In serial sections, the vast majority of FKBP12+ neointimal cells were identified as DCs by OX-62 and S100 immunolabeling. Likewise, ultrastructural analysis of neointimal cells demonstrated typical ultrastructural features of DCs. At both 14 and 28 days, immunoreaction of FKBP12 was predominantly detectable in luminal neointima, coincident with OX-62+S100+ DC aggregation. Single signals of the rapamycin receptor were also present in deep neointimal layers, where cells with DC immunoreactivity and ultrastructural DC features were absent. Of note, media and adventitia consistently revealed no immunolabeling for FKBP12, OX-62 or S100.
Conclusions: Rapamycin receptor FKBP12 is strongly expressed by neointimal dendritic cells during early neointima formation. Since rapamycin is known to induce DC apoptosis in vitro, it may selectively interfere with neointimal DC accumulation. In addition, our data may help to explain the beneficial effects of fast-release (<15d) rapamycin-eluting stents, as rapamycin-sensitive FKBP12+ cells were predominantly present at early time points post angioplasty.

P2268 Glycoprotein IIIa PIA2 polymorphism and worse outcome of stable coronary disease: interaction with smoking

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Background: Platelet integrin glycoprotein IIbIIIa plays a primary role in platelet aggregation and acute thrombus formation at the site of vascular injury. A platelet PIA polymorphism of the GPIIIa gene in exon 2 is associated with function abnormalities. We studied whether the PIA2 allele was associated with a different outcome in patients with two or three vessel-disease prospectively followed.
Methods: We performed PIA genotypes in 592 patients of MASS II Study (Medical, Angioplasty or Surgery Study), a randomized study to compare treatments for multivessel CAD and preserved left ventricle function. The duration of follow-up averaged 3 years. Differences in baseline characteristics among groups were analyzed using student's test for continuous variables and chi-scare test for categorical variables. Survival curves were calculated with the Kaplan-Meier method, and differences between the curves were evaluated with the log-rank statistic. We assessed the relationship between baseline variables and composite end-point using Cox proportional hazards survival model.
Results: There were no significant differences among individuals within each genotype group for baseline clinical characteristics and the randomized therapeutic option. In addition, the composite end-point of cardiac mortality and refractory angina requiring revascularization showed a trend towards a worse outcome in patients with the PIA2 allele. To further study the relationship between baseline variables, PIA genotype and composite end-points we stratified our analysis for risk factors known to have impact on the outcome of CAD. Interestingly, we disclose a significant association between the presence of PIA2 allele and the composite end-point only in the subgroup of current smoking patients ($p < 0.001$). In addition, in a Cox proportional hazards model adjusting for sex, age, previous myocardial infarction, hypertension, diabetes, and type of treatment, presence of the PIA2 allele was still associated with a 3.25 fold increase (IC) in the risk of presenting one of the composite end-points studied only in smoking patients ($p = 0.006$).
Conclusion: We showed a significant association between the PIA2 variant of platelet glycoprotein IIIa and a worse outcome in stable coronary artery disease patients in three years of follow-up. This association was only operant in smoking individuals thus characterizing an important gene-environment interaction. Our data have important implications for the prospect of future tailoring individual therapeutics.

P2269 The correlation between testosterone level and coronary artery disease

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It has been proposed that testosterone (T) may predispose to coronary artery disease (CAD) and may partially explain the sex difference of CAD. However, a low evidence exists about the correlation of T level and CAD. The aim of our study was to evaluate the correlation between T level and CAD.
Methods: We studied 69 men (M), (aged 30 - 70 years), without valvular heart disease, cancer prostate, without treatment with androgens, nizoral and corticosteroids who were admitted in the clinic of cardiology of the University Hospital Center in Tirana from february - may 2002 for diagnosis of CAD. They underwent exercise tress testing and/or coronaryarteriography and were divided in two groups(GR) in the base of their results: First group(IGR) (42 M without CAD) (negative response in >9,5MET in exercise stress testing and/or normal coronaryarteriography)and second group(IIGR) (27 M with CAD) verified in coronaryarteriography. All of them had serum T level measured in the day of the examination between 9:00 - 10:00 with radioimmunoessay method.
Results: There was no difference between two GR in age (47 ± 8.40 vs 53 ± 8.24 years), and diabetes (7.14% vs 18.5%), (p = NS). IIGR had more risk factors as smoking, ($p=0.001$) heredity, ($p = 0.001$), high blood pressure, ($p = 0.04$) and dyslipidemia, ($p = 0.02$). Mean T level for all M was 5.43 ng/ml. T level was significantly lower in IIGR with CAD (4.16 ± 1.24 ng/ml, range 0.11-6.1 ng/ml vs 6.26 ± 2.18 ng/ml, range 2.12 - 10.57 ng/ml in IGR,($p<0.001$). An inverse correlation between them ($r= -0.512$, $p=0.000$) existed which indicated that a low T level is an independent risk factor for CAD. In IIGR, 9 M had 1 vessel disease(VD), 6 M had 2 VD and 12 M had 3VD. T levels were respectively 4.84 ± 0.91 ng/ml vs 3.93 ± 0.90 ng/ml vs 3.76 ± 1.44 ng/ml, (p = NS)
Conclusion: Low T level is an independent risk factor for CAD. The lower T level, the more aggravated CAD.

P2270 Thyroid function is associated with presence and severity of coronary atherosclerosis

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Background: Overt hypothyroidism has been found to be associated with cardiovascular disease. Moreover, subclinical hypothyroidism is a strong indicator of risk for atherosclerosis and myocardial infarction. We hypothesized that variation of thyroid function within the normal range may influence the presence and severity of coronary atherosclerosis.
Methods: We studied a total of 100 consecutive men and women (59 men, 41 women, age 63.7 $\pm$ 11.0 years) who underwent coronary angiography. Blood was tested for serum thyrotropin, and for free tri-iodothyronine and free thyroxine. In addition to the assessment of thyroid function, conventional risk factors for coronary artery disease (CAD), clinical characteristics, and angiographic results of coronary artery assessment were obtained. Two experienced cardiologists blinded for clinical and laboratory data reviewed the cinefilms. CAD severity was scored as 0 for those with smooth normal epicardial coronary arteries, 0.5 for plaquing ($<$50% diameter stenosis), and 1, 2, or 3 for those with single-, double-, or triple-vessel epicardial coronary artery stenosis of $>$50%, respectively.
Results: CAD severity was scored as 0, 0.5, 1, 2 and 3 in 14, 26, 25, 22, and 13, respectively. Higher levels of serum free thyroid hormone concentrations were associated with decreased severity of CAD. Serum free tri-iodothyronine was 2.99 $\pm$ 0.33 pg/mL in patients with a CAD severity score of 0 to 1 and 2.74 $\pm$ 0.49 pg/mL in patients with a CAD severity score of 2 and 3 ($P<0.01$). Moreover, serum free thyroxine concentrations showed a trend to higher levels in CAD severity score 0 to 1 patients compared to CAD severity score 2 and 3 patients (11.65 $\pm$ 1.87 pg/mL versus 10.9 $\pm$ 2.3 pg/mL; P=0.09). Higher levels of serum thyrotropin were associated with increased severity of coronary atherosclerosis (1.37 $\pm$ 1.02 mU/L versus 1.98 $\pm$ 2.13 mU/L in severity score 0 to 1 versus CAD severity score 2 and 3 patients; p=0.049). When grouped into three subsets according to their serum free tri-iodothyronine levels ($<$ 2.79, 2.8 to 3.09, and $\geq$3.1 pg/mL) the prevalence of CAD score 2 and 3 was significantly higher in patients with low serum free tri-iodothyronine levels (48.5%) compared to patients with medium or high tri-iodothyronine concentrations (32.25% and 25% for the medium and upper terzile, respectively, P for trend <0.05).
Conclusion: These data in patients referred for coronary angiography suggest that variation of thyroid function within the statistical normal range may influence the presence and severity of coronary atherosclerosis.

P2271 The relationship between serum levels of testosterone and inflammatory cytokines in men with coronary artery disease

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Background: Coronary artery disease (CAD) is an inflammatory condition, with numerous cytokines proposed to mediate initiation, progression and rupture of the atherosclerotic plaque. Evidence also supports a protective role for testosterone in men with heart disease(1) and in the regulation of cytokine function (2). This study examined the relationship between serum cytokines and testosterone in men with either one, two or three vessel CAD.
Methods: Early morning blood samples were taken from 75 men with angiographically proven CAD ($>$75% occlusion). Serum levels of total and bioavailable testosterone were measured together with tumour necrosis factor-alpha (TNF-alpha), interleukin-1-beta (IL-1-beta) and interleukin-6 (IL-6). Comparisons were made between eugonadal men and those with total testosterone $<$7.5nmol/L or bio-available testosterone $<$2.5nmol/L.
Results: A significant step-wise increase in serum levels of IL-1-beta was seen in patients with either; one, two or three vessel CAD: 0.18 (0.04), 0.28 (0.08) and 0.45 (0.08) pg/ml respectively (P=0.03, ANOVA). No differences were seen in serum levels of TNF-alpha or IL-6 between groups. Eighteen subjects had low androgen levels. Compared with eugonadal subjects, levels of IL-1-beta were significantly elevated: 516 $\pm$ 127fg/ml v 253 $\pm$ 42fg/ml (p=0.03).Levels of TNF-alpha or IL-6 did not differ significantly between groups. A significant inverse relationship was seen between levels of IL-1-beta, and both total (rp=-0.262, p=0.024) and bio-available testosterone (rs=-0.283, p=0.015). No association was seen between cytokines TNF-alpha or IL-6, and total or bioavailable testosterone.
Conclusion: This study suggests that testosterone has immunosuppressive effects. The data supports the involvement of IL-1-beta in the development of CAD, and suggests that low testosterone levels may be associated with activation of this pro-inflammatory cytokine, in men with CAD. Whether this represents cause or effect is unclear but the data may support a rationale for androgen replacement therapy in men with CAD.
References: [1] English K.M. et al. (2000), Circ. 102: 1906-1911; [2] Pugh P.J. et al. (2001), Br. J. Pharmacol. 135: P131.

P2272 Cardioprotective effects of tranlational inhibitor Puromycin in rabbit myocardial ischaemia and reperfusion

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Myocardial tissue injury following ischemia and reperfusion is to a large amount related to neutrophil accumulation with subsequent generation of oxygen free radicals and protease release. These events trigger translocation of nuclear transcription factors (i.e., NFkB), mRNA synthesis and de novo protein expression. We studied the effect of Puromycin, known to block translation in a rabbit model of 60 min. myocardial ischemia followed by 3 hours of reperfusion. Puromycin (0,4mg/kg KG) or its vehicle were injected 5 minutes prior to reperfusion. Myocardial injury following Puromycin treatment was significantly reduced compared to vehicle treated animals (11%$\pm$2.7% vs 29%$\pm$2.1% necrosis related to ischemic myocardium, $p<0.05$). Plasma creatine kinase (CK) activity, another marker for myocardial injury, increased from 2.5$\pm$0.4 IU/g protein at baseline to 33.3$\pm$2.3 IU/g protein following 3 hours of reperfusion in the vehicle group. Administration of Puromycin significantly decreased plasma CK release throughout the reperfusion period (14.2 $\pm$ 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 Puromycin treated animals compared to the vehicle group ($p<0.01$). In the ischemic-reperfused zone of vehicle treated animals histologic analysis demonstrated increased leukocyte accumulation when compared to sham operated animals. In contrast, Puromycin treatment significantly decreased PMN accumulation compared to the vehicle group ($p<0.01$). Further, we utilized proteomic profiling to identify gene products involved in inflammatory injury that occurs as a consequence of myocardial ischemia and reperfusion. A pattern of 450 spots with identical positions was found on every gel of myocardial tissue of sham animals, vehicle and puromycin treated animals. We analyzed 11 spots, which were significantly altered, using mass spectrometry. Superoxide dismutase, alpha-crystallin-chain-B, mitochondrial stress protein, Mn SOD, creatine kinase, and troponin T were identified by mass spectrometry. All of these proteins were significantly decreased in the vehicle group following myocardial ischemia and reperfusion when we compared to sham treated animals (i.e. control myocardial tissue). Treatment with puromycin preserved levels of these structural and anti-inflammatory proteins. Our results demonstrate that blocking of translation with Puromycin resulted in a marked reduction of myocardial tissue injury following ischemia and reperfusion.

P2273 C-reactive protein, coronary disease activity and severity of coronary atherosclerosis in patients with angina pectoris

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Purpose: C-reactive protein (CRP) has been shown to predict adverse cardiovascular events in a variety of clinical settings. However, it is possible that elevated CRP may simply be a surrogate of coronary artery disease (CAD).We hypothesise that CRP is a marker of disease activity rather than an indicator of CAD. We aimed to assess whether CRP levels correlate with extent of CAD and the morphology of coronary stenoses, and whether CRP is an independent predictor of future cardiovascular events.
Methods: We studied 825 consecutive patients (mean age 63$\pm$10 years, 74% men), 700 with chronic stable angina(CSA) and 125 with acute coronary syndromes(ACS) without ST-segment elevation. The primary end-point was the composite of non-fatal acute myocardial infarction, readmission to hospital with Braunwald class IIIb unstable angina requiring treatment and/or urgent revascularization or cardiac death during the one year follow-up. High sensitivity CRP (hs-CRP) was measured on the COBAS Integra (Roche Diagnostics Limited, Lewes, East Sussex, UK). Blood samples were drawn at admission to hospital in ACS patients and at the time of diagnostic coronary angiography in CSA patients.
Results: 68 CSA patients (10%) suffered the combined end-point. Serum hs-CRP level was higher in these patients compared to those who did not have events (log10 CRP 0.50$\pm$0.6 vs 0.35$\pm$0.5;P=0.02), even after adjustment using multivariate analysis. Hs-CRP was also significantly higher in patients with ACS compared to CSA patients (log10 CRP 0.55$\pm$0.7 vs 0.37$\pm$0.5; P=0.005). Hs-CRP was not significantly correlated with CAD extent or severity. However, hs-CRP correlated with number of angiographic complex coronary artery stenoses (r=0.36, p=0.03) in patients with ACS. After backward stepwise multiple regression analysis, the independent predictors of number of angiographic complex lesions in ACS patients were number of diseased coronary vessels with $\geq$50% lumen reduction (P=0.002) and hs-CRP levels (P=0.03).
Conclusion: CRP concentrations predict future cardiovascular events in patients with CSA, independently of CAD severity. CRP concentrations are higher in patients with ACS and correlate with number of complex lesions in these patients. Therefore, CRP is a marker of disease activity and not an indicator of CAD severity or extent.

P2274 S100 protein and its relation to cerebral microemboli in on-pump and off-pump coronary artery surgery

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Objectives: S100 protein has been used as a marker for cerebral injury. Studies have reported lower levels in off-pump coronary artery surgery (CABG) compared to on-pump surgery. However, most of these are flawed as S100 protein from extracerebral sources were included (e.g. blood from cardiotomy suckers). Microemboli (high intensity transcranial signals or HITS) during CABG have been implicated as a cause of postoperative neurocognitive dysfunction. The aim of this study was to compare the number of HITS during on-pump and off-pump CABG, measure S100 accurately by excluding extracerebral sources, and assess whether any changes in S100 were related to HITS.
Methods: 35 patients admitted for CABG were randomised to on-pump or off-pump surgery. Bilateral transcranial Doppler ultrasonography was performed on the middle cerebral artery to detect HITS. S100 was measured preoperatively, at termination of bypass in on-pump surgery, at completion of anastomoses in off-pump surgery, and 48 hours postoperatively. A cell saver was used instead of cardiotomy suction in the on-pump group, in order to limit extracerebral contamination of the S100 assay.
Results: The number of HITS were 2016 (SD 1897) during on-pump and 16 (SD 21) during off-pump surgery ($p<0.0001$). In on-pump surgery S100 increased from 0.05 $\pm$0.03 μg/l to 0.50$\pm$0.028 μg/l ($p<0.0001$) at termination of bypass. In off-pump surgery S100 increased from 0.08$\pm$0.05 μg/l to 0.35$\pm$0.20 μg/l ($p<0.0001$) at completion of anastomoses. The mean intraoperative S100 in the on-pump group was 1.6 times greater compared to that in the off-pump group (95% CI 0.88-2.8; p=0.1). There was no evidence of a relationship between intraoperative S100 and HITS in both groups. By 48 hours S100 decreased to 0.22$\pm$0.14 μg/l in the on-pump and 0.21$\pm$0.09 μg/l in the off-pump group ($p<0.0001$ compared to preoperative value).
Conclusions: We have demonstrated a significantly higher number of cerebral microemboli in patients undergoing on-pump compared to off-pump CABG. By limiting contamination from extracerebral sources, we have shown no significant difference in S100 between on-pump and off-pump CABG. Furthermore, we have shown no link between cerebral microemboli and S100 protein.

P2275 Plasma homocysteine levels independently correlate with angiographic extension of coronary artery disease

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Objectives: We evaluated the influence of plasma homocysteine (Hcy) levels on the presence of angiographically proven coronary artery disease (CAD) and on the extent of coronary atherosclerosis.
Background: Several studies have reported that elevated plasma Hcy are related to an increased risk of cardiovascular disease. The correlation between Hcy and extension of CAD at the angiographic study was instead not well established.
Methods: In this cross-sectional study, we recruited 234 consecutive patients undergoing selective coronary angiography in our Institution. In all patients we measured total fasting plasma homocysteine levels using high performance liquid cromatography (HPLC). CAD was diagnosed by the presence of a significant stenosis (at least 50% of the lumen area) in one or more of the major epicardial coronary vessels. With this criteria 151 patients had angiographically proven CAD and 83 had not. The extent of coronary atherosclerosis was assessed by the number of major epicardial coronary vessels with significant stenosis; left main disease was countered as disease of two vessels.
Results: Plasma Hcy is independently associated with the presence of CAD in a multivariate analysis (13.7$\pm$4.7 μmol/l vs 10.8$\pm$3.8μmol/l; Odds Ratio 1.82 [95%confidence interval 1.37-2.42]; $p<0.001$). The number of stenotic vessels significantly correlates with Hcy levels (one vessel disease 12.9$\pm$4.2 μmol/l, two vessels disease 13.2$\pm$4.9μmol/l, three vessels disease 14.6$\pm$4.8μmol/l; $p<0.001$, analysis performed by ANOVA).

Hcy and extent of CAD

	0 vessel (n=83)	1 vessel (n=37)	2 vessels (n=51)	3 vessels (n=63)	p
Homocysteine	10.8$\pm$3.8	12.9$\pm$4.2	13.1$\pm$4.9	14.6$\pm$4.8	<0.001

Conclusions: We conclude that total plasma fasting Hcy is a independent risk factor for CAD. In this study we found a strong correlation between Hcy levels and the extent of CAD. This support the role of homocysteine in the developement of coronary atherosclerosis.

P2276 Paclitaxels antiproliferative effect reduces vein graft failure in-vitro and in a porcine model of saphenous vein interposition grafting

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Objective: Recent use of paclitaxel with eluting-stent technology has confirmed its ability to inhibit neointimal proliferation following vessel injury, through interuption of the cell cycle at the metaphase/anaphase boundary. We proposed that paclitaxel pre-treatment of saphenous vein prior to grafting would inhibit neointimal proliferation and consequently reduce late vein graft failure.
Methods: In-vitro evaluation of short-term paclitaxel exposure on neointimal proliferation involved saphenous vein pre-treatment by suspension in Paclitaxel (10 μmol/L) or vehicle control, for 1 hour, prior to plating and 14-day organ culture. Twenty-four hours prior to analysis, vein samples were exposed to bromodeoxyuridine (BrdU), to allow assessment of cell proliferation. Samples were analysed histologically, neointimal thickness, mean cell density and a ratio of proliferating vs. non-proliferating cells was calculated for paclitaxel-treated segments (n=8) and vehicle-treated controls (n=7). Subsequently, ten Large-White pigs(25-33.5 kg) underwent bilateral saphenous vein to carotid artery interposition grafting. Each animal received a paclitaxel (10 μmol/L) treated and a vehicle control graft. Animals were sacrificed at 28 days, vein grafts were harvested and pressure fixed prior to histological/morphometric analysis.
Results: In-vitro paclitaxel exposure resulted in a significant reduction in neointimal thickness, compared with vehicle control: 77.80 $\pm$ 48.80mm vs. 148.35 $\pm$ 82.73mm (p=0.008). Cell proliferation was reduced with exposure to paclitaxel (p=0.049), but cell density (p=0.55) did not significantly differ from control. Only patent grafts were included in the in-vivo analysis - see table.

Parameter	Control (n=8)	Treated (n=8)	p value
Lumen Area (mm^2)	30.18 $\pm$ 13.75	25.71 $\pm$ 13.81	0.20
Neointimal Area (mm^2)	2.59 $\pm$ 1.17	1.72 $\pm$ 0.94	0.002
Medial Area (mm^2)	6.78 $\pm$ 1.74	5.24 $\pm$ 1.31	0.0002
eointimal/Medial Ratio	0.38 $\pm$ 0.14	0.32 $\pm$ 0.14	0.08

Conclusion: Our data demonstrates that paclitaxel pre-treatment reduces neointima formation by inhibiting cell proliferation. The results from our in-vivo studies suggest that paclitaxel may be a highly attractive candidate for the prevention of late vein graft failure.

P2277 Plasma brain natriuretic peptide, myocardial performance index and coronary heart disease

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BNP is a peptide hormone secreted from ventricular myocytes in response to ventricular volume expansion and pressure overload. **Purpose:** to assess the value of MPI (sum of isovolumetric contraction and relaxation times divided by ejection time) and plasma levels of BNP and the N-terminal split product of the prohormone, Nt-proBNP, for the early diagnosis of left ventricular dysfunction (LVD) in patients with CHD. **Methods:** Investigation of all patients referred during a period of 16 months from general practitioners for the first evaluation of LVD as the cause of untreated dyspnoea. The examiner performing the assessment of left ventricular function was blinded to the hormone levels. Plasma levels of BNP and Nt-proBNP were measured under standardized conditions. Systolic dysfunction (SD) was defined as an ejection fraction <40% and isolated diastolic dysfunction (IDD) as an ejection fraction >45% in combination with abnormal diastolic flow patterns assessed by echocardiography.Time intervals for calculating MPI were measured from mitral inflow and LV outflow recordings. **Results:** The mean age was 62.4 years (SD$\pm$12.4) and 54% were men. Fifty-four patients had manifestations of CHD with 19 patients having SD, 20 patients having IDD and 15 patients with no signs of LVD (NLVD). In the SD group the median MPI was 0.79 (0.92/0.6, i.e. an upper quartile of 0.92 and a lower quartile of 0.6). The median BNP concentration was 363 pg/ml (489/129 pg/ml)and the median Nt-proBNP concentration was 2394 pg/ml (4497/1177 pg/ml). In the IDD group the median MPI was 0.5 (0.55/0.46), median BNP concentration was 42 pg/ml (72/31 pg/ml) and median Nt-proBNP concentration was 222 pg/ml (425/168 pg/ml). In the NLVD group the median MPI was 0.38 (0.39/0.36). The median BNP concentration was 8 pg/ml (16/1 pg/ml) and the median Nt-proBNP concentration was 69 pg/ml (92/25 pg/ml). The MPI, BNP and Nt-proBNP concentrations were all significantly different among the three considered groups (IDD versus NLVD $p<0.0001$; SD versus IDD $p<0.0001$).
Conclusion: plasma BNP or Nt-proBNP concentrations combined with MPI seem to be important parameters in early detection of LVD in patients with a history of CHD.

Patiens	MPI	BNP (pg/ml)	Nt-proBNP (pg/ml)
NLVD	0.38 (0.39/0.36)	8 (16/1)	69 (92/25)
IDD	0.50 (0.55/0.46)	42 (72/31)	222 (425/168)
SD	0.79 (0.92/0.60)	363 (489/129)	2394 (4497/1177)

VALVE INTERVENTIONS

P2278 Unexpected findings in anticoagulation management in patients with valvular heart disease after valve surgery

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The management of anticoagulation (AC) has important prognostic implications in patients (pts) with valve prostheses.
One of the objectives of the Euro Heart Survey (EHS) on valvular heart disease was to identify the management of AC after valve replacement and, whenever possible, to evaluate the rationale of the treatment modalities.
Methods: Among 5001 pts enrolled into the survey between April and July 2001, 1454 had already undergone surgery before inclusion and were evaluated for chronic AC. In addition, 1269 pts underwent valve surgery during the survey, allowing for assessment of postoperative AC.
Results: In the group of 1454 pts with chronic AC, oral AC were used in 98% of pts with mechanical prostheses, 40% for bioprostheses, and 52% after valve repair (VR). Atrial fibrillation was the reason for oral AC in 71% of pts with bioprostheses and 83% with VR.
In the early post-operative course of the 1269 pts who were operated on during the survey, unfractionated heparin was used in 45% and low molecular weight heparin(LMWH) in 41%. At discharge, oral anticoagulants were prescribed in 96% of pts with mechanical valves, 59% with bioprostheses, and 76% after VR. The reason for oral AC at discharge was atrial fibrillation in 30% of pts with bioprostheses and 29% after VR. The percentage of pts who had received education for AC at discharge was 23%.
Conclusion: The EHS shows that: 1) In the chronic phase, in nearly half of pts, one of the advantages of bioprostheses or VR is obviated by the need for oral AC, mainly due to atrial fibrillation. 2) In the early post-operative period, LMWH is frequently used although not approved in this indication. 3)At discharge, a high proportion of pts with bioprostheses or VR did not receive oral AC although their use is recommended during the first 3 post-operative months. 4) Education is seldom applied. Thus overall management of anticoagulation needs to be improved after valve surgery.

P2279 An eight year experience with the Ross procedure

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Background: The Ross Procedure continues to gain acceptance as a primary option for aortic valve replacement (AVR) in young patients. We report on our first 117 Ross Procedures.
Methods: Data was compiled from the STS database, chart reviews, patient questionnaires and the Ross Registry. The Cusum method was used to analyze "learning curve".
Results: There were 3 mortalities (2.6%), from heparin-induced thrombocytopenia, pulmonary embolism, and MI. Complications included: 5(4.3%) with reoperation for bleeding, 2(1.7%) with transient renal failure requiring dialysis and 2(1.7%) with heart block requiring PPM. There were no strokes. Six (5.1%) were readmitted within 30 days; 2 for delayed tamponade and 4 for atrial fibrillation. Four patients have undergone autograft reoperation, 2 required mechanical AVR, 2 repairs of an annular false aneurysm. One patient required pulmonary homograft replacement. Follow-up echo data showed 7 patients (6.0%) had mild to moderate AI and one (0.9%) had moderate to severe AI. Questionnaire response (88%) revealed 90% of patients experienced no significant limitations in activities of daily living (ADL).
The learning curve dropped below 180 minutes perfusion time after 35 patients. In the last 82 patients, there were no autograft reoperations, 2(1.7%) reoperations for bleeding, and only 4(3.4%) had mild AI on follow-up echo.
Conclusion: The Ross Procedure carries a low morbidity and mortality, has few autograft or homograft failures in the first 8 years and no limitation to ADL for the patients. Once a surgeon has surpassed the learning curve, the Ross Procedure should be considered the primary operation for young patients with aortic valve disease.

P2280 Prevalence of severe pulmonary hypertension in 540 consecutive patients with mitral stenosis undergoing mitral balloon valvotomy: immediate and long-term results

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The prevalence of severe pulmonary hypertension (PH) in pts with severe mitral stenosis (MS) and its long-term regression after mitral balloon valvotomy (MBV) are not well established. **Method:** Data of 540 consecutive pts from our MBV database were analyzed. Pts were divided according to systolic pulmonary artery pressure (PAP) at the time of MBV into 3 groups. Group A (PAP $<$ 50 mmHg; N=335); group B (PAP 50-79 mmHg: N=178); and group C (PAP $\geq$ 80 mmHg: N=27). Pts were evaluated clinically and echocardiographically 3 months after MBV and yearly thereafter for up to 13 years. **Results:** No deaths were encountered. The prevalence of mild, moderate and severe pulmonary hypertension prior to MBV in these 540 pts were 62%, 33%, and 5%, respectively (Table 1). Although pts in group C had smaller pre-valvotomy mitral valve area (MVA) and higher PAP than groups A and B, there were no differences in MVA or in PAP among the three groups at long-term follow-up.

Parameter		Group A N=335 (62%)	Group B N=178 (33%)	Group C N=27 (5%)	P Value
Age (y)		31 ± 10.5	30.0 ± 11.4	27.5 ± 8.9	0.25
Catheter PA	B	38 ± 10	59 ± 7.7	96 ± 16.1	<0.0001
Pressure (mmHg)	I	32 ± 9.7	46 ± 11.5	71 ± 13.9	<0.0001
Total pulmonary resistance	B	611 ± 231	919 ± 388	1515 ± 377	<0.0001
(dyn/sec/cm^{-5})	I	452 ± 197	633 ± 339	1030 ± 420	<0.0001
PVR (dyn/sec/cm^{-5})	B	163 ± 120	332 ± 220	801 ± 304	<0.0001
	I	160 ± 108	290 ± 209	675 ± 324	<0.0001
Left atrial pressure (mmHg)	B	23.2 ± 5.4	27.9 ± 5.6	29 ± 4.9	<0.001
	I	14.4 ± 4	16.6 ± 5.2	14.5 ± 5.5	<0.0001
MVA (cm^2)	B	0.94 ± 0.18	0.87 ± 0.20	0.81 ± 0.18	<0.001
	I	1.95 ± 0.32	1.93 ± 0.29	1.99 ± 0.36	0.69
	F	1.75 ± 0.66	1.72 ± 0.35	1.72 ± 0.34	0.83
Doppler PAP (mmHg)	B	40 ± 13	53 ± 16.8	75 ± 18.5	<0.0001
	F	29 ± 8	32 ± 13	30 ± 6	0.03

B = before; I = immediately after; F = follow-up; PVR = pulmonary vascular resistance

Conclusion: (1) Moderate or severe PH is present in 38% of pts with severe MS; (2) MBV is safe and effective in treating pts with MS and severe PH; and (3) severe PH regresses to normal after successful MBV.

P2281 Short-term effect of oral anticoagulation on documented left atrial thrombi in candidates for percutaneous transvenous mitral commissurotomy

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Background: The presence of left atrial thrombus (LAT) in mitral stenosis patients is a contraindication to percutaneous transvenous mitral commissurotomy (PTMC). Although resolution of LAT after long-term oral anticoagulant therapy can enhance the possibility of safely performing PTMC. Its short-term effect, which would be much more clinically important, has been less clearly established. **Objectives:** To estimate the disappearance rate of documented LAT among candidates for PTMC who were treating with oral anticoagulation for 6 months and to determine its significant predictors. **Design:** Prospective cohort study. **Methods:** Between August 1996 and February 2002, a total of 687 consecutive PTMC candidates underwent both transthoracic and multiplane transesophageal echocardiographic studies (TTE, TEE). Of these, 219 patients demonstrated LAT by TEE and were started oral anticoagulation (INR 2.0 to 3.0). The fates of the left atrial thrombi at the first 6th-month follow-up were assessed. **Results:** Among 219 PTMC candidates with documented LAT (mean age 39.6 ± 7.4 years, range 19-62 years; 73% females), complete resolution of LAT was demonstrated in 53 cases at the first 6th-month follow-up, with an overall disappearance rate of 24.2% (95%CI: 18.5% to 29.9%). All 53 patients subsequently underwent successful PTMC. None of the cases, with LAT in the left atrial body (n=27), had thrombus resolution. Among the 166 patients whose LAT persisted, the thrombus size had nevertheless been reduced by approximately 20% from the baseline ($p<0.001$). By multiple logistic regression analysis, the significant predictors of thrombus resolution included a clinical status of New York Heart Association functional class 1 or 2 (OR=6.42: 95%CI=2.03, 20.26), a thrombus size less than 1.6 cm^2 at the first study (18.07: 6.76, 48.33), left atrial spontaneous echo contrast of less than or equal to Grade 1 (6.62: 2.21, 19.86), and INR of greater than or equal to 2.5 (10.91: 2.78, 42.85). **Conclusions:** About a quarter of PTMC candidates with LAT could avoid heart surgery and safely undergo PTMC after 6 months of oral anticoagulant therapy as their thrombus disappeared. Patients with less clinical severity, smaller size of thrombus, less severity of grading of left atrial spontaneous echo contrast, and tolerance to high INR could enhance such an outcome.

P2282 A prognostic model for good immediate result of percutaneous mitral valvuloplasty for mitral stenosis patients

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Purpose: Currently, PMV has been widely applied for symptomatic MS patients. Selection of patients for PMV based on mitral valve (MV) morphology alone was not appropriate. The purpose of this study is to develop and validate the prognostic model to predict the immediate results of percutaneous mitral valvuloplasty (PMV) that can be used to improve the selection of candidates for PMV in Thailand.
Methods: From December 1993 to September 2000, PMV was performed in 1,575 patients. Mean age was 40 years (SD=11) and mean MV score was 8.4 (SD=1.6). Technical failure occurred in 10 patients. Good immediate results, defined as mitral valve area (MVA) $\geq$1.5 cm^2 with mitral regurgitation (MR) $<$3/4 Sellers' grade after procedure, were obtained in 1,018 patients (65%). The 1,379 effective procedures using Inoue technique were randomly allocated into two subsets: one to derive the model and another to validate it.
Results: The prognostic model included six predictors: age, gender, previous PMV, pre-procedural MVA, pre-procedural left atrial diameter, and MV score. The model was well calibrated (goodness-of-fit test, p-value=0.86) and well discriminated (area under the receiver-operating characteristics [ROC] curve=0.81). Model performance in the validating set of 459 procedures was good (area under the ROC curve=0.80; goodness-of-fit test, p-value=0.45). When the cut-off point of predicted probability of 0.65 was chosen, the model had a sensitivity of 79%, a specificity of 70%, a positive predictive value of 81%, and a negative predictive value of 66%.
Conclusions: Selection the candidates of PMV should consider the predicted probabilities of good results obtained from the model. The prognostic model does provide the useful information to decision making of both patients and physicians.

P2283 Randomized comparison between Inoue balloon and metallic commissurotome in the treatment of mitral stenosis: immediate results, 6-month and 3-year follow-up

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Background: The long-term results of percutaneous mitral valvuloplasty (PMV) with the Inoue balloon (IB) are well established, so as the immediate results of the procedure using the metallic commissurotome (MC). The MC can be reused several times after proper resterilization, decreasing the cost of the procedure. There are no comparative data on longer outcome of both techniques on a randomized basis.
Purpose: to describe the comparative immediate results, short- and medium-term follow-up (FU) of PMV using either the IB or the MC technique.
Material and Methods: 50 consecutive patients (pts) with rheumatic mitral stenosis (mitral valve area – MVA$<$1.5 cm^2) and FC $\geq$2 NYHA were randomized to PMV using the IB (n=27, mean age=37.3$\pm$11.9 years) or the MC (n=23, mean age=39.9$\pm$11.1 years) technique. There were no differences between the groups regarding baseline clinical characteristics. Six months and 3 years after the procedure, the pts were asked to return for clinical and echocardiographic FU.
Results: The success rate (MVA $\geq$1.5 cm^2 with no mitral regurgitation (MR) $>$2/4 – Sellers) was 100% in the IB group and 91.3% in the MC group (p=0.15)-2 pts in this group developed MR grade 3/4, requiring elective surgery. Two pts in the IB group underwent late ($>$6 months) valve replacement because of progressive MR. All of the procedures in the MC group were performed with the same device. The immediate and FU results are depicted below.

	IB	MC	p-value
Wilkins' score/16	7.07$\pm$1.61	7.17$\pm$1.58	0.82
MVA pre (cm^2)	1.11$\pm$0.19	1.09$\pm$0.17	0.40
MVA post (cm^2)	2.00$\pm$0.36	2.17$\pm$0.13	0.04
MVA 6m FU (cm^2)	1.98$\pm$0.38	2.06$\pm$0.27	0.22
MVA 3y FU (cm^2)	1.87$\pm$0.34	1.86$\pm$0.32	0.89
Restenosis (n)	2	3	0.65

Conclusions: The MC provides greater immediate MVA than the IB after PMV, but after 6 months and after 3 years of FU this difference is not significant anymore. This suggests valve stretching as an important mechanism of valve dilation with the MC. The restenosis rate with both techniques are similarly low after 3-year FU, making the MC superior to the IB in terms of cost-effectiveness.

P2284 Early detection of complications related to heart valve prostheses by quasi-continuous acoustic monitoring

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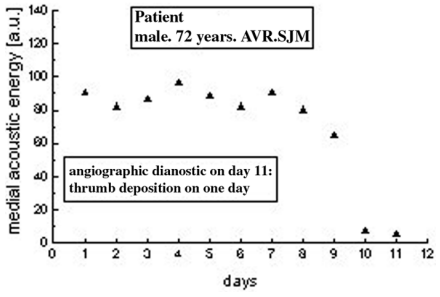
Mechanical heart valve prosthesis still remain a risk for thrombosis. Every year about 2 ... 6% of the mechanical heart valve bearers suffer a severe complication due to the valve's tendency for thromb deposition. In the current prevention plans patients consult the physician for echocardiographic valve inspections only a few times a year, whereas a thrombus on the valve grows in about 72 h. Therefore a thrombosis on the valve is usually not discovered and treated in an early stadium.
We tested a method of quasi-continuous and external (non-invasive) acoustic monitoring of the heart valve. A new monitoring device enables the heart valve bearer to check the implant in a simple and 1 minute short procedure every day. By analysis of the characteristic sound emission a very distinct acoustic fingerprint of the implanted valve can be determined. The characteristics of the acoustic fingerprint are: peaks in the acoustic spectra, energy in frequency bands, decay times in the bands, and time separated signals in valves with multiple leafs. For attendant examinations thrombs were simulated in a pig experiment and in a water test setup.



The acoustic pattern undergoes characteristic changes during the formation of a thrombosis, clearly recognized by the apparatus. First results clearly indicate the detection of thrombus formation and the feasibility of this method. The figure shows the record of the acoustic energy before and during acute valve thrombosis. In conclusion, thromb deposition on heart valve prostheses can be detected in an early stadium by daily acoustic self testing. Therefore almost immediately – on demand - further diagnosis and an early treatment can set in, and more serious and subsequent complications may be avoided.

P2285 Could statins slow the degeneration of aortic biological prosthesis?

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Background: It has been recently suggested in retrospective studies that statins could slow the progression of aortic valve stenosis. There is no information in the literature about a possible effect of statins in slowing the degeneration of aortic biological prosthesis.
Methods: From our database 1988-2002, we retrospectively selected all patients with aortic biological prosthesis with at least 2 echocardiographic examinations $>$6 months one apart of the other. The study population consisted of 141 patients (85 males, 56 females; mean age 70$\pm$10 years) followed for 47$\pm$36 months (range 6-151). During the follow-up, 18 patients (13%) were treated with statins, while 123 patients were not. At the first examination, there were no significant differences between the two groups according to age, sex, peak aortic velocity, degree of aortic insufficiency, left ventricular ejection fraction, prevalence of hypertension, diabetes, smoking. Patients treated with statins were more likely to have a history of hypercholesterolemia (p$<$0.01) and proven coronary artery disease (p$<$0.01). The duration of follow-up was similar in the two groups.
Results: The annual rate of progression of peak aortic velocity was lower in statin-treated patients (0.04 m/s/y vs 0.12 m/s/y; p=0.027). A rate $\geq$0.2 m/s/y was found in 29/123 of not-treated patients (24%) and in 0/18 (0%) of statin-treated patients (p=0.046). A worsening of aortic insufficiency $\geq$ 1/3 degrees was observed in 2/18 (11%) of statin-treated patients and in 43/123 (35%) of not-treated patients (p=0.079). A severe stenosis ($\geq$4 m/s) and/or a severe insufficiency of the prosthesis was reached by 17/123 (14%) of not-treated patients and by 0/18 (0%) of statin treated patients (p=0.196).
Conclusion: In our study, statin-treated patients with aortic biological prosthesis showed a significant lower annual rate of progression of peak aortic velocity. There was also a trend of reduction in worsening of aortic insufficiency in the statin group. To our knowledge this is the first demonstration of a possibile positive effect of statins in preventing the aortic biological prosthesis degeneration. A prospective randomized controlled trial is needed to confirm this first retrospective observation.

P2286 Prognostic value of brain-type natriuretic peptide in aortic stenosis

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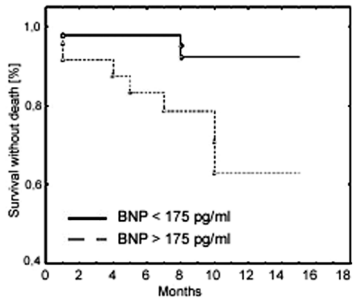
Background: B-type Natriuretic Peptide is elevated in patients with heart failure and aortic stenosis (AS).
Methods and Results: Seventy patients with severe AS and preserved left ventricular function were prospectively followed. C terminal B-type Natriuretic Peptide (BNP) serum level was assessed at the enrollment and was compared to echocardiography, clinical characteristics and outcome. The study population comprised 40 men and 30 women [mean age, 72±11 years]; mean AVA, 0.7±0.2cm^2; transaortic mean pressure gradient, 51±21mmHg and left ventricular fraction shortening, 39±9%. BNP values differed significantly in asymptomatic patients [n = 17] compared to symptomatic patients [n=50]: 52±50 pg/ml vs 185±154 pg/ml respectively, $p<0.001$. Mean BNP levels were significantly associated with NYHA functional class [$p < 0.001$]. BNP > 70 pg/ml detects symptomatic patients with a sensitivity, specificity and accuracy of 83%, 82% and 83% respectively. Correlation to aortic valve area was weak but significative ($r^2 = 0.16$, $p < 0.0001$). By multivariate analysis, BNP>60 pg/ml was an independent predictor for death or aortic valve replacement (OR 2.8, $p < 0.05$). Five patients death from cardiovascular reason before surgery have a BNP > 175pg/ml including one asymptomatic patient died from a sudden death. BNP > 175 pg/ml was the only independent predictor value for death (OR 5.8, $p < 0.05$). According to Kaplan-Meier analysis, survival was significantly better for patients with a BNP below 175 pg/ml (figure).



Conclusions: BNP serum levels is helpful for the clinical evaluation of patients with severe AS and unclear symptoms. Indication for surgery should be taken for patients with high BNP levels considering the predictive value of this marker for adverse cardiac events or death.Kaplan-Meier cumulates survival rates

P2287 Plasma brain natriuretic peptide: a prognostic marker in valvular aortic stensosis?

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Surgery in asymptomatic aortic stenosis(AS) is controversial. Recent guidelines from the European Cardiac Society recommend asymptomatic patients have exercise testing at 6-12 month intervals to assess symptom generation, exercise capacity and blood pressure response. Brain natriuretic peptide (BNP), produced by left ventricular myocardium in response to wall stress, is elevated in AS and is a strong predictor of outcome following myocardial infarction.
Methods: 34 patients with haemodynamically significant AS and 18 controls underwent maximal symptom limited cardiopulmonary exercise testing (Bruce protocol) with determination of resting plasma BNP. Proven CAD, AF, COPD and diabetes were exclusions. Patients were divided into symptomatic (Sym n=17) and asymptomatic (Asy n=17) groups. Resting BNP was examined as a predictor of exercise variables by univariate and multivariate analysis.
Results: see table. Symptomatic patients were older than asymptomatic and control subjects. Sym AS was associated with reduced exercise capacity (corrected for age and sex), an enhanced ventilatory (VE/VCO2) and a blunted SBP response to exercise. BNP was increased in both AS groups compared to controls. BNP was independently associated with age (r=0.51, p=0.01) and mean pressure gradient (r=0.54, p=0.05) in AS. BNP was higher in NYHA III (192.5, 27-407) v NYHA II (33.5, 16-74) and NYHA I (16, 9-36 pg/ml) p=0.009. In AS, BNP predicted exercise capacity (r=-0.40, p=0.02) and SBP response to exercise (r=-0.58, $p<0.001$) independent of age and stenosis severity. In controls, BNP was not correlated with exercise performance.
Conclusion: BNP is increased in severely symptomatic AS and is an independent predictor of exercise capacity and SBP response to exercise. Serial monitoring of plasma BNP may obviate the need for repeated exercise testing and help optimise the timing of surgery in asymptomatic aortic stenosis patients.

BNP and exercise performance

	Age	AVA cm^2	Ex time (% pred)	Exercise VE/VCO2	SBP Ex-rest	BNP (pg/ml)
Controls	50.3 (18)	1.6 (0.5)	124 (16)	28.4 (6)	64 (19)	16 (4-17)
Asy AS	47.1 (20)	0.7 (0.4)	84 (28)	29.7 (6)	37 (25)	62 (10-86)
Sym AS	67.7 (11)	0.5 (0.2)	53 (27)	34.9 (8)	19 (22)	148 (22-228)
p	<0.001***	<0.001**	<0.01*	<0.001***	<0.001*	<0.001**

Data = mean (SD), BNP=median (IQ range). *All groups different. **AS v controls. ***Sym AS v Asy AS/controls

INFARCT AND VIABILITY IMAGING

P2288 Prediction of functional recovery in chronic ischaemic heart disease: head-to-head comparison of ^{18}F-fluorodeoxyglucose positron emission tomography and contrast-enhanced magnetic resonance imaging

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Contrast-enhanced (ce) magnetic resonance imaging (MRI) is comparable with ^{18}F-fluorodeoxyglucose positron emission tomography (PET) for the assessment of myocardial viability and predicts functional recovery after revascularization. A head-to-head comparison of ceMRI and PET for the prediction of functional recovery has not yet been performed. We investigated 17 patients (65±9 years) with chronic ischemic heart disease and left ventricular dysfunction (EF 29±12%) with ceMRI (inversion-recovery gradient-echo sequence after administration of 0.2 mmol/kg gadolinium; 1.5 T, Intera, Philips, Best, The Netherlands) and PET (ECAT, Siemens, Erlangen, Germany). Cine MRI (true-Fisp) was performed at baseline and at 6 month follow-up. 13 patients received myocardial revascularization (PTCA in 10, CABG in 3) and 4 patients were managed medically. Data were analyzed using the 17-segment model as proposed by the Amercian Heart Association. The segmental extent of hyperenhancement was quantified with ceMRI. A threshold of 50% hyperenhancement was set as cutoff for viability. This threshold was derived from a previous study directly comparing ceMRI and PET for myocardial viability assessment. Wall motion was assessed qualitatively using a 5-point scale (normal to dyskinesia).
Results: In the patients who underwent revascularization EF improved from 33±11% to 42±9% ($p<0.001$) and mean wall motion score of severely dysfunctional segments improved from 3.5±0.6 to 1.6±0.5 ($p<0.001$). Improved dysfunctional segments showed less hyperenhancement (16±23% vs. 61±30%; $p<0.001$) and higher FDG uptake (82±21% vs. 59±19%; $p<0.001$) compared to dysfunctional segments without improvement. Wall motion at follow-up was related to the amount of hyperenhancement by ceMRI (r=0.74; $p<0.001$) and FDG uptake by PET (r=0.48; $p<0.001$). Accuracy for the prediction of functional improvement was 82% with ceMRI and 75% with PET. In the medically treated patients EF (17±8% vs. 18±6%; p=ns) and mean wall motion score of severely dysfunctional segments (3.6±0.5 vs. 3.5±0.6; p=ns) did not improve. Functional improvement at follow-up was only observed in a minority of segments assessed viable by ceMRI (14%) and PET (18%) while none of the segments scored non-viable improved.
Conclusions: Recovery of segmental function is closely related to the amount of scar by ceMRI. CeMRI is comparable to PET for the prediction of functional recovery after myocardial revascularization and may be an alternative method for the assessment of myocardial viabilty.

P2289 Quantification of myocardial infarct size: comparison of contrast-enhanced magnetic resonance imaging and cardiac enzyme indices

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Introduction Prognosis of patients with acute myocardial infarction depends on the mass of infarcted tissue and remaining left ventricular function. Contrast-enhanced magnetic resonance imaging (ceMRI) allows direct visualization and quantification of myocardial necrosis. For evaluation of the extent of infarcted myocardium, we compared enzyme indices of reperfused and non-reperfused myocardial infarctions (MI) to the MRI measurements of infarct size.
Methods 50 patients (74% male, mean age: 62.5 $\pm$11y) who suffered a first acute myocardial infarction underwent contrast-enhanced MRI on a 1.5 T scanner (SONATA, Siemens) within 7 days of MI. In 34 patients, reperfusion had been achieved by acute percutaneous coronary intervention. Acquisition of short axis slices without inter-slice gap was performed before and 10 minutes after injection of Gd-DPTA (MAGNEVIST®, Schering) (0,1mmol/kg) with an inversion recovery TurboFLASH sequence (TE 4.0ms, TR 8.0ms, flip angle 20°) in multiple breath-holds. The pattern of hyperenhancement representing MI was quantified by planimetry and consequently the mass of infarcted tissue and its percentage of left ventricular mass were calculated. Based on serial measurements of creatin kinase-myocardial band (CKMB) and troponin I (TnI) every 6 hours from onset of MI to normalization of cardiac enzymes, peak values and area under the curve (AUC) were determined. Simple regression analysis was performed for comparison of MRI data and enzyme indices.
Results In patients with reperfusion therapy, AUC of CKMB ($r=0.84$, $p<0.01$) and TnI ($r=0.8$, $p<0.01$) correlated closely to the mass of infarcted myocardium. Correlation for peak CKMB ($r=0.86$, $p<0.01$) and peak TnI ($r=0.79$, $p<0.01$) to infarct size were comparable. In patients who were not treated with acute revascularisation, peak values showed closer correlation ($r=0.6$, $p<0.01$ for CKMB and $r=0.52$, $p<0.01$ for TnI) to infarct size than AUC measurements ($r=0.5$, $p<0.01$ for CKMB and $r=0.4$, $p<0.01$ for TnI), but the overall relationship was poorer.
Conclusion AUC measurements and peak values of CKMB and TnI correlate closely to the mass of infarcted myocardium as assessed by ceMRI, especially in patients with reperfusion therapy.
In patients without acute reperfusion therapy, AUC measurements and peak values of CKMB and TnI show poor correlation to infarct size.

P2290 Assessment of myocardial perfusion pattern using electrocardiogram-gated multislice computed tomography after acute myocardial infarction: a comparative study with rest electrocardiogram-gated single-photon emission computed tomography

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Purpose: After myocardial infarction (MI), two phases contrast enhancement ECG-Gated Multislice Computed Tomography (MSCT) demonstrates early hypoenhancement on the first iodine enhanced acquisition and late hyperenhancement on the delayed acquisition. We planned a systematic study, after early effective reperfusion of acute ST-elevation MI, comparing the results of MSCT with myocardial perfusion imaging using ECG-gated sestamibi SPECT performed within 3 days after MI.
Methods: 15 consecutive patients admitted for a first ST-elevation acute MI, who benefit of early ($<$ 12 hours) effective reperfusion underwent MSCT and ECG-gated SPECT. All the patients had coronaroangiography at admission, assessing patency of the infarcted related artery. SPECT analysis was performed using a 17 segments model to determine the size of the perfusion defect (PD). During ECG-Gated MSCT, a first enhanced iodine acquisition was followed by a delayed acquisition 5 minutes later. Using the same 17 segments model, each segment was classified as normal, hypoenhanced, or hyperenhanced compare to remote non infarcted myocardium for the two acquisitions. For each patient, extent of early defect (ED) and late hyperenhancement (LE) was calculated as number of segments and compared to the results of SPECT analysis.
Results: Topography of MI was anterior (9), or inferior (6) with a mean peak elevation of CK of 1837 $\pm$ 965 ui/l. Mean LVEF was 44 $\pm$ 6%. A total of 255 segments were analysed by SPECT and MSCT for the 15 pts. Gated SPECT showed a perfusion defect of a mean of 5.5 segments (range 2 to 11) per pts. During the first MSCT acquisition, all the pts had an early defect, at least of the subendocardial half of the left ventricle wall in the infarcted area. Mean extent of ED per patient was 6 segments (range 1 to 11). In 13 of 15 pts (86.6%) all the segments with PD were correctly identified by an ED. In 2 pts, ED was smaller than PD (ED= 1 vs 2, and 2 vs 4 PD segments). All the patient had a delayed myocardial hyperenhancement. LE was transmural or surrounded areas of subendocardial persistent hypodensity. LE was larger than the perfusion defect on SPECT in 13 of 15 pts (mean excess of 3.2 segments, range 1 to 6).
Conclusions: After reperfused myocardial infarction, MSCT first enhanced iodine acquisition demonstrates an hypoenhancement in the infarcted region well correlated with the perfusion defect determined by ECG-gated SPECT. The meaning of the delayed hyperehancement remains to be determined. ECG-gated MSCT could be a usefull tool to assess myocardial lesion in this setting.

P2291 Diagnostic value of adenosine stress magnetic resonance imaging in comparison to ^{201}Tl single-photon emission computed tomography myocardial scintigraphy and coronary angiography for detection of coronary artery disease and myocardial scar tissue

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Contrast enhanced magnetic resonance imaging of myocardial perfusion during adenosine infusion (stress MRI) is a new technique for detection of myocardial ischemia in coronary artery disease (CAD).
In this study, the diagnostic value of this method for detecting hemodynamically relevant coronary artery stenoses myocardial scar tissue was assessed and compared to 201-Tl-SPECT myocardial scintigraphy (SPECT) and x-ray coronary angiography findings.
Methods: 40 consecutive patients (pts.) (63$\pm$9y, 29 male) with suspicion of CAD underwent adenosine stress MRI (Siemens Sonata®, 1.5 T), SPECT and x-ray angiography on the following day.
MRI: After bolus injection of 0.1 mmol/kg bw Gd-DTPA (Magnevist®, Schering), ECG gated dynamic acqusition of 60x3 short axis images was done at rest and during 6 minutes of adenosine injection (140 μg/kg bw). For detection of myocardial scar tissue (delayed enhancement) an inversion recovery TSE sequence was used. Myocardial segments on stress MRI and SPECT images were assigned to corresponding coronary arteries. Results were compared to angiography findings.
Results: Angiography revealed relevant stenosis in 52 vessels of 27/39 pts. (69.2%). Hypoperfusion was detected during adenosine infusion in 26/39 pts (61.5%) in stress MRI and 26/38 (68.4%) in SPECT. The sensitivity of stress MRI was 85.2% (SPECT: 84%), the specificity 95.8% (SPECT: 84%). Correlation analysis: Stress MRI/angiography: $r=0.729$, $p<0.001$; SPECT/angiography: $r=0.507$, $p=0.001$; stress MRI/SPECT $r=0.486$, $p=0.002$. Myocardial scar tissue was detected by SPECT in 11/40 pts (27.5%) compared with 19/40 pts (47.5%) by MRI. 10/11 scar tissue findings in SPECT were reproducible by MRI.
Conclusion: Adenosine stress MRI and SPECT scintigraphy show comparable sensitivity. However, stress MRI has significantly higher specificity (96%) in comparison to SPECT (84%). There is better correlation between stress MRI results and angiography findings than between SPECT and angiography. Adenosine stress MRI has higher diagnostic value for detection of coronary stenoses and myocardial scar tissue than SPECT.

P2292 Implications of coronary microcirculation and myocardial viability on post-infarction left-ventricular remodelling and systolic function recovery in patients with an open infarct-related artery

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Purpose: In patients with a first myocardial infarction (MI) and a patent infarct-related artery (IRA) we analysed by means of angiography, intracoronary myocardial contrast echocardiography (MCE) and magnetic resonance imaging (MRI) the role of coronary microcirculation and myocardial viability in early and late ventricular dilation and in late regional systolic function. We aimed to compare all the perfusion indexes with MCE. **Methods:** Twenty-six consecutive patients with a first ST-elevation MI were studied. A patent IRA (TIMI 2 or 3. Stent in 18 cases) was achieved in all patients at the end of the cardiac catheterization performed at the first week (1w; median 5 days post-MI). Blush grade (0-3) and TIMI grade (2 or 3) were quantified. By means of intracoronary MCE, the mean perfusion score (MCE-perf) of the infarcted area (0=no reflow; 0.5=patchy; 1=normal) was calculated. By means of MRI (median 7 days post-MI) end-diastolic volume (EDV: ml/m^2; Simpson's method), wall motion of the infarcted area at baseline (WM: mean % thickening) and after low-dose dobutamine (WM-dob: %), mean thickness (mm), mean perfusion score (MRI-perf; early enhancement) and mean transmurality (MRI-trans; late enhancement: %) were determined. At the sixth month (6m) all the explorations were repeated in the first 13 patients (all of them with a patent IRA). **Results:** At 1w, EDV was related to WM (r=-.52 p=.008), WM-dob (r=-.56 p=.004) and MRI-perf (r=-.62 p=.001). At 6m, EDV was related to MCE-perf 1w (r=-.68 p=.001) and MRI-thickness 1w (r=-.59 p=.03). At 6m, WM was related to WM 1w (r=.67 p=.01), WM-dob 1w (r=.74 p=.006), MRI-perf 1w (r=.61 p=.03) and MRI-trans 1w (r=-.85 p$<$.0001). In the multivariate analysis the independent predictor of EDV at 1w was MRI-perf (p=.001), the independent predictor of EDV at 6m was MCE-perf (p=.003) and the independent predictor of WM at 6m was MRI-trans (p=.001). As a whole 39 studies of perfusion (26 at 1w and 13 at 6m) were performed. Blush 3 had a sensitivity (Se)=77% and a specificity (Sp)=53% (kappa=.31 p=.1), TIMI 3 had a Se=100% and a Sp=35% (kappa=.38 p=.01) and MRI-perf=1 had a Se=70% and a Sp=77% (kappa=.46 p=.01) to predict normal perfusion (MCE-perf=1; 56% of cases). **Conclusion:** In patients with a first MI and a patent IRA, a preserved coronary microcirculation is necessary to prevent remodelling while a lesser transmural necrosis analysed by MRI seems to be the best index to predict late regional systolic function. TIMI 3 is indispensable (but not guarantees) normal perfusion. MRI-perf shows the best agreement with perfusion analysed by MCE.

P2293 Comparison of contrast-enhanced magnetic resonance imaging and ^{201}Tl single-photon emission computed tomography to predict reversibility of left-ventricular dysfunction

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Introduction: Contrast-enhanced (ce) magnetic resonance imaging (MRI) has been shown to accurately assess myocardial viability. Comparative data to nuclear cardiology techniques as 201-Thallium (Tl) single photon emission computed tomography (SPECT) is scarce. We compared ce MRI and Tl SPECT to assess reversibility of left ventricular (LV) dysfunction. **Methods:** 42 patients (pts) with LV dysfunction (EF 34$\pm$9%) were examined on a 1.5T scanner (SONATA, Siemens). Functional cine studies (TrueFISP) and ce images (inversion recovery Turbo FLASH) 10 min after injection of 0.1 mmol/kg Gd-DTPA (Magnevist, Schering) were acquired. Rest-redistribution SPECT was performed according to standard protocols. 21 pts had suffered acute myocardial infarction (MI) and were examined with follow-up cine MRI studies 9 months after MI. The other 21 patients showed chronic LV dysfunction and were repeatedly examined with cine MRI 9 months after revascularization. A 17-segment model of corresponding basal, midventricular and apical slices was analysed independently for ce MRI and SPECT. Segmental hyperenhancement (HE) for MRI and tracer uptake for SPECT were quantified. For MRI, segments were considered to be viable if showing $<$ 50% HE, for SPECT, if showing $>$ 60% of Tl-201 uptake. Functional recovery in the follow-up MRI was correlated with prediction of viability by both imaging modalities. **Results:** In patients with acute MI, 68 of 135 dysfunctional segments showed improved wall motion with follow-up MRI. In these patients, ce MRI showed a sensitivity (sens) of 98% and a specificity (spec) of 76% to detect viable myocardium, whereas SPECT a sens of 79% and a spec of 69%. In patients with chronic LV dysfunction, 57 of 105 dysfunctional segments improved after revascularization. In these patients, ce MRI exhibited 95% sens and 79% spec for detection of viable myocardium as compared to 84% sens and 56% spec for SPECT. **Conclusions:** Ce MRI compares favorably to Tl-201 SPECT for prediction of functional recovery of dysfunctional myocardium in the setting of acute and chronic myocardial ischemia.

P2294 Cardiac magnetic resonance imaging has a prognostic value of after acute myocardial infarction

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Cardiac magnetic resonance imaging (MRI) provides comprehensive tools for the evaluation of the post infarction patient, up to now not available in a single examination. Purpose of the study was to evaluate the prognostic impact of functional and morphological MRI parameters.
Methods: 45 patients (age 57$\pm$13y) were examined by MRI (Philips 1.5T Intera CV) 2 to 10 days and 9 months after acute myocardial infarction (MI). Cine sequences with short and long axis analysis, rest perfusion and late enhancement sequences were performed and analyzed, both quantitatively and qualitatively. In 78% primary PTCA was performed. 47% of the patients had 1-vessel, 33% 2-vessel, and 13% a 3-vessel-disease.
Results: Immediately after MI left ventricular function was normal in 56%, at follow-up in 73% of the patients. Mean infarct size comprised 11.6% (1-34%) of the left ventricular wall mass. Right ventricular involvement defined as wall motion abnormality was visible in 40% of the patients, right ventricular late enhancement was found in 22%, which had only minor implications on global right ventricular function. A left ventricular thrombus was found in 1 patient (2%). A local pericardial effusion was present in 56%, 4% percent had a circular effusion without hemodynamic relevance. A pericardial enhancement (in the sense of pericarditis) was found in 40% (38% locally, 2% circular). All patients showed late enhancement of the infarct region acutely and at follow-up. Papillary muscle infarction was evident in 26% of the cases. Microvascular obstruction (MO) was present in 45% of the patients and significantly correlated to a larger infarct size (acutely, p$<$0.01 and at follow-up, p=0.02). Patients with MO had a significantly higher enddiastolic volume at follow-up (p$<$0.04), and only 61% of these patients had a normal ventricular function as compared to 87% without MO. Infarct size significantly correlated with left ventricular ejection fraction at follow up (r=-0.6, p$<$0.05). During 9 months follow-up mean infarct size decreased from 12% to 8% (p$<$0.01), even more pronounced in patients with MO.
Conclusion: Combined MRI analysis of infarct size, hypoperfused myocardium and left and right ventricular function gives precise prognostic information about myocardial recovery after acute myocardial infarction. MRI allows the exact quantification of myocardial infarction and provides new insights in its pathophysiology. Pericarditis and minor right ventricular involvement goes more frequent with myocardial infarction than clinically observed.

P2295 Contrast-enhanced magnetic resonance imaging and ^{201}Tl single-photon emission computed tomography for assessment of presence, location and extent of myocardial infarction in patients with left-ventricular dysfunction

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Introduction: Close correlation of contrast-enhanced (ce) magnetic resonance imaging (MRI) and positron emission tomography for assessment of scar tissue has been shown recently. We compared ce MRI and 201-Thallium (Tl) single photon emission computed tomography (SPECT) concerning presence, location and extent of myocardial infarction (MI) in patients with left ventricular (LV) dysfunction.
Methods: 54 patients (pts) with LV dysfunction (EF 39$\pm$15%) who had suffered MI (26 chronic MI, 28 within 7 days of acute MI) were examined on a 1.5T scanner (SONATA, Siemens). Ce images were acquired 10 min after intravenous injection of 0.1 mmol/kg Gd-DTPA (Magnevist, Schering) using an inversion recovery Turbo FLASH sequence (TE 4.0ms, TR 8.0ms, flip angle 20°, inversion time 220-300ms). Rest-redistribution SPECT was performed according to standard protocols. A 14-segment model of corresponding basal, midventricular and apical slices was analysed independently for MRI and SPECT. Segmental hyperenhancement (HE) for MRI and defect size for SPECT were visually graded using a 5 point score. Moreover, transmural extent of infarction (TEI) was quantified for MRI by planimetry.
Results: Summed SPECT defect score and summed MRI infarct score showed close agreement for pts with chronic MI (r=0.8, p$<$0.0001) and acute MI (r=0.9, p$<$0.0001). However, SPECT failed to detect 70 of 352 (20%) segments showing particularly subendocardial HE by MRI, and, on a patient basis, missed 6 of 54 (11%) pts with small MI, which had all been detected by MRI. Moreover, of 163 segments assessed to have severe defects by SPECT only 83 (51%) showed transmural HE.
Conclusions: Ce MRI and Tl-201 SPECT show, in overall, close correlation for assessment of presence, location and extent of MI both in the acute and the chronic setting. Potential advantage of MRI is the superior spatial resolution which allows for determination of both the transmural extent of MI and the detection of even small amounts of myocardial necrosis.

P2296 Usefulness of rest gated single-photon emission computed tomography early after reperfused acute myocardial infarction to predict delayed change of left ventricle ejection fraction

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Purpose: After early reperfused acute myocardial infarction (AMI), delayed improvement of left ventricle ejection fraction (LVEF) occurred in some patients and is related to stunned myocardium. We sought to determine if a score of stunned myocardium assessed by rest gated SPECT performed within 3 days after AMI could identify patients with delayed improvement of LVEF.
Methods: 26 consecutive pts admitted for a first AMI early reperfused ($<$ 12 hours), underwent rest gated Sestamibi PECT within 3 days (GSS1) after AMI and at six weeks (GSS2). Infarct size (IS) was determined on GSS1 as the number of segments with $<$ 40% peak activity. Using a 16 segments model, a summed perfusion score (SPS, 4 point score) and a wall motion score (WMS, 5 point score) were calculated on GSS1 and GSS2. A score of stunned myocardium (SSM) assessed as the difference between SPS and WMS was calculated on GSS1. LVEF was calculated on GSS1 (LVEF1) and GSS2 (LVEF2). Delta LVEF was calculated as (LVEF2-LVEF1)/LVEF1. LVEF improvement was defined as Delta LVEF $>$5%.
Results: 26 pts (22 males),mean age 55yrs (27 to 72 yrs) with first ST-elevation AMI were studied. AMI was anterior (12 pts) or inferior (14pts). Mean CK peak level was 1674 ui/l (404 to 4249 ui/l). Pts were successfully revascularized by primary stenting (20 pts), thrombolysis (3pts) or rescue angioplasty (3pts). All the pts had a timi 3 flow in the infarcted related artery. 14 pts had a multivessel disease. On GSS1 mean values of LVEF1, SPS, WMS, SSM and IS were 44.3 $\pm$ 8.3%, 11.7 $\pm$ 5, 14.7 $\pm$ 1.3, 2.64 $\pm$ 0.4 and 3.39 $\pm$ 1.4 respectively. On GSS2, mean values of LVEF2, SPS, WMS were 52.60 $\pm$ 7%, 7 $\pm$ 4.2 and 6.3 $\pm$ 1 respectively. 16 pts (group A) had significant improvement of LVEF (delta LVEF= 30.9 $\pm$ 19%). Group B (10 pts) had no significant change in LVEF (Delta LVEF= - 2.5 $\pm$ 1,8%). Mean age, topography of AMI, multivessel disease, IS and peak CK levels were not significantly different between the two groups. SSM was correlated with Delta LVEF (r= 0.70) and was significantly higher in group A (4.12 $\pm$ 3.9) than in group B (0 $\pm$ 2.7), p $<$0.005.
Conclusions: Score of stunned myocardium assessed by rest ECG-gated SPECT early after AMI is correlated to improvement of LVEF at six weeks. It could represent a safe and valuable tool to promptly identify patients in whom improvement of LVEF may be expected or not.

P2297 Abnormal T1 changes in stunned myocardium following manganese administration

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Manganese ions distributes actively into viable myocardial cells through voltage-operated calcium channels and remain for several hours. Therefore, the accumulation of manganese may indicate calcium channel activity. Manganese is also observable on magnetic resonance imaging (MRI) as T1 enhancement, providing a potential method to impart image contrast in proportion to myocardial function.
Aim: The purpose of this study was to determine whether stunned myocardium exhibits reduced manganese uptake (reduced T1 enhancement).
Materials and methods: Twenty four rats were divided into three groups and subjected to three 10 min episodes of LAD occlusion, a single 10 min occlusion and a control group without occlusion. Inversion-recovery echo-planar MRI was used to measure regional R1 (1/T1) values of the heart and chamber blood before and at 5 min intervals after administering 0.25 mmol/kg MnCl2. Delta R1 was calculated as delta R1 = R1 postcontrast- R1 precontrast.
Results: Administration of MnCl2 caused persistent increase in R1 in normal and stunned myocardium and transient increase in R1 of blood followed by rapid clearance. At 30 min delta R1 of normal myocardium was significantly ($p\leq0.025$) greater than of stunned myocardium (2.18$\pm$0.22 vs 1.39$\pm$0.17, 2.04$\pm$0.29 vs 0.85$\pm$0.06, respectively for single and repeated ischemia), indicating reduced Mn ion uptake in the stunned region. Furthermore, stunned myocardium prepared by repeated episodes exhibited less uptake than that prepared by single episode. Interestingly, the remote myocardium of stunned preparations exhibited greater Mn ion uptake than normal control hearts, suggesting hyperkinesis (2.29$\pm$0.19, 2.08$\pm$0.24, respectively for single and repeated ischemia, vs 1.57$\pm$0.20).
Conclusions: 1. These results suggest that calcium channel activity (as indicated by Mn uptake) is reduced in the stunned myocardium. The reduced activity enables Mn-enhanced visualization of the dysfunctional zone as a hypo-enhanced zone on MRI.
2. Stunned myocardium in animals subjected to three 10 min occlusion showed significant lower manganese uptake, suggesting a relation between calcium influx and the severity of the ischemic insult.
3. Remote myocardium shows higher manganese uptake than normal myocardium, consistent with hyperdynamic function of this region during the first hours post-ischemic insult.

P2298 Prognostic value of rest-redistribution ^{201}Tl single-photon emission computed tomography in patients with chronic coronary artery disease and left-ventricular dysfunction

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Background 201Tl stress myocardial perfusion imaging provides valuable prognostic information in patients with chronic coronary artery disease (CAD) and left ventricular dysfunction. In contrast, the prognostic value of rest-redistribution 201Tl imaging has been less investigated.
Aim To evaluate the ability of rest-redistribution 201Tl SPET to predict the occurrence of major cardiac events in patients with chronic CAD.
Methods The occurrence of cardiac death or non-fatal myocardial infarction was evaluated in 126 patients (114 men; mean age: 58$\pm$10) with chronic CAD and left ventricular dysfunction (EF=39$\pm$11%). Patients underwent rest-redistribution 201Tl SPET and were divided in a Group A (n=60), undergoing medical therapy, and a Group B (n=66), undergoing myocardial revascularization within 2 months from 201Tl imaging. The two Groups were comparable for clinical variables and EF.
Results Of a total of 20 events (9 deaths and 11 myocardial infarction), registered during a mean follow-up of 30$\pm$17 months, 7 were observed in the 60 patients included in Group A (12% of patients) and 13 in the 66 patients of Group B (20% of patients, p=n.s.). By Cox regression analysis only the presence of $\geq$3 severe irreversible defects at 201Tl SPET was significantly associated with adverse outcome (c2=5.06; p=0.024). In the Group A, 4/12 (33%) patients with $\geq$3 severe 201Tl defects experienced a major events, compared to 3/48 (6%) patients with $<$3 defects (p=0.009). In the Group B an event occurred in 2/9 (22%) patients with $\geq$3 defects and in 11/57 (19%) patients with $<$3 defects (p=n.s.). No significant differences in the occurrence of major cardiac events were observed between patients with $\geq$3 severe defects undergoing medical therapy or revascularization.
Conclusions Using rest-redistribution 201Tl imaging the amount of necrotic myocardium is the best scintigraphic predictor of major cardiac events in patients with chronic CAD and left ventricular dysfunction.

IMAGING IN CORONARY ARTERY DISEASE: FROM DIAGNOSIS TO PROGNOSIS

P2299 Safety and feasibility of high-dose dobutamine-atropine stress cardiovascular magnetic resonance for diagnosis of myocardial ischaemia: experience in 1000 consecutive cases

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Background: High-dose dobutamine-atropine stress cardiovascular magnetic resonance (stress-CMR) recently emerged as a highly accurate diagnostic modality. However, no large clinical experience has been reported so far.
Methods: From July 1997 to June 2002, 1000 consecutive stress-CMR examinations were performed in 960 patients (60±10 years; prior myocardial infarction 24%; prior percutaneous or surgical revascularization in 40% and 18%, respectively) with suspected (n=495; 49.5%) or known (n=505; 50.5%) coronary artery disease (CAD). Images were acquired at rest and during a standardized high-dose dobutamine-atropine protocol in 3 short-axis, a 4- and a 2-chamber view. A single-slice segmented gradient echo (TR/TE/flip 5.6/1.9/25), and from 2001 on, a steady state free precession technique (TR/TE/flip 3.0/1.5/55) were used. Dobutamine was infused at doses of 10, 20, 30, and 40 μg.kg-1.min-1, and supplemented by atropine if needed, until ≥85% of age-predicted heart rate was reached. Stress testing was discontinued when ≥85% of age-predicted heart rate was reached, on patient request, maximum pharmacologic infusion, or when new or worsening wall motion abnormalities, severe angina, dyspnea, severe increase or decrease in blood pressure, or severe arrhythmias occurred.
Results: Stress-CMR was successfully performed in all but 4 cases (0.4%; insufficient ECG-triggering). In the absence of ischemia, target heart rate was not reached in 95 cases (9.5%), due to maximum pharmacologic infusion in submaximal negative examinations in 21 cases (2.1%), and limiting side effects in 74 cases (7.4%), including severe chest pain (n=30; 3%), dyspnea (n=10; 1%), nausea (n=4; 0.4%), urinary urgency (n=1; 0.1%), severe increase (n=5; 0.5%) or decrease (n=3; 0.3%) in blood pressure, ventricular extrasystoly (n=8; 0.8%), paroxysmal atrial fibrillation (n=5; 0.5%), and patient request (n=8; 0.8%). Total number of side effects included one case (0.1%) of sustained and 4 cases (0.4%) of non-sustained ventricular tachycardia, 16 cases (1.6%) of paroxysmal atrial fibrillation, 2 cases (0.2%) of transient second degree AV block and 31 cases (3.1%) of nausea. Image quality was non diagnostic in 6 cases (0.6%), due to breathing or motion artifacts. Four hundred twenty pts (42%) showed a new or worsening wall motion abnormality, while 475 (47.5%) did not.
Conclusions: High-dose stress-CMR is safe and feasible in patients with suspected or known CAD. However, patients must be closely monitored, and resuscitation equipment and trained personnel must be available.

P2300 Myocardial perfusion imaging improves diagnosis and risk stratification in patients with stable chest pain

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Background: Myocardial perfusion imaging (MPI) is a widely used method for the non-invasive diagnosis of coronary artery disease (CAD) and has been shown to be more accurate than exercise electrocardiography (ETT). However the ETT continues to be the first line investigation in many institutions, and has been advocated as the screening tool in specialist clinics for stable chest pain syndromes. We hypothesised that one-stop MPI with gated technetium-99m sestamibi would provide a definitive answer and reduce unnecessary investigations.
Methods: Accordingly 503 patients with stable chest pain (mean age 60 ± 12 years, 57% males) presenting to their primary care physician, underwent prospective randomisation to either same day ETT or same day MPI with gated technetium 99m-sestamibi SPECT. Bayes' theorem was used with the Diamond and Forrester criteria to stratify patients according to likelihood of CAD. Independent and blinded reporting was performed in the two groups. Patients were allocated clinic follow up or further investigations to assess or confirm the diagnosis.
Results: The proportion of patients requiring a further test to confirm or diagnose CAD in the ETT arm was 74%(175/237). In the MPI arm it was 17% (45/266) ($p<0.0001$). In the ETT arm 120 coronary angiograms were requested, on clinical grounds, for the 182 patients with an intermediate or high post-test likelihood of CAD (69%). However only 44 coronary angiograms were requested for the 82 MPI patients (54%) deemed to have an intermediate or high post-test likelihood of CAD (p=0.08). The proportions of patients with normal coronaries on angiography in the ETT and in the MPI arms were 33% (36/108) & 12% (5/42) respectively (p=0.01). Of the five MPI patients with normal coronaries, 3 had significant artefact on SPECT imaging (with significant diagnostic uncertainty) and only 2 were false positive. The rate of referral for revascularisation, as a proportion of the total number of angiograms performed, was 45% and 60% for the ETT and MPI arms respectively (p=0.14).
Conclusion: MPI with gated sestamibi SPECT significantly reduced the requirement for further cardiac investigations to diagnose CAD. Also, the proportion of normal coronary angiograms was significantly reduced in the MPI arm. The rate of referral for revascularisation was slightly higher in the MPI arm, due to extra functional information. Thus a MPI strategy in patients with stable chest pain may have significant resource implications.

P2301 Prognostic significance of fixed perfusion abnormalities on stress ^{99m}Tc-sestamibi single-photon emission computed tomography in patients without known coronary artery disease

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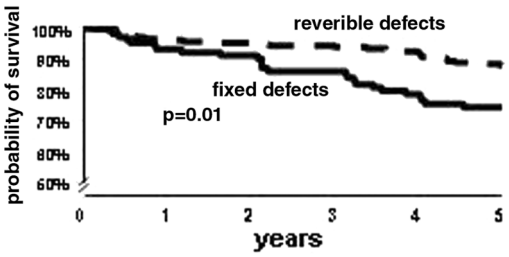
Background: Fixed perfusion abnormalities in patients with known coronary artery disease (CAD) are associated with myocardial damage and adverse outcome. However the significance of these abnormalities in patients without known CAD is unclear. Aim of the study was to assess the prognostic significance of fixed versus reversible perfusion abnormalities in patients without known CAD.
Methods: We studied 327 patients (age 58 ± 11 year, 215 men), with no history of previous myocardial infarction or revascularization, who demonstrated myocardial perfusion abnormalities on stress (exercise or dobutamine) sestamibi SPECT. Follow up end points were all cause of mortality and hard cardiac events (cardiac death and non fatal myocardial infarction).
Results: Myocardial perfusion abnormalities were reversible in 226 (69%) and fixed in 101 (31%) patients. During a mean follow up of 7 years, 72 (22%) patients died (cardiac death in 30) and 15 patients had non-fatal myocardial infarction. The annual mortality rate was higher in patients with fixed than with reversible abnormalities (4.4% vs 2.7%, $p<0.01$); whereas annual hard cardiac event rate was not significantly different between both groups (2.5% vs 2% respectively). In a multivariate analysis model, the summed stress score was an independent predictor of hard cardiac events (risk ratio = 1.7; CI 1.3-5.4). The presence of a fixed perfusion abnormality was independently associated with increased risk of death after adjustment for clinical and stress test data and the summed stress score (risk ratio = 2.5; CI 1.3-3.7).



Survival according to defect type.

Conclusion: In patients with suspected, but no prior history of CAD, fixed perfusion abnormalities are associated with a higher risk of death compared to reversible perfusion abnormalities.

P2302 Myocardial gated single-photon emission computed tomography efficacy in patients admitted in emergency department with acute chest pain and no diagnostic electrocardiogram

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Purpose: we prospectively evaluated the utility of 99mTc-Tetrofosmin myocardial Gated-SPECT (GSPECT) in identifying patients with acute coronary syndromes among those who present to emergency department with chest pain, no diagnostic ecg and no history of CAD.
Methods: 64 patients (pts) with acute chest pain and no diagnostic ECG for CAD underwent GSPECT in a six months period. At the time of injection: 42 pts referred chest pain and 22 pts no pain until 4-6 h. The last group underwent stress GSPECT until 6 hours in case of no resting perfusion defects. A total of 1280 segments (S) was evaluated in a 5 points scale (from 0: normal to 4:severe defect), with viability threshold tracer uptake as >60% of peak. LVEF and thickening were obtained from both rest and stress Gated scan.
Results: On the basis of perfusion results we subdivided pts into two groups: Gr.A not hospitalized (30pts) and Gr.B hospitalized (34 pts).
Gr.A pts had a mean of 1 risk factor, showed normal resting (20 pts with pain) or rest/stress scan (10 without pain at injection), excluding CAD. No cardiac events occurred after six months.
Gr.B pts had a mean of 2 risk factors (22 with and 12 without pain at injection). Pts with pain showed: severe abnormal rest scan in 18 pts and low/mild rest defects in 4 pts. All of the pts without pain showed ischemia stress induced with normal perfusion scan at rest.
Gr.B pts underwent coronary angiography, showing: no anomalies in 4 pts with low perfusion defects and normal GSPECT LVEF function; severe stenosis in 30 pts matching with severe perfusion defects. Ten of this last group showing basal GSPECT LVEF <35% and extensive abnormal regional thickenig%, were unresponsive to thrombolysis therapy and underwent PTCA rescue. A four months later stress-rest GSPECT showed post-stress and basal LVEF >50% in all of them, normal perfusion scan in 3 pts, fixed defects in 3 pts, and partially reversible defects in the last 4 pts with post-stress abnormal segmental thickening, suggesting further revascularization.
Conclusions: In emergency department, myocardial GSPECT has a high value to detect acute coronary syndromes in patients with chest pain and no diagnostic ECG, by assessing both perfusion and LV function and reducing inappropriate hospitalization. In case of CAD, it can also stratify patients at risk by assessing severity, extension and dysfunction CAD related, better suggesting therapy.

P2303 Coronary artery disease, the silent troublemaker in diabetes

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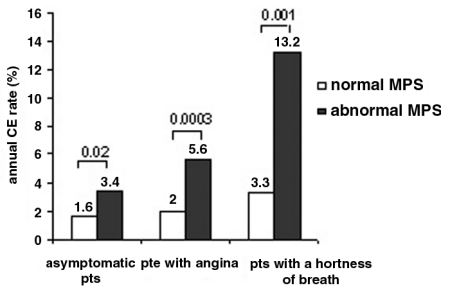
Background: The prevalence of silent ischemia (SI)in diabetic patients (dpts) has been reported to be as high as 65%. However, little is known about the impact of SI on outcome in these dpts. The goal of this study was therefore to compare the outcome of dpts with SI, angina, and shortness of breath (SOB=NYHA≥2).
Methods: We identified 1430 consecutive dpts without known coronary artery disease (CAD). All dpts underwent rest Tl-201/stress Tc-99m sestamibi myocardial perfusion SPECT (MPS) and were followed-up > 1 year. MPS was interpreted using a 20 segment model to define summed stress (SSS), rest (SRS=extent of scar) and difference score (SDS=extent of ischemia) and related to symptoms and outcome. Critical events (CE): cardiac death (CD)or myocardial infarction (MI).
Results: During follow-up, 98 CE occurred (3.1% per year, 64 MI, 52 CD). Dpts with SI had no significantly different outcome than dpts with angina, but dpts with SOB had a more than 2-fold risk to suffer CE. The annual CE rates for asymptomatic dpts (n=701), dpts with angina (n=605), and dpts with SOB (n=124) were 2.2%, 3.2%, 7.8%, respectively. Furthermore, Cox proportional hazards model identified older dpts (HR 1.04; p<0.0001), dpts with SOB (HR 2.1; p=0,005) and dpts with hypertension (HR 1.7; p=0.02) to be more likely to have CE. In addition, MPS (SRS and SDS, HR 1.06 (p=0.006) and 1.07 (p<0.0001), respectively) yielded incremental prognostic value to prescan information. All dpts were effectively risk stratified by MPS (SSS) as shown in figure below.



Annual CE rates by SSS and symptoms.

Conclusions: Dpts were effectively risk stratified by MPS regardless of their symptomatic status and might therefore benefit from routine risk stratification by MPS. Furthermore, SOB, but not angina was an independent predictor of outcome.

P2304 Gated ^{99m}Tc-tetrofosmin single-photon emission computed tomography for differentiation of myocardial scar from attenuation artifact

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Aim: Fixed perfusion-scan defects may result from attenuation artifacts. Gated 99m-Tc-tetrofosmin SPECT may help differentiate myocardial infarction (MI) from artifact. Fixed defects with decreased function (wall motion and thickening) probably represent MI, whereas attenuation artifacts have normal function or not markedly reduced function
Methods: Ungated resting and gated stress 99m-Tc-tetrofosmin SPECT was performed in 153 consecutive patients referred for evaluation of coronary disease. From resting and summed gated stress images, 107 patients (70%) were identified with isolated fixed defects. Function of the defects was assessed subjectively from gated stress images and results were correlated with clinical (history and/or ECG Q-waves) evidence of MI.
Results: Of 62 patients with fixed defects and clinical MI, 60 (97%) had abnormal defect function. Of 45 patients with fixed defects but no clinical MI, 16 (36%) had decreased function of the defect, possibly indicating silent MI. In 29 of the 45 patients (64%) with no clinical MI, defect function was normal. Because most (90%) of fixed defects with normal systolic function occurred in men with inferior fixed defects (86%) or women with anterior fixed defects (3%), these were most likely attenuation artifacts. By reclassifying patients with fixed defects and normal function as normal, patients with unexplained fixed defects (no clinical MI) decreased from 29% to 10%.
Conclusions: Gating provides a considerable added value to 99m-Tc-tetrofosimn SPECT in characterizing fixed defects and potentially improving test specificity.

P2305 Usefulness of non-invasive multislice computed tomography coronary angiography as first-line imaging technique in patients with chest pain: initial clinical experience

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Objective: Aim was to investigate the usefulness of Multi-Slice Detector Computed Tomography coronary angiography (MS-CTA) as first-line imaging technique in patients (pts) with known or suspected coronary artery disease (CAD) and low to intermediate probability of a severe coronary lesion.
Background: Comparative studies with invasive coronary angiography (ICA) indicated a good sensitivity and specificity in non-invasive detection of CAD. We report on our initial clinical experience using MS-CTA without compelled ICA.
Methods: 136 pts with chest pain underwent MS-CTA on an outpatient basis (age 60±10, suspicion of CAD: n=95, suspicion of restenosis: n=24, after CABG: n=17).
Results: 8.2 ± 2.7 coronary segments could be evaluated per pt. Based on the MSCT results, the presence of flow- limiting stenoses was excluded in n=77 (57%) pts (group I). An additional ICA was recommended in n=59 (43%) pts (group II). A telephone interview was performed after 455 ± 166 days to evaluate the further clinical course. An ICA had been performed in meantime in 27/136 (20%) pts, and could be avoided in the majority of pts. Nevertheless, 58/136 (42%) pts reported on improved clinical symptoms and 42/136 (31%) pts of better quality of life.
Conclusions: MS-CTA was found to be useful to evaluate the need and to reduce the total number of performed ICA in pts with unclear chest pain. It appears to be the first non-invasive modality which might be used on a clinical routine basis in selected groups of pts.

P2306 Can attenuation correction in myocardial single-photon emission computed tomography improve the diagnosis ischaemia accuracy

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Attenuation Correction Spect has been described as a useful method to improve diagnosis of myocardial ischaemia. So, the aim of this study was to know if the currently use of attenuation correction thecnique improve our accuracy in detecting myocardial ischaemia.
Methods: A two step study was desing: in a first step the semiquantive differences between the reports with attenuation correction (AC), and without attenuation correction (NCA) were established. In a second step, findings on AC/NAC studies and coronariographic studies findings were correleted.
83 consecutive patients p, 58 p with coronary artery disease CAD, were studied with stress/rest 99Tc Sestamibi SPECT with and without AC attenuation and with coronariography. In the first step semiquantitative analysis in the AC and NCA studies were performed by two advanced observers in 41 p (35 males), dividing the myocardial left ventricle into sixteen segments, corresponding to LAD, RCA, and LCX territories. Statistical signification was stablished by Wilconxon test.
Secondly, 42 patients (31 males) were evaluated with myocardial perfusion SPECT with and without AC, and in the following days with coronariography. The studies were considered positive for ischaemia when having two or more reversible defects on perfussion SPECT so as signiticative stenosis in coronariographic studies. Statistical analysis was only performed in the RCA territory.
Results: In the semiquantive, study statistical significance, $p<0{,}001$, was only found in the RCA territory.
Coronariographic studies revelated 1 vessel disease, 21p (7 RCA), 2 vessels disease, 9p (7 RCA), 3 vessels disease, 9 p, and 3p normal studies.
Comparison between Statistical analysis of the AC and NAC perfussion SPECT findings and coronarigraphyc findings in the RCA territory were:

Sensibility	NCA 56,5%/CA 69,5%
Specificity	NCA 68,4%/CA 78,9%
PPV	NCA 68,4%/CA 80%
NPV	NCA 65,5%/CA 68%
Accuracy	NCA 61,9%/CA 73,8%

Conclusions: The currently use of attenuation correction thecnique in the perfussion imaging allows improve results in the diagnosis of myocardial ischaemia. This is specially true for RCA territory.

P2307 Right-ventricular ischaemia in patients with proximal right coronary artery stenosis

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Introduction: In patients with coronary artery disease, myocardial perfusion scintigraphy of the left ventricle (LV) has been shown to be of clinical and prognostic value. However, feasibility and clinical value of right ventricular (RV) perfusion is unknown. Especially in patients with inferior LV ischemia due to proximal right coronary artery (RCA) stenosis, in whom RV ischemia can be anticipated. The aim of this study was to determine feasibility, reproducibility and the value of thallium-201 (Tl) stress/rest RV scintigraphy to identify patients with RCA stenosis proximal to the RV branches.
Methods: For reproducibility testing, 6 consecutive Tl studies were randomly analysed 3 times by two independent observers. Twenty normals (group 1), 8 patients with proximal RCA stenosis ($>70\%$) without inferior LV ischemia (group 2) and 13 patients with inferior LV ischemia due a single proximal RCA stenosis ($>70\%$) (group 3) were studied. After tomographic reconstruction, stress/rest RV Tl uptake was expressed as a percentage of maximal septal uptake. Only segments of the RV free wall were used to minimize the effect of septal spillover.
Results: In 53/55 (96%) subjects RV perfusion analysis was feasible (2 normal subjects could not be analysed). Segmental inter- and intra-observer variability expressed as the correlation coefficient was 0.90 ($p<0.002$) and 0.98 ($p<0.001$), respectively.
In group 3, RV Tl stress-uptake is decreased compared to group 1 and 2. In addition, group 3 is characterized by Tl redistribution (rest-stress $>$ 0) which indicates RV ischemia whereas the other groups show normal Tl washout (rest-stress $<$ 0) (see table).

Right Ventricular Thallium uptake

	Group 1	Group 2	Group 3
Stress uptake	36 ± 5*	39 ± 9*	30 ± 10
Rest uptake	35 ± 5	36 ± 10	33 ± 8
Rest-Stress uptake	-1.2 ± 5*	-2.9 ± 6*	2.3 ± 8

(*= $p<0.05$ compared to group 3)

Conclusion: Assessment of RV perfusion using Thallium-201 SPECT is feasible and reproducible. RV perfusion is impaired in patients with inferior LV ischemia due to proximal RCA stenosis compared to normal controls and patients with proximal RCA stenosis without inferior LV ischemia. Therefore, the presence of RV ischemia enables the identification patients with inferior LV ischemia due to proximal RCA stenosis.

P2308 Coronary calcifications versus Framingham and PROCAM risk assessment in patients with a first, unheralded myocardial infarction

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The purpose of this study was to investigate the relationship between the extent of coronary calcifications (CC) quantified by electron beam tomography (EBT) and the predicted 10-year cardiovascular event risk based on Framingham and PROCAM risk prediction algorithms in patients with a first myocardial infarction.
Methods: In 156 patients (pts., mean age 56.7 years, 89% male), EBT was performed within 4 weeks after unheralded, first AMI and before any coronary intervention. CC were quantified using the "Agatston Score". Age-related calcium percentiles were determined based on the "Epidemiology of Coronary Calcification Study", Mayo Clinic, Rochester. The predicted 10-year cardiovascular event risk was determined using the Framingham equation (FRA) and PROCAM algorithm.
Results: Coronary calcifications were present in 148 pts. (95%). The mean AS was 589 ± 976. An AS above the 75th percentile was found in 103 pts. (66%), an AS above the 90th percentile in 69 pts. (44%). The mean FRA risk was 14.1 $\pm$ 4%. A FRA risk $<$ 10% was found in 53 pts., 10-20% in 54 pts., and $>$20% in 49 pts. The mean PROCAM risk was 9.4 $\pm$ 4%, with a PROCAM risk $<$ 10% in 62 pt, 10-20% in 53 pt, and $>$20% in 43 pt. Correlation between AS and FRA ($r = 0.23$, $p = 0.02$) and between AS and PROCAM ($r = 0.28$, $p = 0.01$) was weak but significant. In 84 pts. younger than 50 years, an Agatston Score above the 90th percentile was calculated in 44 pts. (52%), a FRA risk $>$ 20% in 28 pts. (33%, $p<0.01$) and a PROCAM risk $>$20% in 21 pts. (25%, $p<0.01$) and in 74 pts. $>$ 50 years an Agatston Score above the 90th percentile was calculated in 25 pts. (33%), a FRA risk $>$ 20% in 21 pts. (28%, n.s.) and a PROCAM risk $>$20% in 22 pts. (30%, n.s.).
Conclusion: In younger patients the detection of coronary calcifications was superior to the calculation of FRA risk and PROCAM risk for the identification of high risk for MI.

P2309 Prognostic value of stress myocardial perfusion imaging in asymptomatic patients with mildly impaired left-ventricular function

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Background: Left ventricular ejection fraction (LVEF) is useful for predicting the incidence of cardiac events. However, LVEF may not be suitable for predicting the prognosis in asymptomatic patients who show mildly impaired LV function and are suspected for coronary artery disease (CAD).
Purpose: The purpose of this study was to investigate prognostic value of stress myocardial perfusion imaging in these patients compared with LVEF.
Methods: Consecutive patients (n=50, male/female=31/19, mean age=68, diabetes mellitus=17) who were suspected for CAD and underwent stress myocardial perfusion imaging were followed up for 3 years. Follow-up time was censored at the occurrence of hospitalization for congestive heart failure (CHF), or acute coronary syndrome.
Results: During follow-up hospitalization for CHF in 7 patients, unstable angina in 5 patients and acute myocardial infarction in 1 patient occurred. Mean LVEF was 47.0%.Myocardial ischemia in stres perfusion images revealed in 18 patients of 50.LVEF$<$45% revealed in 23 patients of 50. Cox regression demonstrated that myocardial ischemia in stress myocardial perfusion images was better predictor of cardiac events than LVEF as shown in Table 1.

Table1

	Hazard ratio	95%CI	P value
Myocardial ischemia due to myocardial perfusion images	3.550	1.036-12.169	0.044
LVEF$<$45%	1.474	0.450-4.834	0.522

Conclusions: In asymptomatic patients with mildly impaired LV function, myocardial ischemia in stress myocardial perfusion imaging is associated with a higher incidence of cardiac events. Stress myocardial perfusion imaging is useful for predicting cardiac events in asymptomatic patients with mildly impaired LV function.

RISK ASSESSMENT AND MANAGEMENT

P2310 Higher plasma total homocysteine levels in hypertensive subjects

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Introduction: Elevated levels of plasma total homocysteine (tHcy), a sulfur containing amino acid has been shown to be toxic to the vascular smooth muscle and endothelium. Hyperhomocysteinemia may potentially contribute to the higher incidence of cardiovascular events in hypertensive patients. We sought to determine if elevated levels of tHcy is associted with hypertension in a cohort of patients with and without known coronary artery disease.
Methods: Between 1996 and 2002, 3767 subjects were referred to our preventive cardiology clinic (median age 56 ±12 years, 1282 (32%) females, mean systolic and diastolic blood pressures were 129±20 and 78±11 mm of Hg respectively, 1958 (52%) with known coronary artery disease, 2246 (60%) on antihypertensive therapy, 1876 (50%) on lipid lowering therapy, 721 (19%) diabetics and 354 (9%) smokers). tHcy levels drawn on the initial entry visit. Hypertension was defined as blood pressure greater than 140/90 mm of Hg or use of anti-hypertensive medications. A multiple logistic regression model was used to study the association of tHcy with hypertension.
Results: There were 1901 (50%) subjects with hypertension. tHcy levels in subjects with and without hypertension were 13.1±5.9 and 11.7±4.4 μmol/L respectively ($p<0.001$)(see Table 1). After adjusting for age, gender, medications including lipid lowering and antihypertensive therapy and serum creatinine, hypertension remained associated with higher tHcy levels ($p<0.004$).

Table 1

tHcy levels in	Hypertensives (in μmol/L)	Normotensives (in μmol/L)	P value
Overall	13.1±5.9	11.7±4.4	<0.001
No coronary artery disease	12.3±4.9	1.1±3.8	0.001
Coronary artery disease	13.6±6.3	12.5±5.0	<0.001

Plasma Total Homocysteine levels in Hypertensive and Normotensive Sujects With and Without Coronary Artery Disease

Conclusions: Hypertensive subjects with and without coronary artery disease have higher tHcy levels. This may enhance the atherosclerotic risk burden and/or promote progression of cardiovascular risk in hypertensives.

P2311 Serum homocysteine and long-term risk of myocardial infarction and sudden death in patients with coronary heart disease

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Hyperhomocysteinemia is an emerging risk factor for coronary heart disease (CHD).However, results of prospective studies are conflicting and most were done in low-risk cohorts.
The aim of the present study was to prospectively evaluate the risk of incident myocardial infarction and sudden cardiac death (coronary events) in association with serum total homocysteine in patients with preexisting CHD.A nested case-control design was used. Total homocysteine concentration was measured in baseline fasting serum samples from 128 patients with chronic CHD enrolled in the Bezafibrate Infarction Prevention Study (n=3090). Cases were defined as patients who developed coronary events during a mean follow-up of 6.2 years (n=69), these were matched for age and gender with controls without subsequent cardiovascular events.
Homocysteine concentrations in the highest tertile (>15.6 μmol/L) were associated with significantly higher odds of future coronary events compared to the lowest tertile (OR 2.52; 95% CI, 1.10 to 6.19), and with a strong trend of increased risk after adjustment for coronary risk factors (OR 2.27; 95% CI, 0.98-6.22) and for inflammatory mediators (OR 2.30; 95% CI 0.87-5.64). Future risk of coronary events was strongly associated with homocysteine concentration: OR 1.28; 95% CI 1.04-1.69 per 5 μmol/L increment, and OR 3.15; 95% CI 1.36-8.51 per 1 natural log unit increment. These risk estimates remained unchanged after adjustment for coronary risk factors and inflammatory mediators. The association between serum homocysteine and coronary events in patients with preexisting CHD emphasizes the important role of homocysteine level in the prediction of recurrent coronary events in high-risk patients.

P2312 Evidence of increasing risk scores among patients referred for coronary artery bypass surgery

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Purpose: Recent advances in percutaneous coronary intervention (PCI) have led to its greater application, including those patients with complex anatomy and multivessel disease.This is likely to have affected the profile and complexity of patients referred for coronary artery bypass graft surgery (CABG).
Methods: Records of all patients referred for isolated CABG from a single centre between 1997 and 2002 (n=2640) were reviewed and their demographic profiles analysed. Additionally two cohorts of patients from 1997 (n=111) and 2002 (n=110) were identified and a complete EuroScore was calculated for each patient and compared between groups.
Results: The median age profile of patients referred for CABG rose progressively between 1997 and 2002 from 62 to 65 years.Table. "Age profile of patients. 1997 to 2002". In both 1997 and 2002 the median EuroScore of patients turned down for CABG was significantly higher than for those accepted. (1997; 1.9 vs 3.5 and 2002; 2.5 vs 5.9). Median EuroScores of patients referred in 2002 was significantly higher than in 1997 (2.4 vs 3.4 $p<0.001$), this was also the case in both accepted and rejected groups (1.9 vs 2.5 $p<0.05$ and 3.5 vs 5.9 $p<0.001$). The single greatest factor contributing to these observed changes in risk is patient age rather than comrbidity.

Age profile of patients. 1997 to 2002

	Number referred	All patients referred. Median age (IQR)	Number (%) accepted	Accepted patients. Median age (IQR)	Accepted vs rejected p value
1997	420	62 (55-67)	298 (71)	61 (55-66)	0.42
1998	507	62 (55-68)	368 (73)	61 (55-67)	0.76
1999	541	62 (55-69)	374 (69)	61 (55-68)	0.03
2000	468	63 (56-69)	313 (67)	62 (55-68)	0.001
2001	500	63 (57-70)	323 (65)	63 (56-69)	0.07
2002	204	65 (58-72)	137 (67)	65 (58-71)	0.23

Conclusions: This study supports observations of progressively increasing surgical risk among patients referred for CABG. This is likely to be due in part to advances in PCI. This has implications for service planning, resource allocation and audit standards.

P2313 Increased left-ventricular mass, 24-hour blood pressure and exercise blood pressure in unfit versus fit middle-aged men and women

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Background: Twenty-four-hour ampulatory blood pressure (ABP) is directly related to left ventricular mass (LVM). Aerobic fitness is assosiated with lower ABP. Thus, high-fit individuals may have lower LVM when compared to those of low fitness.
Methods: We assessed cardiac structure (Echocardiography) and fitness (ETT-Bruce) in 480 middle-aged women (age:54±10), and 385 middle aged men (age:52±15), to determine the assosiation between aerobic fitness, ABP, and LVM. All were free of heart disease and antihypertensive medication. However, 45% of men and 40% of women were hypertensive. Age-adjusted groups, Low-Fit (n=146), Moderate-Fit (n=157) and High-Fit (n=177) for women, and Low-Fit (n=114), Moderate-Fit (n=130) and High-Fit (n=141) for men, were formed based on exercise time to exhaustion.
Results: Significant correlations were noted between LVM index (LVMI) and daytime ABP for women (r=0.68; p=0.00) and for men (r=0.73; p=0.00). Similar correlations were also noted between ABP and exercise BP at 6min (7METs) in women (r=0.80; p=0.00) and men (r=0.76; p=0.00). After adjusting for age and resting BP, differences ($p<0.001$) were observed among the three fitness groups (see table: **Differences ammong all groups; *Low-Fit vs Moderate and High-Fit).

Fit vs unfit men and women

	Women			Men		
Groups	LVMI**	Ex-SBP**	Day ABP	LVMI**	Ex-SBP**	Day ABP
Low-Fit	140 ± 32	187 ± 21	152 ± 11*	135 ± 30	184 ± 20	152 ± 16*
Mod-Fit	127 ± 32	177 ± 17	145 ± 13	125 ± 25	175 ± 17	147 ± 14
High-Fit	117 ± 27	167 ± 18	142 ± 15	117 ± 26	165 ± 17	144 ± 11

Conclusions: Aerobic fitness attenuates LVMI, ABP and exercise BP. The strong associations between exercise SBP at 7 METs and daytime ABP suggest that exercise BP at this level reflects the daytime haemodynamic load.

P2314 Abdominal adiposity indexes and risk of coronary heart disease in men

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Purpose: The predictive independent value of abdominal adiposity on coronary heart disease (CHD) is uncertain possibly because of poor abdominal adiposity markers. The goal of the present study was to compare abdominal adiposity indexes as predictors of CHD in men.
Methods: This study was carried out in a cohort (PRIME Study) of 9667 men free of CHD, aged 50-59 y at baseline and followed for 5 years. Weight, waist and hip circumference, height were measured at baseline. Among the 9667 men, a total of 316 CHD events [myocardial infarction (MI), CHD death (COD), unstable angina (UA) and angina (AN) pectoris] occurred during the follow-up.
Results: After adjusting for age, recruiting center, education levels, smoking, physical activity and alcohol intake the relative standardized risk (RR) of total CHD events was 1.23 [1.10-1.37] for waist circumference, 1.25 [1.12-1.40] for waist-to-hip ratio (WHR) and 1.29 [1.16-1.44] for waist-to-height ratio (WHG). Further adjustment for diabetes, hypertension, dyslipidemia, systolic blood pressure, cholesterol, triglycerides and HDL-cholesterol attenuated these associations RR: 1.02 [0.90-1.16] for waist circumference, RR: 1.10 [0.97-1.25] for WHR and RR: 1.08 [0.95-1.218] for WHG. Altogether the results suggest a modest relationship between abdominal adiposity, as assessed by waist girth, waist-to-hip ratio and waist-to-height ratio. However, the later variables were no longer related to CHD after adjustment on hypertension, dyslipidemia and diabetes, suggesting a contribution of these factors to CHD risk in men.
Conclusion: These findings suggest that waist girth, waist-to-hip ratio and waist-to-height ratio are not independent risk markers of CHD in men aged 50-59y.

P2315 The added value of pre-discharge dobutamine stress echocardiography in the long-term risk stratification of chest pain patients

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Background: Dobutamine stress echocardiography (DSE) has been proposed as a risk stratification tool prior to discharge from the emergency room in chest pain patients with a normal or non-diagnostic electrocardiogram. The value of DSE may differ depending on the risk estimate of the attending physician based on clinical judgement.
Objective: To evaluate the added value of DSE in the long-term risk assessment relative to physicians' risk estimates.
Patients and Methods: 398 consecutive patients with chest pain of less than 6 hours duration and a normal or non-diagnostic electrocardiogram were included after ruling out acute coronary syndrome with an emergency department rule-out protocol. On admission and at discharge the physician estimated patient-specific probability of a cardiac event in the next 6 months (pre-test probability). A pre-discharge DSE was performed, without disclosure of result to the treating physician. The DSE likelihood ratios were used to transform physician's estimates into posttest probabilities. Pretest and posttest probabilities were compared with observed event rates using calibration statistics and receiver-operating characteristic (ROC) curves.
Results: The 6-month cardiac event rate was 7.5%. DSE likelihood ratios were 7.8 (95% CI: 4.2 to 14) for a positive and 0.63 (0.47 to 1.8) for a negative result. Physicians' probabilities were well calibrated. The area under the ROC curve did not significantly improve by including the DSE results. In the intermediate risk group with pretest probabilities between 6 and 30%, negative predictive value of DSE was 96%.
Conclusion: Due to the overall low event rate and an undiscriminating negative likelihood ratio, the DSE has limited additional value in the long-term risk stratification of chest pain patients. However, in the intermediate risk group, DSE has additional value. Moreover, it may be clinically relevant to rule-out cardiac ischemia in selected patients.

P2316 Cardiovascular risk factors and 10-years probability for cardiovascular events in HIV-infected patients

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Objective: Due to side effects, such as hyperlipidaemia and insulin resistance, there is an increasing concern that antiretroviral drugs lead to an epidemic of cardiovascular diseases in HIV-infected patients.
Design: The present study characterizes the cardiovascular risk profile of HIV-infected individuals and the impact for cardiovascular events.
Methods: To gain insight into the risk of cardiovascular events in HIV-infected individuals, the following risk factors were recorded in 309 HIV-infected adults: gender, age, lipids, smoking behaviour, family history of cardiovascular events and blood pressure. All HIV-infected patients entered the department of internal medicine between 1997 and 2002 (HIV-acquisition: 59.2% by homosexual contact, 28.5% by heterosexual contact, 9.1% by intravenous drug abuse and 3.2% by blood transfusion). Overall 10-years probability for cardiovascular events had been determined by the Framingham algorithm.
Results: HIV-infected patients exhibited an elevated tobacco use. 63.4% of the HIV-infected patients were regular smoker, over 99% of them consuming cigarettes. Only in 3.2% of the HIV-infected patients the daily cigarette consumption was less than 5 cigarettes, while 12.6% smoked more than 40 cigarettes each day. Total cholesterol (5.80±0.12mmol/L vs. 5.24±0.11; $p<0.001$), LDL-cholesterol (3.68±0.13mmol/L vs. 3.33±0.11; p=0.038), and triglyceride (3.41±0.30mmol/L vs. 2.27±0.19; p=0.001) concentrations were especially elevated in HIV-infected patients treated by highly antiretroviral drugs (protease inhibitors). A history of hypertension was present in 10.4% of all HIV-infected patients. The population of HIV-infected individulas presents an increased rate of males (77.7%), owing to the rate of homosexual men.
Conclusions: Cardiovascular risk factors are increased in HIV-infected patients. The present data enforces the concerns of premature artherosclerosis and an rising rate of cardiovascular events in HIV-infected patients. Therefore, an increased fraction of patients with HIV-infection in cardiology has to be assumed in future.

P2317 Coronary events in HIV patients. Angiographic features. A case control study

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In recent years, several acute coronary events have been reported in HIV patients. We tried to analyze coronary disease in HIV patients through a case control study.
Method: We compared all HIV patients consecutively hospitalized with a primary event acute coronary syndrome (ACS) to non HIV patients matched for age, gender, and type of ACS. Risk factors and the coronary angiogram features were analyzed. The analysis was conducted blind regarding the patients' infectious status. The clinical evolution at one year is reported.
Student's t test was used for comparison.
Results: From July 1997 to November 2002, 26 HIV patients (24 men) were admitted with acute coronary syndrome. Mean age was 47±8 years.
Twenty-three patients had received tritherapy (n=21) or bitherapy (n=2) for an average of 4.3 ±1.8 years. Among these patients, 12 had a treatment containing a protease inhibitor. Three patients had received no anti-retroviral treatment. Among the 26 HIV patients, 13 were admitted with a ST-elevation-ACS and 13 with a non-ST-elevation-ACS. The control group consisted of 52 non HIV patients.
Comparison of the usual risk factors shows more frequent excess weight in the non HIV group: 7.6% vs 40%; p=0.003 but lower LDL-cholesterol: 1.27 ±0.48 vs 1.47 ±0.39; p=0.047 and a higher triglycerides level in the HIV group: 3.07 ±2.28 g/l vs 1.78 ±0.77 g/l; p=0.0004.
According to the TIMI classification, type A lesions were found significantly more often in the HIV group: 44% vs 2%; $p<0.05$.
Regardless of the culprit lesion, atheroma was less frequently found in the HIV group: both on the culprit vessel (48% vs 81% in the non HIV group; p=0.007) as in the whole coronary network (58% vs 77% in the non HIV group; p=0,09). Seven patients in the HIV group (27%) vs 2 patients in the control group (3,8%) were re-admitted within 9 months due to a relapsed acute coronary event (p=0.005).
Conclusion: HIV patients presenting an ACS have a greater incidence of hypertriglyceridemia and a reduced LDL-cholesterol level. From the angiographic viewpoint, coronary events in HIV individuals occur in an angiographically healthy coronary network relatively unaffected by atherosclerosis. Indeed, the culprit lesion is often an isolated type A lesion which lends itself readily to revascularization by PTCA.

P2318 The characteristics, management and outcome of patients with acute coronary syndrome hospitalized on weekdays versus weekends. A national survey

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We hypothesized that patients (pts) with acute coronary syndromes (ACS) admitted during weekends may receive less evidence-based treatment and may have a less favorable prognosis in comparison to pts admitted during weekdays. In a 2-month national survey conducted in 2002, 2049 consecutive ACS pts were hospitalized in all 26 CCU's operating in Israel. Of them 528 pts (26%) were admitted on weekends (Friday-Saturday) and the other 1521 pts were admitted on weekdays (Sunday-Thursday). Age (64 vs. 64 yrs), men (76 vs. 78%), prior MI (28 vs. 26%) and diabetes (32 vs. 30%) were similarly distributed in both groups. Management and prognosis of these two groups of pts were as follows. [Weekdays vs. Weekends]. After multiple adjustment for age, sex, prior MI, diabetes, Killip II+, ST elevation, reperfusion therapy and coronary angiography, the OR of death among pts admitted on weekends was not different from those admitted on weekdays (30-day OR 0.99; 95% CI 0.61-1.56;6-month OR 0.98; 95% CI 0.67-1.41).

Weekdays vs. Weekends

	Weekdays (n=1521) %	Weekends (n=528) %
ST-elevation ACS	48	53*
Killip 2+	20	23
Aspirin	92	92
Thrombolysis (pts with ST-elevation)	29	44*
Primary PCI (pts with ST-elevation)	28*	19
Ticlopidine/Clopidogrel	49	48
IIb/IIIa Antagonist	13	13
Coronary angiography	70	66
Q-wave MI	43	46
Mortality: 30-day	5.5	5.3
6-month	9.1	9.0

*$p<0.05$

Conclusion: In this survey conducted in all operating CCU's in the country, ACS pts admitted on weekends presented similar characteristics, were treated similarly, except for primary PCI, and exhibited the same prognosis as counterparts admitted during weekdays. National surveys play a major role in assessing adherence to guidelines and for evaluation of ACS management in weekdays versus weekends.

P2319 Self management of anticoagulation with the INRatio system: agreement of self testing and central laboratory INR measurements and concordance in the therapeutic range after a 2-day teaching program

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Self management of oral anticoagulation (OAC) decreases complication rates and improves quality of life. Good agreement of self-determined and routinely performed laboratory INR measurements is a precondition for successful self-management of the OAC therapy.

Method: This three-center study compared the INR measurements of 76 newly oral anti-coagulated patients (57,4 years, 71% male), who used the INRatio™ system (Hemosense), with the INR-values determined in the central labs (CL). After participation in a structured quality-controlled training program patients were monitored for six weeks. Pre-defined observation times were T0 (before training), T1, T2 (directly after each training unit), W2 (after 2nd week), W4 (after 4th week) and W6 (after 6th week). Capillary blood samples were taken by the patients and measured with the INRatio. Simultaneously, plasma samples were determined in the CL. One of these CL functioned additionally as a reference lab (RL) (Stago Compact/Innovin) for independent re-determination of shock-frozen samples. Agreement was studied at any time separately according to the method suggested by Bland/Altman. As measures of disagreement, root mean square differences (RMSD) were calculated and visualized using dissimilarity maps. The rates of measurements within the individual therapeutic ranges were determined at T0, T2 and W6.

Results: Before training (T0), self-test INR values (ST) were on average. 15 units lower than RL values ($p<0.001$), with a decreasing trend towards less extreme INR determinations ($p<0.001$). After training and six weeks later (T1, T2, T3), the tendency towards lower values prevailed, but the trend to less extreme measurements weakened. Compared to CL, on average no shifts in ST values were observed, but there was a slight trend to more extreme values after training ($p=0.012$ at W6). After six weeks, 95% of the self-determined INR values were within the range of –1.1 to +0.6 from RL and within the range of –1.2 to+0.8 from CL. RMSDs were similar at all times, after six weeks 0.36 INR (ST vs. RL), 0.37 (ST vs. CL) and 0.47 (CL vs. RL). The rate of INR determinations within the therapeutic range improved from 31.6% (T0) over 33.8% (T2) to 60.3% (W6), according to RL.

Conclusion: The agreement between self testing results with the INRatio™ and central laboratory measurements was very good at all times. RMSDs of less than 0.5 INR demonstrate an excellent similarity of ST results with lab methods.

The accuracy aspect of the investigation support the use of the INRatio™ system as self management device.

ENVIRONMENTAL AND LIFESTYLE DETERMINANTS OF CARDIOVASCULAR RISK

P2320 Current smoking and development of type 2 diabetes in patients with coronary artery disease and decreased functional capacity

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Purpose - The data regarding possible contribution of cigarette smoking to development of type 2 diabetes are scarce and inconclusive. Moreover, the possible role of smoking on the diabetes incidence in patients with coronary artery disease (CAD) and decreased functional capacity has not been specially investigated. The present study was aimed to evaluate the association between cigarette smoking and development of type 2 diabetes in patients with decreased functional capacity related to CAD over a 7.7-year follow-up period. SUBJECTS AND METHODS - The study sample comprised 630 nondiabetic patients aged 45-74 years, with a fasting blood glucose of $<$ 126 mg/dl and with impaired functional capacity (New York Heart Association $>$ or = II functional class). The detection of a fasting blood glucose of $>$ or = 126 mg/dl during follow-up was defined as the criterion for new diabetes. The patients were divided on two groups: 1) Non smokers (never- and past smokers pooled together) – 552 patients; 2) Current smokers – 78 patients.

Results - Smokers were younger but they had relatively unfavorable lipid profile (with respect to apolipoproteins A, triglyceride and HDL-cholesterol levels). No significant differences between the groups were found for weight, body mass index, total cholesterol and blood pressure. During the follow up, development of new diabetes was recorded in 98 patients: in 80 (14.5%) of non smokers and in 18 (23.1%) of smokers, p = 0.05. Among the non smokers, there were no significant differences in the diabetic incidence between 357 never-smokers and 195 past smokers: respectively 48 (13.4%) and 32 (16.4%), p= 0.34. In addition, all-cause mortality among the smokers (23.1%) was significantly higher than in non smokers (12.7%), p= 0.01. Multivariate analysis identified the current smoking as an independent predictor of increased risk of new diabetes development with a hazard ratio of 1.94 (95% confidence interval 1.16-3.25).

Conclusion - Current smoking was associated with independent two-fold increased risk for development of type 2 diabetes in patients with established CAD and impaired functional capacity over a 6 to 9 year follow-up period. Therefore, smoking is an additional important modifiable risk factor that could be targeted for prevention of diabetes.

P2321 Even a little secondhand smoke is dangerous for the heart: the CARDIO2000 study

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Background: During the few past years special attention has been given to the effect of secondhand smoke on human health, especially to the incidence of lung cancer and cardiovascular disease. The purpose of this study was to investigate the association between environmental tobacco smoke exposure (at least 30 min/day) and the risk of developing acute coronary syndromes (ACS), in cardiovascular disease-free individuals.
Methods: The CARDIO2000 is a case-control study, was conducted in Greece, during 2000- 2001. Cases included 847 individuals with a first event of ACS and 1078 cardiovascular disease-free controls. Cases and controls were frequency matched on age (within three years of age), gender and region. ACS was defined as a diagnosis of first acute myocardial infarction or unstable angina. Exposure to secondhand smoke was measured by self-report as follows: after the second day of hospitalization, for the cases and at the entry for the controls we asked them whether they are currently exposed to tobacco smoke from other people (home or/and work) for more than 30 minutes per day. The responses were categorized into three levels: no exposure, occasional exposure ($<$ 3 times per week), and regular exposure. In addition we, also, asked for how many years they have been exposed. Because these were self-reported assessments and prone to bias, we compared these results to reports obtained from subjects' relatives or friends, using the Kendal's tau-coefficient that showed high agreement.
Results: Seven hundred and thirty-one (86%) of the patients and 605 (56%) of the controls reported exposure of 30 minutes per day or more to secondhand smoke. Among non-smokers, patients were 47% more likely to report regular exposure to environmental smoke (OR=1.47, 95% CI: 1.26 – 1.80) compared to controls. The risk of ACS was, also, elevated in active smokers (OR=2.83, 95% CI 2.07 – 3.31) regularly exposed to environmental smoke. Moreover, the quantitative dose-response equation showed that the odds ratios of developing ACS are clearly described by an exponential function of years of exposure to environmental tobacco smoke (Odds ratio = 1.0332 e0.022 x {years of exposure}, R2 = 78%). That is, even a little second hand smoke ($<$ 5 years) is associated with 15% increase of the coronary risk.
Conclusions: Our findings support that even a short exposure to second hand smoke increases the risk of developing acute coronary syndromes. The consistency of these findings with the existing totality of evidence presented in the literature supports the role of secondhand smoke in the etiology of ACS.

P2322 Synergistic effect of stromelysin-1 (matrix metalloproteinase-3) promoter 5a/6a polymorphism with smoking on the onset of young acute myocardial infarction

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Background: Plaque rupture with thrombosis is well established as a critical factor in the pathogenesis of acute myocardial infarction (MI). Stromelysin-1, also called matrix metalloproteinases-3 (MMP-3), can degrade extracellular matrix and are identified extensively in human coronary atheroslcerotic plaques, and may contribute to the weakening of the cap and subsequent rupture. In this case-control study, we analyzed the distribution of 5A mutation in the promoter region of stromelysin-1 gene and its association with the onset of young MI group in Taiwan. **Methods:** We studied 150 consecutive patients with acute MI onset at age under 45 (mean age 43.95 years; 84% men) with MI and 150 sex- and age-matched control subjects (mean age 44.51 years) of 5A/6A mutation at stromelysin-1 promoter by using polymerase chain reaction and direct DNA sequencing. **Results:** The frequency of the 5A mutation (5A/5A + 5A/6A genotypes) was significantly higher in the young MI than the control group (31% vs 18%, odds ratio [OR] 2.70, 95% confidence interval [CI] 1.3 to 6.8, p=0.009). Multiple logistic regression analysis showed that the 5A allele polymorphism was an independent risk factor (OR 2.36, 95% CI 1.2 to 5.9, p=0.008) as were as smoking (OR 3.92, 95% CI 1.75 to 9.21, p=0.001), diabetes mellitus (OR 3.51, 95% CI 1.41 to 6.32, p=0.0068) and hypertension (OR 1.85, 95% CI 1.96 to 7.63, p=0.001) for the premature onset of MI. Moreover, among patients who did not smoke, the 5A allele polymorphism was associated with an increase in the risk of young MI (OR 4.05, 95% CI 1.2 to 10.3). Furthermore, smoking carriers of the stromelysin-1 5A allele polymorphism had a significantly 9-fold increased risk of young MI (OR 8.55, 95% CI 2.3 to 18.3) when compared with non-smoking non-carriers. **Conclusion:** There was a significant association between the 5A/6A polymorphism in the promoter region of stromelysin-1 gene and young MI in Taiwan. Both the 5A/6A polymorphism of stromelysin-1 gene and smoking are independent risk factors for young MI population. A synergistic effect between these two risk factors for the premature onset of MI had been shown in this study.

P2323 The effect of Mediterranean diet on inflammation markers: the ATTICA study

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Background: The beneficial role of the Mediterranean diet in cardiovascular diseases (CVD) has been established. However, the biochemical and clinical markers that may be affected favorably by such diet have not been evaluated. The aim of this work is to evaluate the effect of the Mediterranean-type of diet on inflammatory markers, like homocysteine, fibrinogen and C-reactive protein, associated to cardiovascular risk in a cardiovascular disease free sample of general population.
Methods: A random algorithm was developed and stratified, by sex- age; multistage sampling was performed, during 2001 - 2002. In this work data from 1128 men (18-87 years old) and 1154 women (18-89 years old) were analysed. The consumption of red meat, chicken, fishes, vegetables, legumes, pasta, salads, cereals, diary products, sweets and fruits was investigated as an average per week, during the past year, using a validated nutritional questionnaire, developed by the National School of Public Health. We defined subjects who adopt this type of diet using as cut-off points the median values of the monthly food consumption score. The plasma levels of C-reactive protein, homocysteine and fibrinogen were measured, after 12 hours fast and without any consumption of tea and coffee.
Results: 24% of men and 36% of women were defined closer to the Mediterranean diet. Data analysis revealed that the adoption of Mediterranean diet is associated with a significant reduction of fibrinogen (312$\pm$33 vs. 328$\pm$ 31 mg/dl, $P<0.05$), homocysteine (12$\pm$3 vs. 14$\pm$5 mg/dl, $P<0.05$) and C-reactive protein levels. Afterwards, we classified the participant into quartiles of the investigated parameters. Multivariate analysis reveled that adoption of Mediterranean diet is associated with 14% lower likelihood of being in the higher quartile of fibrinogen levels (odds ratio = 0.86, $p < 0.01$), 10% lower likelihood of being in the higher quartile of homocysteine levels (odds ratio = 0.90, $p < 0.01$), and 17% lower likelihood of being in the higher quartile of CRP levels (odds ratio = 0.83, $p < 0.01$) as compared with participants in the lower quartiles of the aforementioned factors.
Conclusion: The "ecological" paradox regarding low CVD mortality in Mediterranean populations, as coined by Keys and his colleagues, is partially explained by the favorable modification of several inflammation markers.

P2324 Fruit and vegetable consumption in relation to the development of acute coronary syndromes; the CARDIO2000 study

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Background: Many constituents of fruits and vegetables may reduce the risk for coronary heart disease (CHD), but data on the relationship between fruit and vegetable consumption and coronary risk are sparse in the literature. In this work, we assessed the association between fruit and vegetable consumption and CHD risk.
Methods: CARDIO2000 is a case-control study for the primary prevention of CHD. Stratified sampling from all Greek regions, consisted of 848 randomly selected patients who have just entered to the cardiology clinic for first event of acute coronary syndromes (ACS) (695 males, 58$\pm$10 and 153 females, 65$\pm$9 years old) and 1078 paired, by sex-age-region, controls selected in the same hospitals but without any clinical suspicion of CHD. Using special food-frequency questionnaires from the National School of Nutrition we assessed total diet. Among others, fruit and vegetable intake was measured in weekly basis. Multiple logistic regression analysis assessed the risk of developing ACS, by level of fruits and vegetables intake, after taking into account the effect of several potential confounders.
Results: Three-hundred and sixty-five (43%) of the cardiac patients consumed 1.7$\pm$1 fruits/day and 722 (67%) of the controls consumed 2.8$\pm$1 fruits/day. After adjusting for the conventional cardiovascular risk factors, those in the upper quintile of fruit and vegetable consumption (give number of fruits/day?) had 18% lower risk for CHD (OR=0.82, 95% CI 0.71 - 0.91, $P<0.01$), compared with those in the lowest quintile of intake (give # of fruits/day). A 3.4% reduction in coronary risk (OR=0.97, 95% CI, 0.92 - 0.99, p for trend < 0.01) was noted for each 1-piece/day increase in fruit or vegetable consumption. In particular, green vegetable intake was associated with a 2.8% reduction on coronary risk per item/day (OR=0.97, 95% CI 0.84-0.99, $P<0.05$), and vitamin C-rich fruits with a 4.5% reduction per item/day (OR=0.95, 95% CI 0.83-0.98, $P<0.01$).
Conclusions: Consumption of fruits and vegetables, particularly green leafy vegetables and, especially, vitamin C-rich fruits, have a protective effect against coronary heart disease. The daily servings of fruit and vegetable consumption of optimum health benefits is 3 servings/day.

P2325 Nutrition in the low-income families: able-bodied male population

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Socio-economic reforms, which have been going on in the recent decades in Russia, result in a great number of poor people, cardiovascular disease (CVD) mortality rate growth in the population. In Kabardino-Balkariya, one of Russia's Regions, the cardiovascular mortality rate in the able-bodied men is particularly high. Therefore, an epidemiologic study of nutrition and health in the able-bodied men has been held, in order to detect a potential relationship between the parameters under investigation and economic position of those under examination.

Methods: 650 men of ranging incomes, aged 35 to 60, have been examined. Two methods have been used to study nutrition: by means of interrogation on the 24-hour nutrition, and by keeping the diary records of foods consumption in the family of a person under examination. The WHO-developed methods have been used to study the prevalence of the CVD basic risk factors.

Results: Level of basic foods consumption proved to be substantially dependent on the incomes of those under examination (table).

Description	All men	Group 1*	Group 2**
Protein, g/day	67.0±1.8	31.0±5.3	114.3±4.7
Animal protein, g/day	26.2±1.7	9.7±3.5	61.3±5.7
Fats, g/day	61.6±1.6	25.4±5.3	178.3±14.3
Vegetable fats, g/day	50.4±2.1	2.4±4.7	85.0±4.4
Carbohydrates, g/day	392.4±12.8	170.6±12.9	603.4±66.0
Caloric value (kcal)	2304.0±88.3	998.7±113.1	3786.2±446.5

All men (n=650);*Group 1: The lowest-income men(n=70);**Group 2: The high-income men(n=70);Content of Nutritional Matters and Caloriae in the 24-hour Food Ration Ranging-Incomes Men (M+m)

In the daily ration of Group 1, a substantial deficiency of all the nutrition components needed has been detected. Nutrition in Group 2 is an excessive at each of the indices. The highest arterial hypertension, the highest blood triglycerides content have been found in those of low-protein content in the food ration ($p < 0.01$).

Conclusions: Disorders detected show, that the nutrition – health disbalance is in relation with both the income level, and unavailability of rational nutrition knowledge. Besides the targeted economic assistance to the poor, an educational programme for the entire population is needed, too.

P2326 Amount and type of alcohol intake in relation to cardiovascular risk factors, dietary habits and lifestyle in a French population of middle-aged men

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Background: The protective effect of alcohol on cardiovascular risk may be attributable to ethanol but may also differ according to specific alcohol beverages. These differences however might be confounded by behavioural and lifestyle factors. Our objective was to study the association between lifestyle, nutritional habits (NHs) and cardiovascular risk factors (CRFs) in relation with the amount and type of alcohol intake in a French free-living population.

Methods: A sample of 1110 men, 45-64 years, was randomly selected in three centres: Lille, Strasbourg and Toulouse. A fasting blood sample was taken during a medical examination and data collected on questionnaires. A day-food diary was used to assess NHs and alcohol intake. Socio-economic status, lifestyle, NHs and CRFs were studied in relation with the amount of alcohol intake (five groups: abstainers, 1-19, 20-39, 40-59 and >59 g of ethanol a day); and the type of beverage (beer drinkers (BDs): beer>70% of total alcohol, wine (WDs): wine>70% of total alcohol and mixed (WBDs) consumption).

Results: Abstainers were 12.7%, 71% of the subjects drank between 0.1 and 59 g/d and 16.3% 60 g/d of alcohol or above. Sedentarity ($p<0.01$), the proportion of blue collars ($p<0.001$) and of smokers ($p<0.001$) increased along with the intake of alcohol consumption, and heavy drinkers were more likely to have worse cardiovascular risk profiles (blood pressure, waist-to-hip ratio, glycemia, triglycerides, total cholesterol ...) than those who drank less. Smoking was less frequent and physical exercise more frequent in WDs than in WBDs and BDs; and GGT level, TG level and alcohol dependence score were lower in WDs than in WDBs and BDs. For NHs, after adjustment for age, schooling, centre, smoking, physical exercise, body mass index and diet, energy provided by fat ($p<0.001$), delicatessen ($p<0.001$) and meat ($p<0.001$) was higher and energy from carbohydrate ($p<0.001$), fruit ($p<0.01$) and dairy products ($p<0.001$) was lower in heavy drinkers than in the other groups. The contribution of vegetables, fruit, and dairy products to energy intake was also higher in WDs than in WBDs and BDs, however these differences disappeared after adjustment.

Conclusions: These results show that heavy drinkers have unhealthy behaviours and support the hypothesis that, even in France, wine drinkers have "healthier lifestyles" which thus may account for some higher protective effect of wine consumption.

P2327 Health-related quality of life and heart failure

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Purpose: Besides its high fatality, symptomatic heart failure (HF) is associated with poorer quality of life. The aim of this study was to assess quality of life in the different stages of the continuous pathway that leads through high-risk, asymptomatic cardiac dysfunction to clinically overt HF.

Methods: We studied 430 adults aged 45 years or older, randomly selected from the community-dwellers of Porto. Data were collected by questionnaire, physical examination, ECG and echocardiography (M-mode, 2D). Quality of life was assessed by the Short Form 36 (SF-36) which has been previously validated in the Portuguese population and evaluates eight dimensions on a scale where higher scores represent better quality of life. Participants were classified according to the stages defined by the ACC/AHA: A=high risk, B=asymptomatic cardiac strutural changes, C=clinical HF, D=very severe HF.

Results: Table 1 represents means (adjusted for age, gender and education by analysis of covariance) of the score obtained in the eight dimensions assessed by the SF-36 across stages of the ACC/AHA classification. All dimensions worsen progressively and significantly across the stages, with the poorest quality of life registered in HF patients for all dimensions.

Table 1

	Normal (n=145)	A (n=162)	B (n=94)	C (n=29)
Physical functioning	72	69	68	60
Role limitaions (physical problems)	79	72	66	51
Pain	71	60	61	55
Social functioning	82	74	74	63
Mental health	69	63	62	56
Role limitations (emotional)	79	72	71	52
Vitality	62	53	56	46
General health perceptions	58	52	51	50

Means of SF-36 scores adjusted for age, gender and education, according to ACC/AHA stages

Conclusion: Quality-of-life is significantly impaired in HF patients and worsens progressively as the risk increases even before clinically overt HF is present.

P2328 Prevalence and clinical correlates of depressive symptoms in a large cohort of elderly heart failure patients

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Aim: Depression is a relatively common condition among pts with heart failure (HF) and is associated with poor quality of life and outcome. Aim of the study was to assess the prevalence and correlates of depressive symptoms in a large cohort of elderly HF patients using comprehensive multimensional assessment instruments.
Methods: . A group of 1020 outpatients aged >70 yrs (76±4.8, range 70-93, Males 62%) with stable HF were prospectively studied. Depressive symptoms were assessed by means of the 15-item Geriatric Depression Scale (GDS). We defined clinically relevant a score≥6. Emotional status was also assessed by means of the Emotional Dimension score of the Minnesota LHFQ (MED). Cognitive status and functional capability in activities of daily living (ADL) were assessed by means of Folstein Mini Mental State Examination (MMSE) and a modified 14-item ADL scale. One-year follow-up is ongoing.
Results: 53% of pts were in NYHA III-IV, 26% had diabetes, 63% hypertension, 40% cognitive impairment (MMSE <24). Etiology was 50% ischemic. Charlson index >2 was present in 54.9% and disability (ADL score <11)in 39.8%.
A GDS≥6 was present in 48% of pts. Depressive symptoms were classified as mild: GDS 6-7: 15%; moderate GDS 8-10: 19.2%; severe:GDS>11: 13.2%. Mean MED was 7.2+5.9.
The variables significantly associated to GDS≥6 were: female gender, age, NYHA III-IV class, Charlson index ≥2, cognitive impairment, disability (ADL score <11), education <5 yrs, not married, low income. Prevalence of GDS≥6 ranged from 34.5% among NYHA class II pts to 67% among pts with class IV (p<0.0001).GDS score significantly correlated with all MLHF scores (total, physical and emotional dimensions) (p<0.0001).
At multivariate analysis, disability (OR 2.189, 95%CI 1.589-3.016, p<0.0001),low income (OR 3.283, 95%CI 1.836-5.870, p<0.0001), advanced NYHA class (OR 1.815, 95%CI 1.351-2.438, p<0.0001), cognitive impairment (OR 1.762, 95%CI 1.299-2.390, p=0.0003), not married (OR 1.405, 95%CI 1.018-1.939, p=0.038) and female gender (OR 1.468, 95%CI 1.058-2.038, p=0.021) were independently associated to depressive symptoms.
Conclusions: This study suggests that: 1) depressive symptoms are common in elderly HF pts and are associated to disability, severity of HF, cognitive impairment, socio-economic factors and female gender; 2) the 15-item GDS scale provides a simple means of identifying depressive elderly HF pts who are in need of special interventions.

P2329 Quality of life tools predict symptom severity in survivors of a myocardial infarction

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Objectives: To establish whether the physical and mental component scores (PCS and MCS) of the Short Form 12 (SF-12) quality of life (QOL) questionnaire are as reliable and sensitive as those of the Short Form 36 (SF-36) in distinguishing the severity of symptoms of myocardial ischaemia.
Method: Postal questionnaire survey of 476 four-year survivors of a myocardial infarction identified from the Nottingham heart attack register of which 424 responded (response rate:89%).
Main Outcome Measures: Frequency and severity of Rose angina, severity of Rose dyspnoea and quality of life as determined by the physical and mental component scores (PCS, MCS) of the SF-36 and SF-12.
Results: The PCS and MCS for both the SF-36 and SF-12 could be calculated in 278 (66%) due to missing values. Individual scores were similar for the PCS-36 and PCS-12 but different for the MCS-36 and MCS-12 (paired Wilcoxon sign rank test Z=1.83, p=0.067 and Z=7.44, p<0.001 respectively); on a group basis, there were no differences. PCS and MCS scores of both the SF-36 and SF-12 differentiated patients with varying degrees of breathlessness, presence of angina or exertional chest pain and frequency of chest pain equally well.
Conclusions: The SF-12 retains similar discriminatory power as the SF-36. Despite a statistical discrepancy between individual MCS-12 and MCS-36 results, the differences were so small that they would not be considered clinically relevant. The SF-12 was as reliable and sensitive in this cohort as the SF-36. The brevity of the SF-12 makes it potentially a valuable tool for use in large scale epidemiological and intervention studies.

CARDIOVASCULAR DISEASE IN THE ELDERLY: NEW DIAGNOSTIC TOOLS AND TREATMENTS

P2330 N-brain natriuretic peptide levels in elderly patients during long-term follow-up following complicated myocardial infarction; an OPTIMAAL substudy

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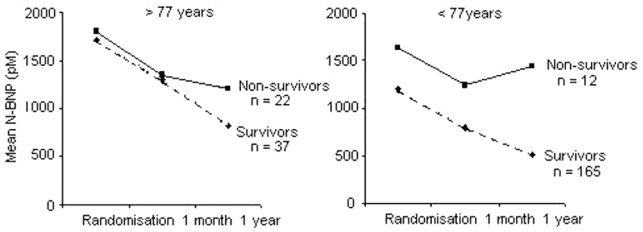
Introduction: Elevated plasma concentration of N-terminal brain natriuretic peptide(N-BNP) is a marker of cardiac dysfunction and is associated with increased mortality both in patients with CHF and following acute MI. N-BNP increases with age, however, little is known about the relationship between N-BNP and mortality in elderly patients during long term follow-up following high risk MI.
Methods: N-BNP was acquired from all 236 patients in the neurohormonal substudy in the OPTIMAAL trial (losartan vs. captopril in patients with CHF and/or evidence of left ventricular dysfunction following MI). N-BNP of surviving and non-surviving patients in the fourth age quartile >77 yrs (n=59) were compared with patients <77 yrs (n=177). N-BNP was acquired at randomisation (median 3 days following MI), after 1 month and 1 year.
Results: Comparing survivors with non-survivors >77 yrs, there was no significant difference in N-BNP at any time point. This was in contrast to increased N-BNP levels in non-survivors compared with survivors <77 yrs (p<0,05). N-BNP was significantly(p<0,05) higher at all time points in survivors >77 yrs compared with survivors <77 yrs. In both age groups survivors demonstrated a continuous significant (p<0,01) decrease in N-BNP from randomisation during one year. There was no decrease in N-BNP among non-survivors in any age group.



Age vs. N-BNP following high risk MI.

Conclusion: Following high risk MI in patients >77 yrs, N-BNP did not predict death at any time point during the first year. This was in contrast to patients <77 yrs in whom there were significantly elevated N-BNP levels among non-survivors compared with survivors. N-BNP did not predict death in patients >77 yrs possibly due to the general increase in N-BNP levels in the surviving part of this population.

P2331 Clinical audit and registry of acute myocardial infarction in Hong Kong

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Background: Acute myocardial infarction (AMI) is a dangerous manifestation of coronary artery disease (CAD). AMI literature in Western population are abundant, but its documentation in Asian remains scanty.
Methods: To evaluate the incidence of AMI hospital admissions and basic clinical data in southern Chinese city, a territory-wide prospective AMI registry and clinical audit was performed in Hong Kong 1995-1996, with predefined entry criteria, outcome measures and uniform evaluation guidelines (hot pursuit). Quality control was counterchecked with Hospital Authority Inpatients Access System (IPAS) AMI data (computer coding ICD-9 410.1)(cold pursuit).
Results: There were 3373 AMI admissions in all hospitals over 24 months, amounting to 26 per 100,000, population per year; under-inclusion of AMI registry would be <20% in comparison with IPAS cold pursuit data. Age-standardized AMI incidence (IPAS data) is 408 (461 in male, 373 in female) per 100,000 population >75 year, 196 (257 in male, 139 in female) per 100,000 population 65-74 years, and 89 (129 in male, 45 in female) per 100,000 population 55-64 years per year. Of the AMI registered, the mean age was 67.6±11.6 years (male 64.8±11.5 years, female 72.9±9.7 years). 45% of patients were >70 years, and only 1.5% were younger than 40 years. The male: female ratio was 2:1; 65% arrived hospital <4 hours of pain onset, and 64.4% received CCU care in hospitals. Risk factors identified included smoking (47.5%), hypertension (33.2%), diabetes mellitus (21.7%) and hypercholesterolaemia (11.2%). 68% had Q wave infarct and 32% non-Q wave infarct. Treatment in hospital included aspirin (85%), heparin (22%), ACE-inhibitors (66%), B-blockers (46%), statin (13%, mean total cholesterol 5.3±2.6mmol/l) and percutenous coronary intervention (4%). Their hospital course were complicated by heart failure (36%), cardiogenic shock (13%), bundle branch block (4%), high grade atrioventricular block (8%), artrial dysrhythrmias (10%), ventricular tachycardia (13%) and fibrillation (9%) and stroke (1%). 30 days mortality was 22.6% (male 19.7%, female 29.8%; 33.8% in patients >70 yeras), due to pump failure (38%) and sudden deaths or primary dysrhythrmias (51%).
Conclusions: AMI incidence in Hong Kong Chinese remains lower than western countries, being one-tenth to one-quarter of western AMI incidence. AMI in southern Chinese conforms to classical patterns, but with older age, more females, higher complications and hospital mortality, and suboptimal utilization of some evidence-based AMI treatment modalities.

P2332 Utility of multidimensional assessment in selection of elderly heart failure patients eligible for outpatients management programs

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Background: Heart failure (HF) is primarily a disease of the elderly. Recent AHC/ACC Guidelines recommend as Class I the assessment (A) of patient's ability to perform activities of daily living (ADL). Aim of this study was to evaluate the utility of A in selecting elderly pts eligible for hospital-based outpatient's management programs (OMP) using standard assessment instruments.
Methods: 86 pts aged >70 yrs (77,45±5,9, range 70-94, 48,8% women), from 2 HF clinics were studied before entering an OMP. Multidimensional data were collected using an ad-hoc questionnaire, including: socio-environmental factors, Charlson comorbidity index, ability to perform basic (BADL) and instrumental (IADL) ADL (i.e. self-sufficiency in the ability to use telephone, prepare foods, taking medications, getting outside independently), cognitive function (MMSE). Pts who did not presented to scheduled visits and drop-out from the OMP were defined as non-compliant (NC).
Results: At baseline 62% of pts were in NYHA III-IV, 91.9% were on ACE-i/ARB and 50,8% on betablockers. Etiology was 55% ischemic, mean EF% was 33±11, and Charlson index was 2.36±1.5; 40.2% of pts had cognitive impairment, 13% previous stroke, 55.8% ≥2 IADL dependencies (IADLDep) and 38.8% ≥1 BADL Dep. At a 1-year f-up 37.2% of pts were NC. All-cause mortality and re-admission (RA) rate were 18.6% and 42.9%. The univariate variables associated to NC were: IADL Dep (OR 8.22 95%CI 2.73-24.76 p=0,0001), renal impairment(OR 7.7 95%CI 1.93-30.89 p=0.001), low income (OR 8.1 95%CI 1.6-41.62 p=0.004), not married (OR 3.045; 95% CI 1.18-7.82, p=0.019), Charlson index ≥2 (OR 3.08 95%CI 1.139-8.321 p=0.024), significant osteoarthrosis (gait impairment) (OR 3.04 95%CI 1.161-7.96 p=0.021). At multivariate analysis, renal dysfunction (OR 6.6, 95%CI 1.42-30.81 p=0.016) and IADLDep (OR 8.1; 95%CI 2.53-26.01 p<0.0001) were independently associated to NC.
Conclusions: This study demonstrates that: 1) disability and cognitive impairment are frequent in community-dwelling elderly HF outpts and mortality and RA rates remain high despite optimal adherence to treatment guidelines and structured hospital-based follow-up; 2) NC to OMP is frequent in elderly HF pts: as a result of disability, comorbidities and socioeconomic problems, rather than simple ageing itself; 3) Assessment of functional ability by means of a simple set of multidimensional data collected during the baseline visit is useful to identify pts eligible to hospital-based OMP and exclude those "frail" high risk pts, to follow-up with targeted home-based programs.

P2333 The blood pressure response to the Valsalva manoeuvre: an independent predictor of mortality in elderly cardiac patients?

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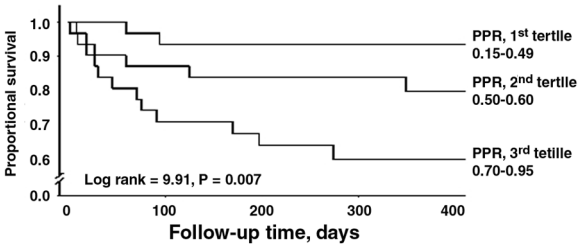
Introduction: Both the absolute number as the proportion of elderly cardiac patients are increasing. The prognosis of elderly cardiac patients is poor. Yet, it is difficult to estimate prognosis for the individual patient. The blood pressure (BP) response to the Valsalva maneuver (VM) is related to cardiac filling pressure and may be used to estimate prognosis. We studied whether the BP response to the VM was associated with mortality in elderly patients with various cardiac disorders.
Methods: In 93 patients, aged 71±5 yr (mean±SD) undergoing right-sided cardiac catheterization, the VM was performed. Continuous BP was measured non-invasively with Finapres®. From the BP response to the VM, the pulse pressure ratio (PPR) was calculated as the ratio of the lowest and highest PP. Survival was assessed from medical files or by telephone. Kaplan Meier survival was calculated for PPR tertiles. Cox regression was used for the prognostic value of PPR together with established prognostic variables.
Results: The follow-up period was 28 months. Survival differed significantly over the tertiles (see figure). PPR was an independent predictor of death; Hazard Ratio: 1.56 (per step of 0.1); 95%CI: 1.14 - 2.12, P=0.006), in a model with age, gender, LVEF, heart failure admittance, myocardial infarction, heart rate, presence of pulmonary rales, and NYHA class.



Kaplan Meier curves for PPR tertiles.

Conclusion: In this selected group of elderly cardiac patients, the PPR of the Valsalva maneuver was an independent non-invasive prognostic marker for all-cause mortality. Prospective studies on the predictive value of the PPR, together with established predictors for mortality, are warranted. Supported by the Netherlands Heart Foundation, Grant 98.043.

P2334 Platelet function in the elderly: the difference between stable and unstable angina

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Background: The functional status of platelets in older patients with acute coronary syndromes(ACS) may be reduced, in contrast to increased platelet activity seen in stable older subjects. **Methods:** Platelet functional status was assessed using light-transmittance aggregometry with ADP and flow cytometric assay of platelet surface membrane markers in 55 patients presenting with ACS and 41 patients presenting with stable angina each of whom had demographic and medication data recorded. Multiple regression analysis on each platelet function variable was used to define independent predictors.
Results: Patients ranged in age from 38 to 92 years with a mean of 66. Aggregation was found to decrease with advancing age, but only among the ACS patients, In multivariate analysis, age was the best predictor of decreased aggregation (Beta= -.558, r2=.353, p<0.001) among the patients with ACS. Age was also the best predictor of decline in platelet labeling with PAC-1, an antibody against the GP IIb/IIIa active site (Beta =.561, r2=.276, p=<.001) and of decline in platelet surface P-selectin (Beta=-.442, r 2=240, p=<.001). Age did not predict total GPIIb/IIIa expression in either ACS or stable patients, nor platelet-leukocyte aggregates (co-labeling with antibody to CD 151 and CD 14).
Conclusion: In older patients with ACS there is decreased platelet activity at presentation, indicated by an age-related decrease in ADP aggregation and decreased platelet surface expression of the active conformation of GPIIb/IIIa and P-selectin. The absence of an age-related decrease in expression of total GPIIb/IIIa, and of platelet-leukocyte aggregates, suggests a complex interaction between age and platelet physiology. Decreased activation of GPIIb/IIIa in older patients with ACS may relate to the observed increase in hemorrhagic complications in the elderly following GP IIb/IIIa inhibitor therapy, as well as thrombolytic.

P2335 Safety and tolerability of early in-hospital beta-blocker initiation in elderly patients with heart failure and left-ventricular dysfunction

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Background: Recent Guidelines recommend to initiate betablocker (BB) treatment in all eligible pts with heart failure (HF) and left ventricular dysfunction (LVD). However, elderly pts are usually underprescribed BB because of perceived side effects and the lack of available data on BB safety in this subset of pts.Avalaible data suggest that in-hospital initiation of BB treatment is feasible in advanced HF pts (Copernicus Trial: Circulation. 2002;106:2194) and allows accurate monitoring of potential adverse effects. Aim of this study was to prospectively assess the feasibility, safety and outcome of early BB treatment with Carvedilol in elderly pts hospitalized forHF.
Methods: A total of 164 consecutive HF pts aged >70 yrs (mean age 76.5 ± 6, range 70-99, 61% males,) with EF<40% and hospitalized for acute decompensation of HF were considered for early in-hospital BB treatment. Etiology was 62% ischemic, Charlson's comorbidity index was 2.2 ±1.5 (diabetes 30%, COPD 30%, peripheral arterial disease 24%), mean duration of symptoms of HF was 13±10 months. Mean HR and SBP were 78±14 b/min and 124±20 mmHg, respectively).
Results: BB therapy with Carvedilol (C) was started 4.5± 2.5 days after admission in 120 pts (73%). At baseline visit, mean NYHA class was 2.8 ± 0.6, mean Left Ventricular (LV) Ejection Fraction (EF%) was 28 ± 8 and mean LV End-diastolic volume (ml/m^2) was 103 ± 40 ml/m^2. During hospitalization 90% of pts received ACE-inhibitors, 60% digoxin, 94% furosemide (75% at doses >40 mg/d), 40% nitrates and 18% oral anticoagulants. No drug-related deaths were recorded. Mean length of stay was 11±6 days. Eleven/120 pts (9.1%) did not tolerated BB therapy. Seven drop-out (64%)occurred during hospital stay: 5 pts did not tolerated start dose (6.25 mg) (1 for HF decompensation, 4 for bronchospasm), and 2 pts suffered ventricular arrhythmia and advanced AV block during in-hospital dose titration. The remaining 4 drop-out occurred after discharge (36.4%)(1 for fatigue, 1 for depression and 2 for bradycardia). At 12-months follow-up, mean C daily dose was 22.1±14 mg/day (range 6.25-50 mg).
Conclusions: This study suggests that: 1) early in-hospital initiation of BB therapy is feasible also in elderly pts with LVD and recent HF decompensation and allows surveillance of potential adverse effects and rapid identification of intolerant pts; 2) When carefully monitored, Carvedilol is well-tolerated either at short or long-term in the elderly.

P2336 Effect of trimetazidine in elderly patients with ischaemic dilated cardiomyopathy

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Trimetazidine (TMZ) was reported to protect myocardium from ischemia probably by improving the myocardial energy utilization. Elderly patients have an increased incidence of ischemic dilated cardiomyopathy often related to diffuse coronary artery disease that reduces myocardial blood flow.
The purpose of the present study was to assess the effects of Trimetazidine on left ventricular (LV) dimensions and systolic function in 47 elderly patients (40 males and 7 females, mean (SE) age = 78±3.0) with ischemic cardiomyopathy and LV systolic dysfunction (LV ejection fraction <40%).
Patients were randomized to receive either TMZ (tds) or Placebo (tds) and were evaluated at baseline and after 6 months. Measures of LV dimensions included: LV end-diastolic (LVEDVI) and end-systolic (LVESVI) volume indices, LV ejection fraction (LVEF).
Demographic data were comparable between the two groups with respect to sex, age and race. In the Placebo group, baseline LVEDVI was (mean ± S.E.M) 67 ± 3.2 ml/m^2, the change at 6 months 3.7 ± 1.8 ml/m^2, and for the TMZ group, baseline LVEDVI was 66 ± 3.5 ml/m^2, the change at 6 months -4.1 ± 1.2 ml/m^2 (p=0.001 between groups). The changes in LVESVI were 0.26 ± 0.9 ml/m^2 and -2.2 ± 1.04 ml/m^2 for Placebo and TMZ, respectively (NS).
LVEF increased by 5.3±1.3% (p<0.05) after 6 months in the TMZ group while remained unchanged in the Placebo group -1.8±1.9% (NS).
In elderly patients with systolic dysfunction TMZ has beneficial effect on LV volumes and on LVEF compared to placebo, this effect may be related to the cardiac metabolic effect of TMZ.

P2337 Is enhanced external counterpulsation suitable for the treatment of angina in elderly patients with a history of congestive heart failure?

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Background: Cardiovascular disease is being transformed from an acute cause of premature death to a chronic disease of the elderly. When treating elderly patients (≥75 years) with symptomatic coronary artery disease and heart failure (HF), it is unclear whether the acute risks of revascularization are counterbalanced by better functional outcomes. Enhanced external counterpulsation (EECP) is a noninvasive analogue of the intra-aortic balloon pump designed to increase myocardial perfusion pressure and decrease cardiac workload. EECP has been demonstrated to be safe and effective in treating angina in patients ≥75 years; however, its safety and effectiveness in elderly patients with HF is unknown.
Methods: The study group consisted of 1,185 angina patients consecutively enrolled in the International EECP Patient Registry who were ≥75 years. Of this group, 443 (37%) reported a history of symptomatic HF.
Results: Prior myocardial infarction (78%), non-cardiac vascular disease (48%) and diabetes (42%) were present significantly more often in the HF group (p<0.001). Prior coronary revascularization (86%), as well as female gender (31%) was also more prevalent in the HF group (p<0.05). Elderly HF patients experienced more severe angina and reported a mean frequency of 10.8 angina episodes/week (p<0.001). Mean left ventricular ejection fraction was 39±15%. Of elderly patients with HF, a course of treatment was completed by 76%, with a mean number of 32 treatment hours. Acute congestive heart failure (5%) was the only adverse event that occurred more frequently during EECP treatment in the HF group. Of elderly HF patients who completed treatment (N=308), 82% reported angina reduction of at least one Canadian Cardiovascular Society class; overall, there was a mean decrease of 7.8 angina episodes/week, and 81% of patients who were using on demand nitroglycerin before treatment were able to discontinue its use after EECP. Patient assessed quality of life after a course of EECP was improved in 45% of elderly angina patients both with and without HF.
Conclusion: Symptomatic CAD in elderly patients is of immense public health and economic importance. Episodes of angina, as well as nitroglycerin use, were decreased, while quality of life improved in many elderly patients with symptomatic coronary artery disease and heart failure. EECP provides a low-risk, non-invasive alternative that can assist the clinician in treating elderly patients with cardiovascular disease.

P2338 Cardiac catheterization in a large cohort of octogenarians: complication rate in diabetic versus non-diabetic patients

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Background: Octogenarians with Diabetes mellitus type 2 are perceived as a high risk population for procedure-related complications. Since only few studies reported complication rates in this population in the era of coronary stenting, we set out to assess their risk in a large cohort of patients. Methods: We studied 1070 consecutive patients >80 years (82.6±2.6 years; 526 males, 544 females; 396 with Diabetes (DM), 674 without Diabetes (Non-DM)),who underwent cardiac catheterization between January 1995 and July 2000. Results: Age (DM: 82.4±2.4 vs. Non-DM: 82.8±2.8 years; p=n.s.) and number of acute myocardial infarctions (MI) (DM: 27%, Non-DM: 23%; p=n.s.) were similar in both groups. There were more women in the DM (57%) than in the Non-DM group (44%; p<0.001). Diabetics had more 3-vessel disease (DM: 35% vs Non-DM: 29%; p<0.02); there were significantly more balloon angioplasties performed in non-diabetic patients (DM: 27% vs Non-DM: 43%; p<0.001), whereas a higher, but non-significant number of diabetic patients underwent bypass surgery (DM: 36% vs Non-DM: 30%; p=0.16). A total of 32 patients (3%) died (DM: n=6; non-DM: n=26): 5 deaths occurred during procedures (3 patients died during rescue PTCA, 2 during emergency surgery), 16 patients were already admitted in cardiogenic shock, 6 died due to complications associated with acute myocardial infarctions (e.g. ventricular septal defect), 2 due to decompensated aortic stenoses, 2 patients due to pulmonary embolism, 1 due to aortic dissection type A. At the puncture site 39 complications occurred (DM 3% vs. non-DM 4%, p=n.s.) Conclusions: Despite the notion that it is the diabetic patient among the octogenarians who have the highest complication rates, this study shows in a large cohort of patients that their complication rates are well comparable to non-diabetic patients, and would thus not warrant a more conservative treatment strategy in these patients.

P2339 Mid-term outcomes of unprotected left main coronary artery stenting in the elderly

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Background: Until now, left main coronary artery (LMCA) stenosis was commonly treated by coronary artery bypass grafting. However elderly patients with LMCA disease have prohibitive operative risk and as a consequence, percutaneous coronary intervention (PCI) is now proposed as an alternative to CABG.
Methods: Between January 2000 and June 2002, a group of 50 consecutive elderly patients who were judged poor candidates for CABG underwent stenting for unprotected LMCA stenosis. Six-months clinical follow-up was obtained in 100% of patients.
Results: The mean age was 80.26 $\pm$ 4.38 years with an average surgical EUROSCORE of 8.12 and mean ejection fraction 48.7 $\pm$ 11.8%.
Cardiogenic shock was present in 8% of patients and 36 pts (72%) had an acute coronary syndrom with ST elevation (10 pts) or without ST elevation (26 pts). An intra-aortic balloon pump was inserted pre-procedure in 12%. Left main stents were deployed without predilatation in 34% of cases (1.1 $\pm$ 0.2 stents, diameter 3.7 $\pm$ 0.3 mm, length 11.55 $\pm$ 2.4 mm, inflation pressure 14.3 $\pm$ 3.4 atm). Kissing balloon inflation was performed in distal LMCA (30 pts) in 66.6% of cases. Angiographic success was obtained in all cases. The left main MLD increases from 0.73 $\pm$ 0.41 to 3.38 $\pm$ 0.46 mm and % stenosis decreased from 75.7 $\pm$ 11.9% to 7.2 $\pm$ 8.7%. The procedural success rate was 98% and there were 6 in-hospital deaths (12%). At 6-months follow-up there were 2 deaths, 5 TLRS and MACE free survival was 75%.
Conclusion: Unprotected LMCA stenting is a safe alternative revascularisation procedure with acceptable immediate and six months clinical outcome in elderly patients with relative contra-indications to surgery.

P2340 Homocysteine levels and prognosis after myocardial infarction in older patients

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Background: Plasma homocysteine (Hcy) levels have been associated with higher rates of atherothrombotic events in patients with and without cardiovascular disease. The role of Hcy as a postinfarction prognostic marker in older patients is unknown.
Methods: We measured Hcy levels levels by HPLC before hospital discharge in a series of patients >65 years old with an AMI and compared their outcomes according to Hcy levels.
Results: The population consisted of 184 patients aged 75$\pm$7 years old, 34% women, with a high prevalence of risk factors (66% hypertension, 50% dyslipemia, 35% smoking, 26% diabetes) and of previous cardiovascular diseases (42%). 77% were Q-wave MIs and 51% received reperfusion therapy. Mean Hcy level was 13.9$\pm$6.1 μmol/ml. Complete follow-up was obtained in 183 patients, with a median time of 21 months. The incidence of major events according to Hcy terciles is shown in the table.

Outcomes by Hcy tertiles

	Hcy tercile 1	Hcy tercile 2	Hcy tercile 3	P value
Hcy cut-off (μmol/ml)	< 11.57	11.57 - 14.70	> 14.70	-
Cardiovascular death	8.1%	11.3%	13.6%	.33
Reinfarction	4.8%	6.5%	13.6%	.08
Stroke	1.6%	3.2%	0	.50
Composite endpoint	12.9%	14.5%	24.5%	.07

On the contrary, none of lipid levels (total cholesterol, LDL- and HDL-cholesterol or triglycerides) had relationship with outcomes. Hcy correlated with age, plasma creatinine, albumin and vitamin B12 levels and previous hypercholesterolemia. After adjustment for these confounders, Cox regression analysis selected Hcy as an independent predictor of combined events (8.2% increase in risk per 1 μmol/ml of Hcy level increase; 95%CI: 1.4% - 15.5%).
Conclusion: Plasma Hcy levels may be useful for risk-stratification after AMI in older patients. Research on preventive therapies based on Hcy-lowering interventions is warranted.

THE HEART IN HYPERTENSION

P2341 Central pulse pressure is an independent correlate of coronary artery disease in men receiving no antihypertensive medications. Results from the multicentre ESCAPP study

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Several epidemiologic studies have shown the impact of pulse pressure on long term clinical outcome. The correlations between pulse pressure and the development of atherosclerotic coronary artery disease (CAD) are less well documented. The purpose of the ESCAPP study was to assess potential correlations between CAD and central pulse pressure in a population of patients without valvular heart disease undergoing diagnostic coronary angiography for the first time. From July 2001 to January 2002, 1337 patients referred for coronary angiography were enrolled in the 75 participating centres. Among them, 280 (198 men, 82 women; SBP/DBP: 133 $\pm$ 76/76 $\pm$ 12 mmHg; mean age 58 $\pm$ 12 years) had no antihypertensive medications (Group 1) and 1057 received at least one potentially antihypertensive treatment (beta-blockers, ACE-I, ARBs, Calcium antagonists, diuretics) (Group 2). Pulse pressure (PP) was measured invasively in the aortic root before any contrast injection.
Results: 53% of Group 1 patients had at least 1 $\geq$ 50% coronary stenosis. Central PP (61 $\pm$ 21 vs 56 $\pm$ 17 mmHg) was significantly higher in patients with CAD ($p<0.01$). Using multivariate analysis, PP was no longer associated with CAD when age was added to the model, but a strong interaction with gender was observed. In men, but not in women, PP was an independent predictor of the presence of CAD, along with older age and dyslipidemia. In addition, CAD extent was related to higher levels of PP (no CAD: 54 $\pm$ 13mmHg, 1 or 2 stenoses: 55 $\pm$ 16 mm Hg, > 2 stenoses: 60 $\pm$ 14 mmHg, $p<0.03$). In Group 2, PP was also higher in patients with CAD, but the predictive value of PP disappeared in multivariate analyses including age as a covariate.
Conclusion: In an untreated population of men, central PP is an independent predictor of the presence and extent of CAD. In women and in patients receiving antihypertensive medications, the correlation with PP disappears when age is included in the multivariate model.

P2342 Blood pressure control in hypertensive patients with left-ventricular hypertrophy from a survey in general practice: the INSUBRIA study

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Objective: To evaluate the rate of blood pressure (BP) control among known hypertensive patients in general practice in northern Italy.
Patients and Methods: 588 general practitioners took part in the study, each one enrolling 5 to 10 consecutive hypertensive patients. For each patient the followings were assessed: cardiovascular (CV) risk, according to the hypertension management guidelines (OMS/ISH 1999), clinic BP (3 measurements at 5 minutes interval) and antihypertensive therapy. Left ventricular hypertrophy (LVH) was assessed by EKG or echocardiography in 2663 pts (84%). We present here the results from the first 3167 subjects (1320 men, 64$\pm$11 years, BMI 27$\pm$4.3 kg/m^2, known duration of hypertension 8.9$\pm$6.9 years).
Results: The CV risk was low in 228 pts (7.2%), medium in 1288 pts (40.7%), high in 730 pts (23.1%) and very high in 916 pts (29%); 3087 pts (97.5%) were on antihypertensive drug treatment, 1234 pts (40%) with 1 drug, 1601 pts (51,9%) with 2 drugs and 252 pts (8.1%) with 3 or more drugs. Considering non-diabetic hypertensives (2737 pts), BP control (clinic BP < 140/90 mmHg) was achieved in 1098 pts (40.1%), systolic BP was controlled (<140 mmHg) in 1199 pts (43.8%) and diastolic BP (< 90 mmHg) in 2038 pts (74.5%); Subdividing the pts on the basis of CV risk group, BP control was achieved in 124 pts at low risk (54.4%), 519 at medium risk (40.3%), 271 at high risk (37.1%) and 328 at very high risk (35.8%); the rate of BP control progressively and significantly (p=0.012) decreased from low risk group to very high risk group.
Left ventricular hypertrophy was present in 800 pts (30%). BP control was lower in patients with left ventricular hypertrophy (273/800, 34%) than in pts without LVH (764/1863, 42%, p=0.017). In LVH+ patients the distribution of other cardiovascular risk factor, target organ damage and associated diseases was similar to LVH- patients.
Conclusions: In this general practice survey almost all the hypertensives were on drug treatment; a satisfactory systolic and diastolic BP control was achieved in less than 50% of the pts, with a higher prevalence of diastolic BP control over systolic BP control. Moreover the rate of BP control in patients with left ventricular hypertrophy, generally considered as an adjunctive risk factor, was lower than in patients without left ventricular hypertrophy.

P2343 Complications and prognosis of acute myocardial infarction in the hypertensive patient. The PRIMVAC registry

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Purpose: To analyse the acute complications and prognosis of acute myocardial infarction (AMI) in hypertensive patients compared with normotensive patients.
Methods: The arrhythmic, mechanical and ischemic complications were recorded, together with intra-Intensive Care Unit mortality among the patients with AMI admitted to the Intensive Care Units of the 17 hospitals participating in the PRIMVAC registry in the Valencian Community (Spain) in the years 1995-2000. The patients were divided into two groups according to the presence of high blood pressure (HBP): group A (with known HBP) and group B (normotensive). A bivariate analysis was carried out with the Pearson chi-square test, followed by the development of two logistic regression models (inter method) in which the response variables were primary ventricular fibrillation and mortality, and the confounding variables were patient age, sex, diabetes mellitus, hypercholesterolemia, smoking, previous AMI, Q-wave AMI, and fibrinolysis.
Results: A total of 12,071 patients were registered during the study period, of which 46% presented HBP (5,550 cases). Regarding the electrical complications, atrial fibrillation was more frequent in the HBP group (11.3% vs 8.4%; $p<0.00001$), while ventricular fibrillation was more common among the normotensive patients (4.7% vs 5.7%; $p<0.01$). The frequency of complete atrioventricular block was similar in both groups (5.6%). Papillary muscle rupture was rare in our series, with a greater incidence in the HBP group (0.3% vs 0.1%; $p<0.01$). Killip grade I was more frequent among the normotensive individuals (65.2% vs 59.6%; $p<0.0001$), while Killip grades III and IV were more frequent in the HBP group (23.1% vs 19.8%; $p<0.0001$). Regarding the ischemic complications 6.8% of the hypertensive patients suffered postinfarction angina – the proportion being very similar among the normotensive patients (6.1%). Reinfarction occurred in 172 patients in group A (3.1%), with a similar incidence in group B (2.6%). Global mortality was 12.4% in group B (810 patients), versus 14.4% in the group A (798 patients) – the difference being statistically significant ($p<0.001$). The multivariate analysis showed that HBP is not a statistically significant mortality risk factor ($p=0.46$), though it does constitute a risk factor for primary ventricular fibrillation ($p<0.05$; RR: 0.83).
Conclusions: Hypertensive patients do not present comparatively greater mortality during the acute phase of myocardial infarction, though primary ventricular fibrillation is more common in such subjects.

P2344 Outcome in hypertensive patients with suspected coronary artery disease after adjustment for left-ventricular mass index

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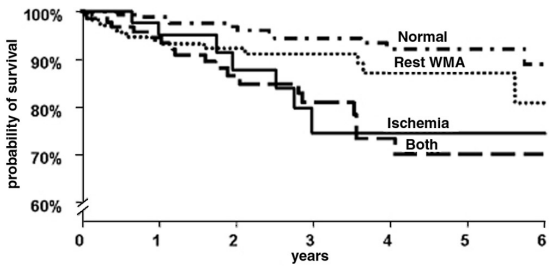
Objective: To assess the incremental value of dobutamine stress echocardiography (DSE) for the prediction of mortality and cardiac events in hypertensive patients.
Background: There are currently no outcome data to suggest an incremental value of stress echocardiography in the risk stratification of hypertensive patients after controlling for left ventricular mass index (LVMI).
Patients and methods: We studied 596 hypertensive patients (mean age 62 ± 12 years, 382 men) who underwent DSE for evaluation of known or suspected coronary artery disease. End-points during follow-up were hard cardiac events (cardiac death and non-fatal myocardial infarction) and total mortality.
Results: Left ventricular hypertrophy was detected by echocardiography in 119 patients (20%). During a median follow-up of 3 years, 101 patients (17%) died (43 cardiac deaths) and 19 patients had non-fatal myocardial infarction. In an incremental multivariate analysis model, clinical predictors of hard cardiac events were age, history of congestive heart failure, and LVMI. The percentage of abnormal myocardial segments with DSE was incremental to the clinical model (chi^2 41 vs. 27, $p<0.001$). Clinical predictors of total mortality were age, smoking, hypercholesterolemia, history of congestive heart failure, and LVMI. The peak wall motion score index was incremental to the clinical model ($chi^2 = 45$ vs. 40, $p<0.05$). The annual hard cardiac event rate and the mortality rate were higher in patients with abnormal as compared to patients with normal DSE (3.8% vs. 1.8%, and 5.7% vs. 3% respectively) (see figure).
Conclusions: DSE provides incremental data for the prediction of mortality and hard cardiac events in hypertensive patients after adjustment for clinical data and LVMI.



Survival curves for hard cardiac events.

P2345 Cardioinhibitory type responses of carotid sinus stimulation are closely associated with carotid artery stiffness in essential hypertensive subjects

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Purpose: To investigate for a possible association between the extent of cardioinhibitory type response of carotid sinus stimulation (CSStim) and the functional status of carotid artery in untreated hypertensive patients
Methods: Towards this end, CSStim (with simultaneous recordings of the ECG and the BP at the brachial artery) was performed in 102 untreated, newly diagnosed patients with stage I-II essential hypertension (aged 54 years, office BP=154/97 mmHg; without a history of cardiac or vascular disease or syncope) and in 70 normotensive controls matched for age and sex. Cardioinhibitory type of CSStim responses was evaluated by calculating an index, defined as the ratio of the longest R-R interval on the ECG recording during stimulation to RR interval at rest. Carotid distensibility was calculated as a function of changes in diameter (determined by echocardiography) and pulse pressure (determined sphygmomanometrically in the brachial artery) by the use of the formula: Distensibility=2x (pulsatile changes in diameter)/((diastolic diameter)x(pulse pressure)).
Results: The two groups did not differ regarding demographic and laboratory data. Hypertensive subjects compared to controls had increased relative wall thickness (0.48 vs 0.43, $p<0.005$), decreased carotid distensibility (1.2 vs 1.68 dyne-1cm^{2}10-6) and increased CSStim response index (1.74±1.03 vs 1.37±0.99, $p<0.005$). By a multivariate model including age, office pulse pressure, left ventricular mass index and CCA distensibility, it was revealed that only CCA distensibility was a significant determinant of CSStim responses index ($p<0.005$).
Conclusions: Hypertension-induced alterations in carotid artery elastic properties accompany changes in CSStim responses. These findings may contribute in the understanding of the mechanisms between atherosclerotic disease and exaggerated carotid sinus massage responses.

P2346 Incremental prognostic value of stress ^{99m}Tc-tetrofosmin myocardial perfusion tomography in patients with systemic arterial hypertension

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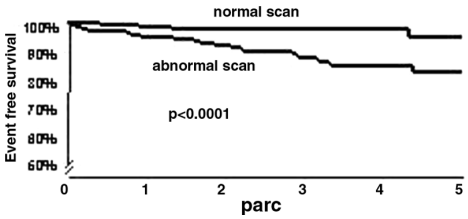
Background: There are currently insufficient data to indicate a role of stress myocardial perfusion imaging as a prognostic tool in hypertensive patients.
Objectives: to assess the incremental value of stress myocardial perfusion imaging for the prediction of cardiac death in hypertensive patients relative to clinical data.
Patients: We studied 601 hypertensive patients (age 59 ± 10 year, 387 men) who underwent exercise bicycle or dobutamine (up to 40 μg/kg/min) stress 99-m technetium tetrofosmin SPECT for evaluation of coronary artery disease.
Outcome: Cardiac death during folow up.
Results: An abnormal scan (reversible or fixed perfusion abnormalities) was detected in 293 (49%) patients (134 had reversible abnormalities). During a mean follow-up period of 3.1 ± 1.3 years, 109 (18%) patients died, of these patients 42 (39%) died due to cardiac causes. Independent predictors of cardiac death were age (hazard ratio =1.04, CI 1.01-1.08), history of previous myocardial infarction (hazard ratio = 2, CI 1.1-3.7), stress rate-pressure product (hazard ratio = 0.94, CI 0.87-0.98) and abnormal scan (hazard ratio = 4.7 CI 1.9-11.4). Both reversible and fixed abnormalities were predictive of death. The annual cardiac death rate was 5.3% in patients with abnormal and 0.5% in patients with normal perfusion scan (figure).



Mortality with normal vs abnormal scan.

Conclusion: Stress 99m technetium tetrofosmin myocardial perfusion imaging provides prognostic information incremental to clinical data for the prediction of cardiac death in hypertensive patients. Patients with a normal study have a low cardiac death rate and therefore these patients do not require further diagnostic evaluation of coronary artery disease.

P2347 Ultrasonic integrated backscatter cyclic variation is related to myocardial systolic function but not to interstitial fibrosis in left-ventricular hypertrophy

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Tissue characterization by ultrasonic integrated backscatter (IBS) analysis (acoustic densitometry) may be used to evaluate changes in the composition of left ventricular (LV) walls, such as those observed in LV hypertrophy (LVH). However, the relative contribution of myocardial fibrosis as opposed to changes in systolic function on IBS indices is still largely unclear. The relationships between the degree of LVH, IBS cyclic variation (CV) and average image intensity (AII) were investigated in both a human and an animal model of LVH, i.e. in untreated hypertensive patients (HT Pts), compared to age- and weight-matched controls (NT Pts), and in SD rats with pressure overload induced by abdominal aortic banding (B), compared to sham-operated animals (S). LV mass index (LVMi) was estimated in patients by Cornell-Penn criteria (g/m^2) and measured in animals by LV weight (g/100 g body weight). Systolic blood pressure (BP, mmHg) was measured by sphygmomanometry and carotid artery catheterization, respectively, to measure stress-corrected endocardial (FSendo, %) and midwall (FSmw, %) fractional shortening. In the animal model, LV interstitial collagen fraction (CF, %) was measured by Syrius red analysis.
LVMi and IBS-CV were inversely correlated, in both the human (r=-0.55, $p<0.02$) and the rat model (r=-0.49, $p<0.05$) of LVH. IBS-CV was correlated with FSmw (an index of myocardial systolic function) (r=0.61 and r=0.45, respectively, $p<0.01$ for both), but not with FSendo (an index of chamber systolic function). Collagen fraction was not correlated to IBS-CV (r=0.14 p=0.35) or to AII (r=0.45; p=0.08).
Results: see table.

	n	LVMi	FSendo(%)	FSmw(%)	BP(mmHg)	IBS-CV(dB)	CF(%)	AII(dB)
NT Pts	15	93±15	39±2	24±3	124±7	7.0±0.9		
HT Pts	15	134±20*	38±3	21±2*	165±8*	5.1±0.7*		
S rats	20	1.91±0.15	64±10	23±3	101±5	5.4±0.7	0.64±0.35	29.9±0.8
B rats	25	2.83±0.42*	56±9	19±3*	158±6*	4.4±0.3*	3.15±1.15*	27.1±1.7*

Means±SEM, *$p<0.05$ HT vs NT Pts or B vs S rats

Conclusions: These results underscore the relationships between the degree of LVH and IBS-CV, possibly related to the reduced myocardial systolic function wich is found in LVH at a time when chamber systolic performance is still preserved. The changes in ultrasonic integrated backscatter indices observed in cardiac hypertrophy are only marginally related to the degree of interstitial fibrosis.

P2348 Time-dependent alterations of angiogenic growth factors, endothelial nitric oxide synthase, apoptotic markers, capillary density and left-ventricular function in the heart of stroke-prone spontaneously hypertensive rats

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Purpose: Stroke-prone spontaneously hypertensive rats (SHRSP) often used as an experimental animal model of malignant hypertension demonstrate a remarkable hypertrophy of cardiomyocytes and a decreased capillary density in the left ventricular wall. The present study aimed to investigate in detail the age-dependent changes in expressions of different molecules related to angiogenesis and apoptosis in SHRSP heart using cDNA microarray analysis, real-time PCR, immunohistochemistry, Western blotting and in situ hybridization.
Methods: The hearts of SHRSP at 6 weeks of age (SHRSP6: prehypertensive stage), 20 weeks of age (SHRSP20: typical hypertensive stage) and 40 weeks of age (SHRSP40: malignant hypertensive stage) and those of age-matched Wistar Kyoto rats (WKY) and spontaneously hypertensive rats (SHR) were compared.
Results: Vascular endothelial growth factor (VEGF), a potent angiogenic growth factor, was highly upregulated in SHRSP20 at both protein and mRNA levels, whereas its angiogenic receptor, KDR, was downregulated compared to the age-matched WKY. In SHRSP40 both VEGF and KDR were significantly downregulated. The total coronary capillary density is significantly decreased already in SHRSP20 compared to WKY. Left ventricular (LV) systolic function assessed by echocardiography was almost unchanged in SHRSP20 heart compared to WKY, but LV diastolic function was impaired. The other potent angiogenic growth factor, basic fibroblast growth factor (bFGF), and its receptor subtype-3 were highly upregulated in SHRSP20, but were downregulated in SHRSP40. Endothelial nitric oxide synthase (eNOS) changed in parallel with VEGF. Pro-apoptotic markers, caspase family and its activated nuclease, were upregulated both in SHRSP20 and SHRSP40, but the upregulation was more prominent in SHRSP20. VEGF, KDR, bFGF, eNOS, and caspase-3 were unchanged in SHRSP6 compared to WKY. The age-dependent alterations of cardiac expressions of target molecules were less pronounced in SHR.
Conclusions: The upregulation of VEGF with concomitant downregulation of KDR in SHRSP20 suggests that VEGF and KDR are regulated through independent molecular mechanisms. The downregulation of KDR further explains the decreased coronary capillary density in SHRSP20 at typical hypertensive stage even with the upregulation of VEGF. Further study to explore the mechanistic insights behind the regulation of VEGF/KDR axis and related angiogenic factors in the heart will help understand the pathogenesis of cardiac lesions in patients with malignant hypertension.

P2349 Interstitial fibrosis is blunted by chronic sympathectomy but not by beta-blockade in experimental pressure-overload hypertrophy

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Pressure-overload hypertrophy (POH) is accompanied by an imbalance between left ventricular (LV) collagen deposition by fibroblasts and its degradation by matrix metalloproteases (MMPs) activity, with net collagen accumulation. Although it has been shown that cardiac deterioration is accelerated by chronic sympathetic overactivity via induction of myocyte toxicity and death, little is known about the possible effects of excessive catecholamine exposure on LV extracellular matrix composition and turnover.

To assess the effects of abrogating sympathetic activity on myocardial interstitial remodeling during experimental POH, Sprague-Dawley rats were subjected to abdominal aortic banding (B) or sham operation (S) to subsequently undergo chronic beta-blockade (Bb, oral propranolol, 60 mg/kg), chemical sympathectomy (Sx, 6-hydroxydopamine, 150 mg/kg i.p. twice a week) or vehicle treatment (Vh). Ten weeks later, carotid systolic blood pressure (SBP, mmHg), LV echo-derived end diastolic diameter (EDD, mm), and excised lung (LUNGi) and LV (LVi) weight indices (g/100g body weight) were measured. Collagen abundance (fraction, %) was assessed by Syrius red computer-aided analysis. To assess the extent of collagen degradation, MMP-2 activity (ng/ml/mg protein, gel zymography) and its specific tissue inhibitor concentration (TIMP2, ng/ml/mg protein, ELISA) were measured.

Results:

	n	SBP	EDD	LVi	LUNGi	Collagen	MMP-2	TIMP-2
S-Vh	9	102±12	7.1±0.3	1.9±0.1	2.9±0.6	0.64±0.35	2.4±0.6	0.39±0.18
B-Vh	10	154±19*	9.5±0.3*	3.0±0.5*	4.3±1.2*	3.15±1.15*	2.8±0.4	0.24±0.11
S-Sx	10	96±15	7.2±0.3	2.0±0.2	3.6±0.4	0.93±0.26	2.7±0.3	0.23±0.08
B-Sx	15	159±18*	8.6±0.3*#	2.5±0.6*#	3.7±0.6	0.86±0.49#	3.7±0.5*#	0.10±0.05*#
S-BB	10	100±15	6.9±0.2	2.1±0.5	3.5±0.9	1.12±0.46	1.1±0.2#	0.19±0.10
B-BB	11	150±12*	8.3±0.3*#	2.5±0.7*#	3.8±1.2	3.16±0.93*	1.7±0.6#	0.10±0.09

Means±SD;*p<0.05 vs corresponding S; #p<0.05 vs corresponding Vh

Conclusions: In the course of experimental POH, chronic sympathectomy (but not beta blockade) profoundly affects the cardiac interstitium, with complete abolition of LV fibrosis accompanied by enhanced MMP-2 activity and markedly reduced expression of its specific inhibitor, TIMP-2. These findings indicate that during the development of experimental hypertensive heart disease sympathetic (over)activity plays a major pro-fibrotic role, which is not mediated by beta-adrenergic effects.

P2350 Patterns of QT-dispersion in athletic and hypertensive left-ventricular hypertrophy

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Aim of the Study: Left ventricular hypertrophy (LVH) has been identified as a powerful predictor of cardiac arrhytmias. An increased QT dispersion on ECG has been shown to be associated with increased arrhytmogenic risk in hypertensive patients. The aim of this study was to assess whether physiological LVH of athletes and pathological LVH of hypertensives show similarities in QT length and QT dispersion.

Methods: 32 subjects were studied: 10 essential hypertensive patients (29.6±5.8ys), 12 athletes involved in agonistic activity (canoeing) (25.3±6.6ys) and 10 normotensive healthy subjects as control group (23.2±3.6ys). The testing protocol consisted of: 1) clinic BP measurement, 2) echocardiography 3) 12 lead electrocardiographic examination (QT max, QTc max, QT min, QTc min, deltaQT, deltaQTc)

Results: There were no significant differences between the body surface area, height and age of the three groups. Clinic blood pressure was higher in hypertensives (143.8±4.8/93.5±6.2 mmHg) versus athletes (121.1±10/79.0±6.0 mmHg) and controls (125.7±5.3/80.0±2.9 mmHg) by definition. Indexed left ventricular mass (LVM/BSA) was significantly greater in both athletes (140.7±24 g/m^2) and hypertensives (124.5±13.2g/m^2) versus controls (88±12.2 g/m^2; p<0.01); being no statistical difference among them. LVH (LVMI >125g/m^2) was observed in all athletes while the prevalence in hypertensives was 50%. In spite of this large difference in cardiac structure there were no significant differences in QT parameters between athletes and control group, while hypertensive patients showed a significant increase in QT dispersion versus the two other groups (deltaQT 88±5.2, 50±1.5, 51±2.4 msec; p<0.01; deltaQTc 94±5.1, 50±1.5, 56±2.8; p<0.01).

Conclusions: LVH induced by physical training activity isn't associated with an increase in QT dispersion whereas pathological increase in LVM secondary to hypertension is accompanied by an increased QT dispersion. These different patterns of QT dispersion add some elements in defining the effective functional differences between pathological and physiological LVH showing that athletes do not present the increased risk for cardiac arrhytmias that has been underlined in hypertensive patients.

P2351 Relationship between coronary vasodilator capacity and myocardial performance in uncomplicated hypertension

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Background: In patients with essential hypertension (HBP), a reduced LV fractional shortening at midwall level (MWS) is associated with increased cardiovascular risk. Aim of the study: to verify the hypothesis of a possible association of depressed MWS with a deeper impairment of coronary function in HBP.

Methods: 60 untreated patients with HBP (37 males, mean age 53±7) and 20 normotensive controls (NT, 12 males, mean age 51±10), without significant CAD and with preserved LV systolic function at endocardial level, underwent 2-D guided M-mode US for assessing MWS; TEE-Doppler was used to monitor coronary flow velocity response in LAD artery to i.v. adenosine (700μg/kg/5min), and to assess coronary reserve (CFR) and minimum coronary resistance (MCR).

Results: HBP patients had, compared to NT, significantly (p at least < 0.05) lower CFR (2.63±0.42 vs 3.50±0.55), and higher MCR (1.25±0.27 vs 0.86 mmHg s cm^{-1}). Afterload-adjusted MWS was normal (>85% of predicted value) in 46 patients (NL-MW) and depressed (≤85% of predicted value) in 14 (Low-MW). Compared to NL-MW, Low-MW had higher MCR (1.20±0.27 vs 1.38±0.20 mHg s cm^{-1}) and lower CFR (2.73±0.48 vs 2.43±0.42) (p <0.01 for both). In the whole HBP population, afterload-adjusted MWS was directly related to CFR (r =0.41, p <0.01), and inversely to MCR (r =-0.40, p<0.01). In a multivariate model after adjusting for age and BP, independent relations of CFR with afterload-adjusted MWS (direct, F value 11.6, adjusted r^2 =0.16) was found.

Conclusions: in hypertensive patients, a depressed MWS is associated with a deeper impairment of coronary flow reserve, which may represent a major mechanism underlying transition towards LV dysfunction. Impairment in coronary vasodilator capacity may also contribute to increased rate of cardiovascular events demonstrated in patients with low MWS.

PROGNOSTIC IMPORTANCE AND TREATMENT OF LIPID DISORDERS

P2352 Obstructive sleep apnea and its therapy: effects on lipid serum levels

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Purpose: Recent studies suggest an association of obstructive sleep apnea (OSA) with cardiovascular risk factors like dyslipidemia. It is unknown whether a consequent therapy of OSA normalizes this risk profile.

Methods: In A Cohort of 470 consecutive patients (age: 55.4 ± 11.13) with OSA (Apnea/hypopnea Index (AHI): 28.15/h ± 22.06), enrolled from the OSAMET-Assessment,Bochum (Obstructive SleepApnea and METabolic Syndrome), the relation between the severity of OSA and serum lipid levels were observed. We further compared the intial lipid- (n = 127) and lipoprotein levels (n = 86) with those after 6 months of bilevel- or continous positive airway pressure therapy (Bi-/C-PAP) in a subgroup of patients without change in their lipid lowering therapy.

Results: Multivariate regression showed a significant association of the AHI and triglyceride (β = 0.114; p = 0.020) and high density lipoprotein cholesterol (HDL-C) serum levels (β = -0.252; p < 0.001) independent of age, body mass index (BMI) and gender, but not on cholesterol and low density lipoprotein cholesterol (LDL-C) serum levels. Bi-/C-PAP therapy reduced the median AHI effectively from 28.15/h (± 22.06) to 2.79/h (± 3.44). HDL-C serum levels increased significantly by 5.8% from average 46.8 (± 15.7) to 49.7 (± 15.2) mg/dl (p = 0.013). Mean serum levels of LDL-C, cholesterol and triglycerides tended to be lower after 6 months in this subgroup. If only pathologic serum levels were observed, all lipid/lipoprotein serum levels improved significantly during Bi-/C-PAP therapy. Multivariate regression revealed a significant linear relation between the therapy induced changes of AHI and HDL-C - (β=0,388; p=0.001) or triglyceride serum levels (β = 0.199, p = 0.044), respectively, independent of the development of the BMI.

Conclusions: This study confirms an independent relation between the severity of the obstructive sleep apnea syndrome and HDL-C or triglyceride serum levels, respectively and shows the reversibility of these effects by Bi-/C-PAP therapy. This potential beneficial effect underlines the importance of consequent OSA therapy.

P2353 Supplementary treatment with abacor®, a soy protein based dietary supplement, reduces plasma concentrations of total and LDL cholesterols in statin-treated hypercholesterolemic patients

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Purpose: To test whether abacor®, a newly developed dietary supplement containing isolated soy protein (supro soy) with standardized high contents of isoflavones, cotyledon fibre and phospholipids, has a cholesterol lowering effect in patients with hypercholesterolemia treated with statins but despite this treatment having plasma cholesterol concentrations above target values.
Methods: Eligible for the study were adults (>18 years of age) treated with statins due to hypercholesterolemia combined with established atherosclerotic coronary disease or elevated cardiovascular risk. Plasma LDL cholesterol concentration at screening (on unchanged statin treatment in at least 6 weeks) should be 3.0 mmol/L or higher but was not allowed to exceed 4.5 mmol/L. In total 67 subjects were screened for the study and 53 (79%) were eligible for participation and were included. Of these 49 subjects (15 women/34 men, 43-79 years of age (59±1, mean±SEM)) completed the study. All patients received usual statin dose in 6 weeks followed by 6 weeks of statin + abacor® and finally 6 weeks of usual statin dose.
Results: Plasma total cholesterol and LDL cholesterol concentrations were significantly lower after 6 weeks of combination treatment, 5.5±0.1 mmol/L, and 3.3±0.1 mmol/L, respectively, than the mean value of the concentrations after the two periods of 6 weeks statin monotherapy, 5.9±0.1 mmol/L and 3.6±0.1 mmol/L, respectively, $p<0.0004$ and $p<0.0006$. No significant differences in plasma HDL cholesterol and triglyceride concentrations were found. Compliance to consumption of both abacor® and statin was high, 95±2% and 98±3%, respectively. A higher number of slight and transient gastrointestinal discomfort was reported during the statin+abacor period, but no significant difference in the number of adverse events were found between the combination period and the statin monotheraphy periods.
Conclusions: The study demonstrates that the soy based dietary supplement abacor® is well tolerated, safe and has a total and LDL cholesterol lowering effect when given as supplement to statins in hypercholesterolemic patients whose plasma lipid concentrations are not adequately controlled. Abacor® may be an attractive alternative to increments in statin dose.

P2354 Increased levels of pregnancy-associated plasma protein-A in patients with hypercholesterolaemia and diabetes: the effect of lipid lowering

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Background: Pregnancy-associated plasma protein A (PAPP-A) is a metalloproteinase produced by vascular smooth muscle cells. Serum PAPP-A levels have recently been linked to plaque instability and are increased in acute coronary syndromes. The relationship between PAPP-A levels and coronary risk factors has not been studied to date. We have therefore investigated whether serum PAPP-A levels are increased in asymptomatic hypercholesterolemic subjects and in patients with diabetes and whether PAPP levels are affected by lipid lowering therapy.
Methods: We examined 32 subjects with severe isolated hypercholesterolemia (HLP group), 20 patients with type II diabetes and mixed hyperlipidemia (DM group) and 26 age-matched healthy controls. All study subjects were free of manifest vascular disease. Serum PAPP-A levels were measured by immunometric assay. Patients with hypercholesterolemia were treated with atorvastatin (20mg/day); patients with diabetes were treated with simvastatin (20mg/day). Patients were examined at baseline and after 12 weeks of treatment.
Results are shown in the Table. In both patient groups, baseline PAPP-A levels were significantly higher than in controls ($p<0.01$, Mann-Whitney U test). Moreover, there was a trend towards higher values in DM group compared to HLP group. There was no correlation between serum PAPP-A and lipid levels. Both treatments substantially reduced serum lipid levels; despite this, there was no significant change in the serum PAPP-A levels in either patient group.

Serum PAPP-A and lipid levels

	Controls	HLP (before)	HLP (after)	DM (before)	DM (after)
PAPP-A [mU/l]	6.32±2.59	8.02±1.86	7.67±1.89	8.98±2.53	8.35±2.50
TC [mmol/l]	4.99±0.60	8.59±1.60	5.87±1.12	6.62±0.83	5.19±0.75
TG [mmol/l]	0.11±0.62	1.67±0.63	1.33±0.37	3.61±2.09	3.25±1.98

The results are expressed as mean±SD; values before and after the statin treatment are shown.

Conclusions: We have demonstrated for the first time that PAPP-A levels are elevated in hypercholesterolemic and diabetic subjects without clinical signs of atherosclerosis. PAPP-A may therefore not only reflect the plaque instability, as suggested earlier, but also serve as a marker of total atherosclerotic burden in asymptomatic subjects with hyperlipidemia. However, PAPP-A levels are not influenced by statin treatment Supported by research project J 13/98 11110000 2-1.

P2355 The close relationship between post-prandial remnant metabolism and insulin resistance

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Objective: The aim of the present study was to investigate the relationship between postprandial remnant-like particles (RLP) metabolism and insulin resistance (IR). Methods: The 78 consecutive subjects who performed a fat-loading test were identified. Those subjects under medical treatment with oral antidiabetics, insulin therapy or lipid lowering therapy were excluded. The study group consisted of 52 randomly selected subjects over the age of 30 (mean age: 51 ± 12 years, including 21 healthy volunteers). All subjects recieved a fat-loading test meal (14g of fat per square meter of body surface area, as fat content similar to a typical Japanese meal) to evaluate postprandial hyperlipidemia. Serum lipid and lipoprotein concentrations during fasting, and 4h after the fat-loading test, were measured. The concentrations of fasting immunoreactive insulin (IRI) and fasting blood glucose (FBS) were measured, and IR was assessed using the index of homeostasis model assessment (HOMA-R). The subjects were divided into two groups according to the value of HOMA-R: an IR group of subjects (n=17) with HOMA-R value ≥ 1.73, and a normal (NR) group of subjects (n=35) with HOMA-R value < 1.73. Results: Both fasting and postprandial RLP-cholesterol (RLP-C) concentrations in the IR group were significantly higher than those in the NR group (6.2 ± 2.6 vs 4.1 ± 1.7 mg/dl fasting value, and 9.7 ± 4.0 vs 5.8 ± 2.9 mg/dl postprandial value). The changes in RLP-C concentration during the fat-loading test were twice as high in the IR group compared with the NR group (3.5 ± 2.4 vs 1.6 ± 1.6mg/dl, P=0.0022). The HOMA-R correlated significantly with both fasting and postprandial triglyceride (r=0.41 and r=0.43, respectively), and RLP-C (r=0.36 and r=0.50, respectively) in all subjects. Multiple regression analysis indicated that postprandial RLP-C concentration was an independent predictor of HOMA-R regardless of age, BMI, and other lipid profiles. Conclusion: Thus, postprandial RLP metabolism is closely related to IR. The subjects with IR may be accompanied with postprandial RLP elevation after the daily fat intake, and the accumulation of postprandial remnant lipoproteins may be the possible cause of atherosclerotic proliferation in metabolic disorder.

P2356 Acute effects of low-density lipoprotein apheresis (HELP procedure) on cholesterol oxidation products and novel vasoactive peptides urotensin and relaxin

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Introduction: LDL-apheresis according to HELP (APH) is used to treat severe hypercholesterolemia in patients (pts.) with coronary artery disease (CAD). It has been argued that either hypercholesterolemia or extracorporeal treatment may enhance oxidative stress. We investigated the influence of a single APH on plasma concentrations (pc) of the cholesterol oxidation products and vasoactive peptides urotensin and relaxin in pts. with heterozygous familiar hypercholesterolemia (FHH) and advanced CAD enrolled in a chronic one/week APH program.
Methods: pc of oxidized LDL, Cu/ZnSOD, relaxin and urotensin were measured by ELISA, malondialdehyd (MDA) by HPLC and the antioxidative serum capacity (ImAnOx) by photometric method. Samples of 12 pts. (6 F, 58 ±9 y) before (pre), immediately after (post1) and prior to next APH (post2) were collected weekly.
Results: pts. with FHH demonstrated higher pc of oxLDL than healthy controls (n=30): 11,4±5mU/l vs 7,7 mU/l ($p<0,05$) proportional to LDL-chol. (r=0,8, $p<0,0001$). With APH LDL-chol. and oxLDL were reduced by 54% and 47%, respectively. MDA declined by 30%. Cu/ZnSOD remained unchanged. Relaxin and urotensine decreased significantly.

Table 1

	pre	post1	pre vs post1	post2	pre vs post2
OxLDL (mU/l)	11.4±6	6.25±3	$p<0.01$	10±3	n.s.
MDA (μmol/l)	1.27±0.3	0.9±0.14	$p<0.01$	1.25±0.2	n.s.
ImAnOx (μmol/l)	317±35	287±46	p=0.03	312±29	n.s.
Cu/ZnSOD (ng/ml)	75±36	71±27	n.s.	64±20	n.s.
Relaxin (pg/ml)	54±52	42±44	$p<0.05$	50±43	n.s.
Urotensin (pg/ml)	4057±983	2318±656	$p<0.0001$	3836±1092	n.s.

Conclusions: Single APH reduces cholesterol oxidation products as well as the vasoconstrictor urotensin without having an influence on cellular Cu/ZnSOD. The antioxidative serum capacity declines to some degree after APH.

P2357 Prognostic value of lipid profile assessed in acute phase of myocardial infarction

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Background: Elevated cholesterol levels affect endothelial function and thrombotic balance which may influence the clinical course of myocardial infarction (MI).
Aim: To assess the value of early cholesterol assessment for in-hospital prognosis in MI.
Methods: The study group consisted of 348 consecutive patients (216 males), aged 65.7 ± 12 years with MI, admitted within 24 hours from the onset of symptoms (mean 6.5 ± 5.5 h). The fasting blood samples for lipid profile were taken during the first 24 hours of hospitalization. Severe in-hospital course of MI was defined as cardiac death or new non-fatal MI.
Results: 40 out of 348 patients had a severe in-hospital course. Their total and LDL-cholesterol levels were significantly higher than the respective values in the remaining patients (Table). Multifactorial analysis revealed that total cholesterol level was an independent predictor of death (OR 14.6; 95% CI [2.8, 75.3]; p = 0.001) and new in-hospital non-fatal MI (OR 12.9; 95% CI [1.7, 100.4]; p = 0.015). The other independent risk factors were age, LBBB and diabetes.

	Total cholesterol	LDL-cholesterol	HDL-cholrsterol	Triglycerides
Severe MI (n = 40)	259.1 ± 34.9	164.7 ± 30.8	53.3 ± 12.9	151.4 ± 90.8
Mild MI (n = 308)	217.8 ± 41.9	137.6 ± 36.1	49.2 ± 13.4	156.3 ± 97.8
p value	< 0.001	< 0.001	NS	NS

All values are mg/dl

Conclusion: Early assessment of lipid profile identifies high-risk patients with MI. The finding that elevated total cholesterol and LDL-cholesterol indicates cmplicated MI supports the use of statins as early as possible in acute myocardial infarction.

P2358 Genetic linkage study of a possible third genomic locus for familial hypercholesterolaemia in Danish families

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Purpose: A locus on chromosome 1p34.1-p32 has been linked to Familial Hypercholesterolemia (FH). It is termed the third FH locus to distinguish it from the 2 loci containing the genes for the LDL-receptor (LDL-R) and apolipoprotein B (apoB). We tested the hypothesis that this locus is linked to the FH phenotype in Danish families without mutations in the genes for LDL-R or apoB.
Methods: Patients with a definite FH clinical phenotype, including an autosomal dominant inheritance pattern in the family, and in whom we found no mutations in the genes for LDL-R or apoB, were asked to participate in a family study. Seventeen families with 140 members in total were informative for linkage analysis, which was performed with the MLINK program from the LINKAGE package. Test of heterogeneity was performed with the HOMOG program. Results were similar when different disease models were used, and data presented here were derived using the following model: 1) an autosomal dominant mode of inheritance; 2) disease gene frequency of 0,001; 3) a person was considered affected if the level of LDL-cholesterol exceeded the age- and sex-specific 95 percentile; 4) penetrance was assumed to be 95% for the affected genotype and 5) penetrance was assumed to be 0,1% for the unaffected genotype.
Results: By linkage analysis we could exclude the third FH locus as a cause of FH in the material as a whole (cf. Table). There was no evidence of heterogeneity, and we therefore considered the material to be homogeneous concerning absence of linkage to the third FH locus. Analysis of the each family suggested that in 3 small pedigrees the FH phenotype nevertheless segregated in a manner consistent with linkage to the third FH locus. Because these families were small, these findings could easily be due to chance. This interpretation is also supported by lack of evidence of heterogeneity. If a gene for FH is identified in the third locus, we shall obviously test the gene for mutations in these families.

Two point lodscores

Marker name	D1S2892	D1S2722	D1S2134	D1S1661
Lodscore Theta=0,001	-8,01	-6,85	-12,3	-1,52*

Lodscore significant if below -2.*Non-informative.

Conclusion: The genetic background of an apparently monogenic disease like FH is more complex than previously thought, and mutations in a possible third FH gene do not seem to be a common cause of FH in Denmark.

P2359 Detection of the low-density lipoprotein receptor and apolipoprotein B gene mutation of patients with familial hypercholesterolaemia using real time polymerase chain reaction and SYBER green chemistry

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The coronary artery disease is the major cause of mortality in Europe. The mechanisms causing the abnormalities in the lipid metabolism are based on the excessive lipid intake in the food, disturbances of lipid metabolism, and genetic defects. The most atherogenic lipoprotein fraction is the LDL fraction containing cholesterol. The excess of it is eliminated by the binding with the LDL receptor localized on the surface of the cells. The mutations occurring in the gene coding the LDL receptor can lead to the defects of the structure and function of the receptor. The effect of these abnormalities is also the hypercholesterolemia. Accumulation of LDL cholesterol in the plasma can also be caused by the mutations in the B 100 apolipoprotein gene – the protein that is the ligand for the LDL receptor.
We studied FH patients in a Central European population. The LDL receptor and apolipoprotein B polymorphisms were determined by melting curve analysis with SYBER Green chemistry using real time PCR methode, and direct sequencing technique. The range of serum cholesterol and LDL-cholesterol was 250-450 and 200-400mg/dl in FH patients. A large number of different mutations of the LDLR gene was identified. In a screening of the LDLR gene mutations of 54 consecutive patients with familial hypercholesterolemia, we discovered new point mutations in 18 exon: one-nucleotide deletion (Asp2731), thirteen-nucleotide deletion (Val2734), C2623A causing Leu850Ile, T2786C, G2728A. Mutations was also located in three different exons (4,7,8); C518G causing a Cys152Trp in exon 4, T1012A causing Cys317Ser in exon 7 and T1102C causing Cys347Arg in exon 8. The mutation in exon 4 and 7 was previously reported in a compound heterozygote for familial hypercholesterolemia. FH can be caused not only by defects in the LDLR but also by mutation in apolipoprotein B causing decreased LDLR binding affinity, so called familial defective apolipoprotein B (FDB). Three different missense mutation in 26 exon of ten patients were found: Pro2712Leu substitution, Arg3500Gln leads to a defective binding of apolipoprotein B to the LDL receptor and a novel point mutation 3532Ile. We conclude, those mutations can alter the structure of the apolipoprotein and reduce their binding to LDL receptor

P2360 The first application of a single low-density lipoprotein apheresis procedure can improve myocardial blood flow

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Introduction: Endothelial dysfunction (ED) reduces coronary vasodilatation capacity and coronary blood flow in patients with hypercholesterolaemia. Cholesterol-lowering drugs may take several weeks to months to achieve serum cholesterol normalisation and hence correction of ED. LDL apheresis produces significant LDL cholesterol reduction within hours. Dynamic quantitative positron emission tomography (PET) performed immediately before and after LDL apheresis offers the possibility of measuring mean global myocardial perfusion at rest and after pharmacological vasodilatation with dipyridamole, using 13N ammonia as the tracer.
Materials and methods: Positron emission tomography studies were performed in 12 patients (1 woman and 11 men, age 47.1 ± 9.4 years) with documented coronary artery disease and hypercholesterolaemia despite maximal lipid-lowering medication immediately before and 18-20 hours after LDL apheresis. This procedure is based on the precipitation at an acid pH of a complex that consists essentially of heparin, LDL, Lp(a) and fibrinogen. In all patients HELP therapy was performed for the first time. Laboratory parameters were obtained immediately before (Pre) and after (Post 1) HELP therapy and 18-20 hours after LDL apharesis (Post 2).
Results: LDL cholesterol showed a reduction from 187±45 (Pre) to 75±27 mg/dl (Post 1) and 85±29 mg/dl (Post 2). Fibrinogene was reduced from 348±65 (Pre) to 126±38 mg/dl (Post 1) and 168±45 mg/dl (Post 2). There were statistically significant improvements in myocardial blood flow following dipyridamole stimulation (150±61 to 165±48 ml/min 100g, $p<0.0062$), coronary flow reserve (2.10±0.82 vs 2.62±1.02, $p<0.0001$) and minimum coronary resistance (0.61±0.23 to 0.53±0.19 mmHg 100g min/ml, $p<0.0001$). Plasma viscosity showed a minor 7.8% decrease.
Conclusion As documented by PET, the study shows that even the first application of HELP therapy in the beginning of a chronic treatment can significantly improve the coronary vasodilatation capacity due to an impressive lowering of total cholesterol, LDL and fibrinogen levels.

P2361 The effects of garlic powder time-released tablets Allicor in early atherosclerosis prevention

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The AMAR study (Atherosclerosis Monitoring and Atherogenicity Reduction) was designed to estimate the effect of time-released garlic-based drug Allicor (INAT-Farma, Russia), 300 mg daily, on the progression of carotid atherosclerosis in 206 asymptomatic men aged 40-74 in 2-years double-blinded placebo-controlled randomized multicenter clinical study. The primary outcome was the rate of carotid atherosclerosis progression, measured individually as the increase in carotid intima-media thickness (IMT) of the far wall of left and right common carotid arteries. High-resolution B-mode ultrasonography was used for carotid arteries imaging. The rate of changes in Allicor-treated group (-0.022±0.008 mm per year) was significantly different (P=0.002) from the placebo group in which there was a moderate progression of 0.014±0.009 mm at the overall mean baseline IMT of 0.935±0.009 mm. Within Allicor-treated group, IMT significant reduction was observed in 58% patients vs 25% in placebo group ($p<0.05$). The further significant IMT increase was registered in 26% patients in Allicor-treated group vs 44% in placebo group ($p<0.05$). At the baseline, serum taken from patients was able to induce 1.6-fold increase in intracellular cholesterol content in cell culture test, on an average. Serum atherogenicity (the ability of serum to induce cholesterol accumulation in cultured macrophages) was lowered in Allicor-treated patients by 45% on an average. Allicor administration also reduced the serum-induced expression of IL-1 and TNF-alpha in cultured human macrophages, thus demonstrating the anti-inflammatory effects of the drug. Moreover, this reduction correlated well with the changes in IMT ($r=0.564$, $p<0.005$ and $r=0.483$, $p<0.02$ for TNF-alpha and IL-1, respectively). In preliminary in vitro studies we have demonstrated that garlic extract increased cholesterol ester hydrolase activity and inhibited acetyl coenzyme A:cholesterol acyl transferase, thus leading to the fall in intracellular cholesterol content. The inhibition of both cellular proliferating activity and the synthesis of connective tissue matrix components were also observed. So, the direct anti-atherosclerotic effect of Allicor treatment on carotid atherosclerosis is possibly due to the prevention of intracellular lipid deposition and inhibition of inflammatory processes.

The results of AMAR study demonstrate that long-term treatment with garlic-based non-statin drug Allicor inhibits the progression of early atherosclerosis in men, thus allowing the new insight into atherosclerosis prevention and treatment.

NEW PERSPECTIVES ON LIPID LOWERING IN CLINICAL STUDIES

P2362 Statin therapies for elevated lipid levels compared across doses to rosuvastatin (STELLAR): non-high-density lipoprotein cholesterol results and goals

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Non-high-density lipoprotein cholesterol (non-HDL-C) represents the blood atherogenic cholesterol, and plasma triglyceride levels are a "marker" for this atherogenic cholesterol. The National Cholesterol Education Program Adult Treatment Panel (ATP) III guidelines recommend non-HDL-C as a secondary goal for patients with triglycerides ≥200 mg/dL who have met their low-density lipoprotein-C (LDL-C) goal. ATP III set non-HDL-C goals 30 mg/dL higher than the LDL-C goals of <100 mg/dL, <130 mg/dL, and <160 mg/dL for patients with high, medium, and low risks of coronary heart disease, respectively. In this multicenter, randomized trial (4522IL/0065), adults with hypercholesterolemia (LDL-C≥160 and <250 mg/dL; triglycerides <400 mg/dL) received 6 weeks of open-label treatment with one of several doses of rosuvastatin (RSV) (Crestor®), atorvastatin (ATV), simvastatin (SIM), or pravastatin (PRA). Pairwise comparisons of RSV with corresponding or higher doses of comparators for % changes in non-HDL-C were analyzed statistically (see table). Also, numbers of patients with hypertriglyceridemia at baseline (35% of all patients) who met both ATP III LDL-C and non-HDL-C goals at 6 weeks were assessed. In the RSV 10-40 mg groups, 80-84% met both LDL-C and non-HDL-C goals, compared with 51-84% in the ATV 10-80 mg groups, 30-60% in the SIM 10-80 mg groups, and 15-37% in the PRA 10-40 mg groups.

In summary, RSV had the greatest effect on non-HDL-C, which is of particular clinical significance in patients with highly atherogenic lipid profiles.

Non-HDL-C: mean % change from baseline*

	RSV	ATV	SIM	PRA
N/group, range	156-160	154-165	158-165	160-164
10 mg	-42	-34 (a)	-26 (a)	-19 (a)
20 mg	-48	-40 (b)	-33 (a,b)	-22 (a,b)
40 mg	-51	-45 (c)	-35 (a,b,c)	-27 (a,b,c)
80 mg		-48	-42 (b,c)	

*Baseline means were 221-230 mg/dL.Significantly different ($p<0.002$) versus (a) RSV 10 mg, (b) RSV 20 mg, (c) RSV 40 mg from analysis of variance (significance level adjusted to account for multiple comparisons).

P2363 Additive effects of angiotensin converting enzyme inhibitor combined with statin on inflammation and fibrinolysis in hypercholesterolemic patients with coronary artery disease

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Purpose: Because the mechanisms of the biological effects of statin and angiotensin converting enzyme inhibitor therapies differ, we studied the vascular responses to these therapies in hypercholesterolemic patients with coronary artery disease (CAD).

Methods: We administered simvastatin 20 mg and placebo or ramipril 10 mg daily during 2 months with washout 2 months to 32 hypercholesterolemic patients with CAD. This study was randomized, double-blind, placebo-controlled, crossover in design.

Results: Simvastatin alone or combined with ramipril significantly changed lipoproteins, and improved the percent flow-mediated dilator response to hyperemia (FMD) relative to baseline measurements by 33±6% and by 50±14%, respectively (both $P<0.001$) and reduced plasma malondialdehyde (MDA), marker of free radical by 8±8% and by 18±9% ($P=0.039$ and $P<0.001$, respectively) and MCP-1 by 7±4% and by 13±3%, respectively ($P=0.019$ and $P<0.001$, respectively), and CRP from 0.22 to 0.14 mg/dl and from 0.22 to 0.15 mg/dl, respectively ($P=0.124$ and $P=0.002$, respectively), and PAI-1 antigen relative to baseline measurements by -4±8% and by 11±7%, respectively ($P=0.690$ and $P=0.018$, respectively). However, simvastatin combined with ramipril changed to greater extent FMD and plasma levels of MDA, MCP-1, CRP, and PAI-1 antigen than simvastatin alone.

Conclusions: Compared with simvastatin alone, added ramipril to simvastatin showed additive effects on FMD and the plasma levels of oxidant stress, inflammation markers and fibrinolysis potential markers in hypercholesterolemic patients with CAD.

P2364 Concomitant statin administration does not affect clopidogrels clinical efficacy. A CREDO substudy

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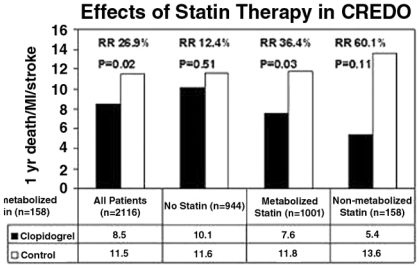
Background: Several statins that are primarily metabolized by cytochrome P450 3A4 (CYP3A4) have been shown to reduce clopidogrel's metabolism to it's active metabolite and attenuate it's inhibition of platelet aggregation ex vivo. However, the clinical impact of this interaction has not been evaluated.
Methods: CREDO was a double-blind, placebo-controlled, randomized trial comparing pretreatment (300mg) and 1 year (75mg) of therapy with clopidogrel (treatment group), to no pretreatment and only 1 month of clopidogrel (75mg) (control group) after a planned PCI. All patients received aspirin. The primary endpoint was a composite of death, MI, and stroke at 1 year. We performed a post-hoc analysis to evaluate the clinical efficacy of concomitant clopidogrel and statin administration, categorizing statin use at baseline to those metabolized by CYP3A4 (atorvastatin, lovastatin, simvastatin), and others (pravastatin, fluvastatin).
Results: Of the 2116 patients enrolled, 1172 (55.4%) were receiving a statin at baseline (1001 metabolized by CYP3A4, and 158 not). Overall in CREDO, the primary endpoint was significantly reduced in the treatment group (8.5% vs 11.5%, RR 26.9%, p=0.025). The benefit of pre- and long-term treatment with clopidogrel was evident irrespective of treatment with a CYP3A4 metabolized (7.59% treatment, 11.77% control, RR 36.4%, 95% CI 3.858 - 57.9, p=0.03) or other statin (5.36% treatment, 13.61% control, RR=60.6%, 95% CI –23.9 - 87.4, p=0.11). Similarly, concomitant therapy with either statin group had no impact on the incidence of major or minor bleeding.

Effects of Statin Therapy in CREDO



Conclusions: Although ex vivo testing has suggested a negative interaction when a CYP3A4 metabolized statin is administered with clopidogrel, this is not observed clinically.

P2365 Effects of fluvastatin on cardiovascular events in renal transplant patients: ALERT (Assessment of Lescol in Renal Transplantation)

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Background: Premature coronary heart disease (CHD) and other cardiovascular diseases(CVD) are the leading causes of death in renal transplant recipients. Hyperlipidemia is a risk factor for cardiovascular morbidity and mortality; however, no studies have demonstrated that lipid-lowering strategies significantly reduce these events in this population. We therefore conducted the first large-scale, randomized, controlled cardiovascular outcome trial comparing the effects of a statin vs. placebo in renal transplant recipients. Fluvastatin was selected because it has demonstrated safety in this population.
Methods: ALERT was an investigator-initiated, multicenter, randomized, double-blind, placebo-controlled trial conducted to assess the effect of fluvastatin in renal transplant patients. Eligible patients were male and female renal transplant recipients aged 30-75 years with total cholesterol 4.0-9.0 mmol/L [155-348 mg/dL] who had received a renal transplant more than 6 months before enrolment and were currently receiving immunosuppressive therapy containing cyclosporine. The primary endpoint of the study was time to first major adverse cardiac event (MACE), defined as cardiac death, nonfatal myocardial infarction, or intervention procedure (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty), with fluvastatin 40-80 mg/d compared with that of placebo, over a minimum of 5 years and a maximum of 6 years follow-up. The study's secondary endpoints included composite cardiac endpoints (MACE or angina pectoris resulting in hospitalization) and composite cardiovascular endpoints (MACE, or nonfatal or fatal stroke, or hospitalization for angina, or limb amputation).
Results: This is the largest study in renal transplant recipients, and the first attempt to modify cardiovascular outcomes. Between June 1996 and October 1997, a total of 2102 patients were randomly assigned to receive either fluvastatin or placebo. Data base lock occurred on February 6, 2003. Results for primary and secondary cardiac and cardiovascular endpoints and selected subgroup analyses will be available for presentation at the Congress.

P2366 Atorvastatin in patients with type 2 diabetes on haemodialysis: design and patient characteristics of a double-blind clinical trial (die deutsche diabetes dialyse study)

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Purpose: A major burden in diabetic patients on long-term dialysis is cerebro-/cardiovascular (CV) morbidity and mortality. Mixed dyslipidemia with moderately elevated low-density lipoprotein cholesterol and high triglyceride levels is common in this population. Statins proved to reduce CV endpoints in primary and secondary prevention, but their efficacy in diabetic patients undergoing hemodialysis (HD) has not been investigated. To examine this question, the 4D-Study (Die Deutsche Diabetes Dialyse Studie) was initiated.
Methods: The 4D-Study is a prospective, randomized, double-blind study investigating the potential of atorvastatin to decrease the rate of cerebro-/CV events in patients with type 2 diabetes on HD. The study involves 171 dialysis centers throughout Germany. As soon as the predefined number of 424 combined endpoints is reached [i.e., CV death, nonfatal myocardial infarction (MI) or fatal/nonfatal strokes] the study will be analyzed. Between 1998 and 2002, 1252 patients were randomized to either atorvastatin 20 mg or placebo. Men or women, aged 33 to 80 years, were entered into the trial with minimum exclusion criteria.
Results: Preliminary descriptive analyses revealed the following baseline characteristics: 55% were men (mean age: 64 years) and 45% were women (mean age: 68 years). Mean time between diagnosis of diabetes and first dialysis was 17.8 years; 17% had a prior MI; 82% of patients with a history of CV disease had a diagnosed hypertension. Mean lipid/lipoprotein levels were 221 mg/dl (total cholesterol), 128 mg/dl (low-density lipoprotein cholesterol), 37 mg/dl (high-density lipoprotein cholesterol), 57 mg/dl (very low-density lipoprotein cholesterol) and 257 mg/dl (triglycerides) with a mean LDL/HDL ratio of 3.9. For LDL cholesterol, 81% of patients showed values higher than the NCEP ATP III target level for high risk patients (i.e., 100 mg/dl). Approximately 68% (HDL cholesterol) and 63% (triglycerides) of patients had values $<$40 mg/dl and $>$180 mg/dl, respectively. Of those patients with a history of MI, 84% had LDL cholesterol levels $>$100mg/dl and 60% had triglycerides $>$180 mg/dl.
Conclusions: The baseline data suggest that the sample selected for this study is representative of patients with type 2 diabetes on HD. No selection bias was detected. A substantial portion of patients could be identified as candidates for lipid-modifying therapy. The study outcome will provide important data on the use of atorvastatin in patients at a high risk of cerebro-/CV morbidity and mortality. Complete baseline data will be presented.

P2367 Effects of selected drugs on exposure to ezetimibe

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Purpose: Ezetimibe (Ezetrol®; Zetia®; EZE) is a recent addition to the armamentarium for treating dyslipidemias. The drug acts by inhibiting intestinal absorption of cholesterol and related phytosterols. The objective of this presentation is to summarize the results of several Phase 1 studies designed to assess potential for pharmacokinetic (PK) drug interaction between EZE and selected drugs.
Methods: The following agents were examined: antacid combination of magnesium/aluminum hydroxide (Mg/Al); cholestyramine (bile-acid sequestrant/resin, CH); cimetidine (H2 histamine receptor antagonist anti-ulcer drug, CI); fenofibrate (anti-dyslipidemic drug, FEN); gemfibrozil (anti-dyslipidemic drug, GEM); and glipizide (oral hypoglycemic drug, GLI). The Phase 1 studies were open (O) or evaluator blind (EB); cross-over (#-way X) or parallel (P); and single (S) or multi (M) dose in normal (NV) or otherwise healthy hypercholesterolemic (HH) volunteers. The dose of EZE was 10 mg PO QD in all but the antacid study, in which each subject received one EZE dose alone and one EZE dose immediately following the antacid.
Results and Conclusions: The general study design and findings with respect to exposure to total EZE (EZE + EZE-glucuronide), as measured by AUC0-24 (ng x hr/mL), are shown in the table. Results of Phase 1 studies suggest that exposure to total EZE is not altered by antacids, cimetidine, or glipizide at the doses tested. Cholestyramine decreased the exposure to total EZE by ~55%, and thus the dosing of these two drugs when used together should be spaced apart. The fibric acid derivatives fenofibrate and gemfibrozil appeared to increase exposure to total EZE by 48% and 70%, respectively.

Exposure to Total EZE*

Interactant Agent	Study Design	Total EZE – EZE alone	Total EZE – EZE + Agent
Antacid 20mL—Mg/Al (6g/9g per 100mL)	O; 2-way X; S; NV; n=12	510 (37)	483 (35)
Cholestyramine—4g Q12h; 14 days	EB; P; M; HH; n=8/group	755 (31)	333 (27)
Cimetidine—400mg Q12h; 7 days	O; 2-way X; M; NV; n=12	898 (34)	955 (38)
Fenofibrate—200mg QD; 14 days	EB; P; M; HH; n=8/group	785 (54)	1070 (45)
Gemfibrozil—600mg Q12h; 7 days	O; 3-way X; M; NV; n=12	637 (44)	1071 (45)
Glipizide—10mg, single dose	O; S/M; NV; n=12	639 (26)	674 (31)

*Total EZE (EZE + EZE-glucuronide)=AUC 0-24 (%CV)

The safety and effectiveness of EZE administered with fibrates have not been established; thus, further clinical trials are warranted.

P2368 Undertreatment of hypercholesterolaemia leads to low goal attainment in real life

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Purpose: To assess reductions in total cholesterol levels among users of lipid-lowering drugs (LLD) in daily practice between 1991 and 2001.
Methods: Data were obtained from a sub-area region of the PHARMO system that includes complete medication, hospital admission and clinical lab assessment data of 80,000 Dutch residents. Total cholesterol levels (TC) and baseline characteristics were compared among LLD users (cases) and non-LLD users (controls). A cohort of 2005 cases who had a baseline cholesterol measurement in the six months before the start of LLD therapy and had at least one measurement after the start of the therapy was identified. Controls were patients with a baseline TC measurement who did not receive LLD. If a patient reached a TC level of less than 5 mmol/l during LLD treatment this was classified as 'attaining goal' according to the Dutch guidelines.
Results: A multivariate analysis of cases and controls indicated that the decision to treat a hypercholesterolemia patient with LLD was determined by the level of TC at baseline, a possible history of manifest cardiovascular disease or diabetes, the use of antihypertensive drugs and high blood pressure. 555 of 2005 patients (27.7%) attained goal at start dose, 1362 did not attain goal and 88 had no lab results before the first change of therapy. Prescribers adjusted therapy in 571 of the 1362 patients (41.9%) who did not attain goal; 137 of these patients attained goal after therapy adjustment (24.0%). In 185 of these 517 patients the effective statin dose was doubled; 47 (25.4%) of these patients attained goal. At the end of the follow-up period of at most three years 650 patients attained goal (32.4%). Goal attainment was dose-dependently related to the potency of initial therapy; goal attainment at the lowest potency (pravastatin 10 mg, fluvastatin 20 mg) was 22.5%, 32.4% at the medium potency (simvastatin 10 mg, pravastatin 20 mg, fluvastatin 40 mg) and 42.5% at the higher potencies.
Conclusions: Although results from this study indicate that the selection of patients and the initial LLD treatment for most patients in the Netherlands are in line with the national guidelines, goal attainment percentages in real-life are low. On the basis of the data we conclude that this is mainly due to the low doses of initial LLD prescribed and lack of dose adjustment. More efficacy is needed to increase the percentage of patients attaining goal. Additionally, increased patient compliance and a better supervision of patients under LLD treatment will increase goal attainment percentages.

P2369 Early benefit from structured care with atorvastatin in hypertensive patients with coronary heart disease

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Patients with arterial hypertension (AH) and coronary heart disease (CHD) benefit from statin treatment at least as much as the average CHD population. The effect of atorvastatin on such patients has not yet been investigated.
Aim: The prospective evaluation of the effect of structured care (SC) of dyslipidemia with atorvastatin (strict implementation of guidelines) versus usual care (UC) (physician's standard of care) on morbidity and mortality of patients with AH and CHD.
Methods: From 1,600 consecutive CHD patients randomized to either form of care in the target-based GREek Atorvastatin and Chd Evaluation (GREACE) Study, 850 had AH; 421 in the SC arm and 429 in the UC arm. All patients were followed-up for a mean 3-year period. In the SC group patients were treated with atorvastatin (dose titration from 10 to 80 mg/day) to achieve the National Cholesterol Education Program (NCEP) low-density lipoprotein cholesterol (LDL-C) treatment goal of <2.6 mmol/L; 100 mg/dL. Primary endpoints were all-cause and coronary mortality, coronary morbidity (non-fatal myocardial infarction and revascularization), and stroke.
Results: In the SC group 97% (n=408) of the patients were on atorvastatin (mean dose 25 mg/day) throughout the study and the NCEP LDL-C treatment goal was reached by 94% (n=396) of the patients. Only 15% (n=64) of the UC patients were on long-term hypolipidemic drug treatment and 3% (n=13) of them reached the NCEP LDL-C treatment goal. During the study 107 out of 429 (24.9%) CHD patients with AH on UC experienced a major vascular event or died vs 55 out of 421 (13%) patients on SC; relative risk reduction (RRR) 48%, $p<0.0001$. RRR for all-cause mortality was 41%, p=0.003, coronary mortality 49%, p=0.001, coronary morbidity 48%, $p<0.0001$, and stroke 58%, p=0.0002. Event rate curves started deviating from 6th treatment month and RRR was almost 50% by 12th month. RRRs remained at that level until the end of the study, time at which they became statistically significant. Long-term treatment with atorvastatin was safe and cost-effective (the direct cost/life-year gained was estimated at $US 7,900).
Conclusions: In secondary CHD prevention patients with AH, SC of dyslipidemia with atorvastatin, to achieve the NCEP LDL-C treatment goal, reduces all-cause and coronary mortality, coronary morbidity and stroke by almost one-half within a 3-year period, in comparison to UC. Clinical benefit is manifested as early as the 6th month of treatment, but becomes statistically significant by the 3rd treatment year.

P2370 Simvastatin significantly raises high-density lipoprotein cholesterol in patients with type 2 diabetic dyslipidaemia and low high-density lipoprotein cholesterol

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Modifications of lipid and lipoprotein parameters, including raising low HDL-C, appear to be important for improving CV risk reduction. Patients with Type 2 diabetes mellitus often have a combined hyperlipidemia that may be refractory to treatment. This combined hyperlipidemia includes low HDL-C and elevated triglycerides. Since data on the efficacy of high dose simvastatin in this population is limited, this study was designed to test the efficacy and tolerability of simvastatin (S) in raising HDL-C and its subfractions in patients with Type 2 diabetic dyslipidemia and low HDL-C.

Adult patients (N=151) with Type 2 diabetes mellitus and LDL-C>100mg/dL, HDL-C<40mg/dL, and triglycerides between 150 and 700 mg/dL were randomized to S 80 mg (S80), S 40 mg (S40), or placebo (pbo) in this double-blind, 3-period (6 weeks each) crossover study. Lipid parameters were assessed using standard methods and the Vertical Auto Profile (VAP) expanded panel.

At 6 weeks, S80 and S40 increased HDL-C and HDL subclasses (Table;shown as adjusted mean percent change from baseline after 6 weeks of treatment) S80 and S40 reduced LDL-C by 47.3% and 40.7%, IDL by 56.8% and 52.5%, and VLDL by 39.5% and 31.6%, respectively, from baseline. Changes for pbo were 2.3% (LDL-C), 7.7% (IDL), and 9.6% (VLDL). Triglycerides were reduced by 30.9% (S80), 28.9% (S40), and 0.1% (pbo). Total-C/HDL-C was reduced by 40.2% (S80), 33.6% (S40), and 2.2% (pbo). S80 was statistically better than S40 in reducing VLDL (p=0.007) and total C/HDL-C ratio (p<0.002). Both doses of simvastatin were well tolerated.

Change in HDL

Subclass (mg/dL)	S80	S40	Pbo
HDL-C	8.5*,**	4.8*	-0.4
HDL2-large	14.0*,**	5.8	4.2
HDL3-small	5.8*	3.5	1.3

*p less than or equal to 0.001 compared with placebo; **p less than or equal to 0.002 compared with S40.

S80 and S40 significantly increased HDL-C levels, and significantly reduced LDL-C, VLDL, IDL, and triglyceride levels compared with placebo (p<.001) in patients with low HDL-C. S80 significantly improved HDL subclasses, especially cardioprotective HDL2. This raises the possibility of additional benefit, independent of LDL lowering effects, in patients with Type 2 diabetes.

P2371 A systematic review on the cost-effectiveness of statins

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Statin therapy is known to reduce the rate of coronary heart disease. However, the scope of treatment is limited by high costs. This asks for clear priority setting aided by cost-effectiveness analyses. Costs are dominated by costs of statins and even though all trials agree on the size of health effect, cost-effectiveness analyses of statins have reported different results ranging from acceptable to non-acceptable ratios.

Aim: To evaluate and explain the level of heterogeneity existing in the different economic analyses of cardiovascular risk management with statins.

Methods: We performed a systematic review of the published statin cost-effectiveness analyses in Medline, the British National Health Service Economic Evaluation database and authors reference lists. Outcomes were standardized on calendar year and currency and compared by categories of absolute risk at start of treatment, age, funding source, time horizon, year of publication, discount rate and perspective of the analysis.

Results: Heterogeneity of cost-effectiveness ratios (CER) was much higher than expected from known heterogeneity of costs and effects. However, most of the studies reported moderate (<40000 dollars per year of life saved) to good (<20000 dollars per year of life saved) cost-effectiveness ratios for those with respectively 1-2.5% risk of coronary heart disease per annum (corresponding to healthy populations at high risk) and 2.5-4% risk of coronary heart disease per annum (corresponding to cardiovascular disease patients). Ages < 45 and > 65 showed worse CER compared to the age group 45-65. Studies with pharmaceutical company funding showed 5 times lower CER compared with studies funded by governments or educational institutions. This difference is most striking at low levels of absolute risk (with high financial impact). Shorter time horizons and older studies (before 1995) were associated with worse CER.

Conclusions: Treatment with statins is cost-effective for a wide range of cardiovascular risk levels. Information about cost-effectiveness at younger and older ages is still scarce and contradictory. Variance in cost-effectiveness analyses is larger than expected from direct observations of costs and effects. This is a serious problem if financial interests are large, and this holds for industry as for government and health care insurers. There is a great need for methods that are more evidence based and less liable to bias. The good news is that the situation is improving: recent CER reach qualitative agreement on which levels of risk to treat efficiently.